

JOSE LLOREDA CAMACHO & CO.

ABOGADOS

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E.

S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-179464- -00001-0000

Fecha: 2011-12-28 17:36:19 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 329 CTOINFORMACION Folios: 261

Act. 329 CTOINFORMACION Folios: 267

Re: PI.-INCYTE CORPORATION.-Solicitud de Patente de Invención en
Fase Nacional PCT para "PIRIMIDINONAS COMO INHIBIDORES
DE PI3K".-Clase C07D 473/34.-Expediente número 11-179.464-

1. Me refiero a mi solicitud de patente radicada ante ese Despacho el 27 de diciembre de 2011.
2. Anexos me permito presentar a usted:
 - (a) Copia auténtica debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado respecto de la cual reclamo prioridad, a saber la solicitud estadinense número **61/221,160** de 29 de Junio de 2009, junto con su traducción correspondiente a las reivindicaciones de dicho documento; y
 - (b) Copia auténtica debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado respecto de la cual reclamo prioridad, a saber la solicitud estadinense número **61/259,765** de 10 de noviembre de 2009, junto con su traducción correspondiente a las reivindicaciones de dicho documento.
3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

TRADUCCION OFICIAL No. 2011-12-22-774
DE UN DOCUMENTO ESCRITO EN INGLES

LOS ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS QUE VIEREN ESTOS PRESENTES:
DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

30 de noviembre de 2011

POR EL PRESENTE CERTIFICO QUE ADJUNTO AL PRESENTE SE ENCUENTRA UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS DE AQUELLOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA A CONTINUACION QUE CUMPLIO CON LOS REQUERIMIENTOS PARA QUE SE LE OTORGUE UNA FECHA DE PRESENTACION BAJO 35 USC 111.

NUMERO DE SOLICITUD: 61/221.160

FECHA DE PRESENTACION: 29 de junio de 2009

EL CODIGO DEL PAIS Y EL NUMERO DE SU SOLICITUD DE PRIORIDAD, PARA SER USADO PARA PRESENTACION EN EL EXTERIOR BAJO LA CONVENCION DE PARIS, ES US61/221,160

Departamento de Comercio
Oficina de Patentes y Marcas de los
Estados Unidos

Por Autoridad del
Subsecretario de Comercio para
Propiedad Intelectual y Director de la Oficina de
Patentes y Marcas de los Estados Unidos
(firma: ilegible)
T. LAWRENCE
Funcionario que Certifica

Recibo de Reconocimiento Electrónico	
ID EFS:	5602248
Número de Solicitud:	61221160
Número de Solicitud Internacional:	
Número de Confirmación:	9246
Título de la Invención:	PIRIMIDINONAS COMO INHIBIDORES DE PI3K
Primer Inventor Nombrado/Nombre del Solicitante:	Yun-Long Li
Número del Cliente:	26161
Presentador:	Christine A. Goddard/Christin Schwartz
Presentador Autorizado por:	Christine A. Goddard
Número de Expediente del Apoderado:	20443-0183P01
Fecha de Recepción:	29-JUN-2009
Fecha de Presentación:	
Estampilla de Tiempo:	12:26:33
Tipo de Solicitud:	Provisional
Información sobre Pago:	
Presentada con Pago	si
Tipo de Pago	Cuenta de Depósito
El pago fue exitosamente recibido en RAM	\$220
Número confirmación RAM	8265
Cuenta de Depósito	061050
Usuario Autorizado	

Listas de Archivos:					
Número del Documento	Descripción del Documento	Nombre del Archivo	Tamaño del Archivo (Bytes)/ Message Digest	Multi Partes /.zip	Páginas (si aplica)
1	Transmisión de Nueva Solicitud	transmittal.pdf	134036	no	2
			f23461b9b4ac9ca7e59058 67f7ba03f3b717f5c1		
Advertencias:					
Información:					
2		application.pdf	584057	si	99
			b88a82899190e2bd0cb2421 ff9406e0ec89b25		

3

Descripción Multipartes/Archivos PDF en .descripción zip					
Descripción del Documento			Inicio	Final	
Especificación			1	69	
Reivindicaciones			70	98	
Resumen			99	99	
Advertencias:					
Información:					
3	Hoja de Trabajo de Derechos (PTO-875)	fee.info.pdf	29623 2735ef528af27cb6e38c22ad b0964a976da0af5	no	2
Advertencias:					
Información:					
Tamaño Total de los Archivos (en bytes):			747716		
Este Recibo de Reconocimiento evidencia recibo en la fecha anotada por la USPTO de los documentos indicados, caracterizados por el solicitante, e incluyendo conteo de páginas, donde aplique. Sirve como evidencia de recibo similar a una Tarjeta Postal, según se describe en MPEP 503. <u>Nuevas Solicitudes Bajo 35 U.S.C. 111</u> Si se presenta una nueva solicitud y la solicitud incluye los componentes necesarios para una fecha de presentación (ver 37 CFR 1.53(b)-(d) y MPEP 506), un Recibo de Presentación (37 CFR 1.54) será expedido en el curso debido y la fecha mostrada en este Recibo de Reconocimiento establecerá la fecha de presentación de la solicitud. <u>Fase Nacional de una Solicitud Internacional bajo 35 U.S.C. 371</u> Si una presentación a tiempo para registrar una solicitud internacional en la fase nacional cumple con las condiciones de 35 U.S.C. 371 y otros requerimientos que aplican se expedirá un Formato PCT/DO/EO/903 que indica aceptación de la solicitud como una presentación de la fase nacional bajo 35 U.S.C. 371 además del Recibo de Presentación, en su curso debido. <u>Nueva Solicitud Internacional Presentada ante la USPTO como Oficina que Recibe</u> Si se presenta una nueva solicitud internacional y la solicitud internacional incluye los componentes necesarios para una fecha de presentación internacional (ver Artículo 11 PCT y MPEP 1810), se expedirá una Notificación del Número de la Solicitud Internacional y de la Fecha de Presentación Internacional (Formato PCT/RO/105) en el curso debido, sujeta a las prescripciones relacionadas con la seguridad nacional, y la fecha que aparece en este Recibo de Reconocimiento establecerá la fecha de presentación internacional de la solicitud.					

SOLICITUD PROVISIONAL PARA CARATULA DE PATENTE

Esta es una solicitud para presentar SOLICITUD PROVISIONAL PARA PATENTE bajo 37 C.F.R. §1.53(c).

INVENTOR(ES)			
Nombre (primero y segundo [si aplica])		Apellido	Residencia (Ciudad y Estado o País Extranjero)
Yun-Long Brian Andrew P.	Li Metcalf Combs	Chadds Ford, PA Moraga, CA Kennett Square, PA	
Se nombran inventores adicionales en las 0 hojas numeradas separadamente que se adjuntan al presente.			

TITULO DE LA INVENCION (500 caracteres máximo)					
PIRIMIDINONAS COMO INHIBIDORES DE PI3K					
DIRECCION DE CORRESPONDENCIA					
Dirigir toda la correspondencia a:					
☒ Número del Cliente 26161					
☐					
☐ Nombre de la Firma o Persona Natural					
Dirección					
Dirección					
Ciudad		Estado		Código Postal	
País		Teléfono		Fax	
PARTES DE LA SOLICITUD QUE SE ADJUNTAN (marque todas las que aplican)					
☐ Hoja Datos de Solicitud. Ver 37 CFR 1.76					
☐ CD(s), Número					
☒ Especificación					
Número de Páginas 99					
☐ Otros (especificar)					
☐ Dibujo(s)					
Número de Hojas					
Derechos Tamaño de la Solicitud: Si la especificación y los dibujos exceden 100 hojas de papel, los derechos por el tamaño de la solicitud debidos son \$270 (\$135 para entidad pequeña) por cada por cada 50 hojas o fracción adicional de la misma. Ver 35 U.S.C. §41(a)(1)(G) y 37 CFR §1.16(s).					
METODO DE PAGO DE DERECHOS DE PRESENTACION Y DERECHOS POR EL TAMAÑO DE LA SOLICITUD PARA ESTA SOLICITUD PROVISIONAL PARA PATENTE					
☐ El Solicitante reivindica estado de entidad pequeña. Ver 37 C.F.R. §1.27.					
☐ Se adjunta un cheque o giro postal para cubrir los derechos de presentación.					
SUMA TOTAL					
DERECHOS (\$)					
☐ Pago con tarjeta de crédito. Se adjunta formato PTO-2038					
220.00					
☒ El Director por el presente está autorizado para cobrar derechos de presentación o acreditar cualquier sobrepago a la Cuenta de Depósito Número: 06-1050. Se adjunta una copia de esta forma para procesamiento de derechos.					

Presentado respetuosamente,

Firma: /Christine A. Goddard/ Fecha: 29 de junio de 2009

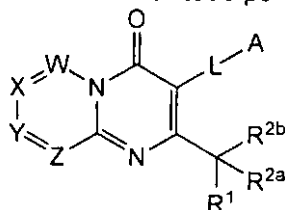
Christine A. Goddard, Ph.D., Reg. No. 46,731

Teléfono No: 617-542-5070

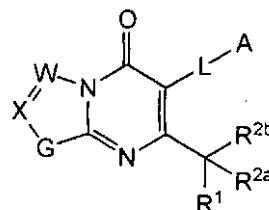
Expediente No: 20443-0183P01 / INCY0096-001 Fecha de Depósito: 29 de junio de 2009

Lo que se reivindica es:

1. Un compuesto caracterizado porque es de Fórmula I o II:



I



II

o una sal aceptable farmacéuticamente del mismo, donde:

A es C_{1-10} alquilo, arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$;

L se encuentra ausente o es $(CR^{7a}R^{7b})_m$, $(CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(O)(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(O)_2(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q$, o $(CR^{7a}R^{7b})_pNR^{7c}S(O)_2(CR^{7a}R^{7b})_q$;

W es N o CR³;

X es N o CR⁴;

Y es N o CR⁵;

Z es N o CR⁶;

G es O, S, o NR^N;

R¹ es OR^A, SR^A, S(O)R^A, S(O)₂R^A, NR^AR^B, NR^CC(O)NR^AR^B, NR^CC(O)OR^A, NR^CC(=NR^E)NR^AR^B, NR^CS(O)₂R^A, NR^CS(O)₂NR^CR^A, heterocicloalquilo, o heteroarilo, donde dicho heterocicloalquilo o heteroarilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre -(C₁₋₄ alquil)_r-Cy¹, halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1};

R^{2a} y R^{2b} se seleccionan en forma independiente entre H, halo, OH, CN, C₁₋₆ alquilo, C₁₋₆ haloalquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₁₋₆ haloalquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, y S(O)₂NR^{c2}R^{d2};

o R^{2a} y R^{2b} junto con el átomo de carbono al cual se encuentran unidos forman un anillo cicloalquilo de 3, 4, 5, 6 o 7 miembros o un anillo heterocicloalquilo de 3, 4, 5, 6, o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre

halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, y S(O)₂NR^{c2}R^{d2};

R³, R⁴, R⁵, y R⁶ se seleccionan en forma independiente entre H, halo, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)₂NR^{c3}R^{d3}, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, y S(O)₂NR^{c3}R^{d3};

R^{7a} y R^{7b} se seleccionan en forma independiente entre H, halo, o C₁₋₄ alquilo;

R^{7c} es H o C₁₋₄ alquilo;

R^{7d} es H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, o C(O)NR^{c5}R^{d5};

R^A es heteroarilo, heterocicloalquilo, heteroarilalquilo, o heterocicloalquilalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre – (C₁₋₄ alquil)-Cy¹, halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1};

R^B y R^C se seleccionan en forma independiente entre H, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y

heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

R^E es H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, o C(O)NR^{c5}R^{d5};

R^N es H o C₁₋₄ alquilo;

Cy¹ es arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1};

R^a, R^b, R^c, y R^d se seleccionan en forma independiente entre H, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

o R^c y R^d junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o

heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

R^{a1} , R^{b1} , R^{c1} , y R^{d1} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

o R^{c1} y R^{d1} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

R^{a2} , R^{b2} , R^{c2} , y R^{d2} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en

forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

o R^{c2} y R^{d2} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

R^{a3} , R^{b3} , R^{c3} , y R^{d3} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

o R^{c3} y R^{d3} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, halo, C_{1-6} haloalquilo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

X

R^o y R^f se seleccionan en forma independiente entre H, CN, NO_2 , OR^{a5} , SR^{b5} , $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, y $C(O)NR^{c5}R^{d5}$;

R^{a5} , R^{b5} , R^{c5} , y R^{d5} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre OH, CN, amino, halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} alquiltio, C_{1-6} alquilamino, $di(C_{1-6}$ alquil)amino, C_{1-6} haloalquilo, y C_{1-6} haloalcoxi;

o R^{c5} y R^{d5} junto con el átomo de N al cual están unidos forman a un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre OH, CN, amino, halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} alquiltio, C_{1-6} alquilamino, $di(C_{1-6}$ alquil)amino, C_{1-6} haloalquilo, y C_{1-6} haloalcoxi;

m es 1, 2, 3, 4, 5, 6, 7, 8, 9, o 10;

p es 0, 1, 2, 3, o 4;

q es 0, 1, 2, 3, o 4; y

r es 0 o 1.

2. El compuesto de la reivindicación 1, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula I.
3. El compuesto de la reivindicación 1, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula II.
4. El compuesto de cualquiera de las reivindicaciones 1-3, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es C_{1-10} alquilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a , SR^a ,

$C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$,
 $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$,
 $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo,
 C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2,
3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6}
alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$,
 $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$,
 $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$.

5. El compuesto de cualquiera de las reivindicaciones 1-3, o una sal aceptable farmacéuticamente
del mismo, caracterizado porque A es arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno
opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre
halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo,
heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$,
 $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$,
 $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y
 $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o
heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma
independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN,
 NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$,
 $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$,
 $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$.

6. El compuesto de cualquiera de las reivindicaciones 1-3, o una sal aceptable farmacéuticamente
del mismo, caracterizado porque A es arilo o heteroarilo, cada uno opcionalmente sustituido con 1, 2, 3,
4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6}
alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a ,

SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

7. El compuesto de cualquiera de las reivindicaciones 1-6, o una sal aceptable farmacéuticamente del mismo, caracterizado porque L se encuentra ausente.

8. El compuesto de cualquiera de las reivindicaciones 1-6, o una sal aceptable farmacéuticamente del mismo, caracterizado porque L es (CR^{7a}R^{7b})_m, (CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O) (CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)₂(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q, o (CR^{7a}R^{7b})_pNR^{7c}S(O)₂(CR^{7a}R^{7b})_q.

9. El compuesto de cualquiera de las reivindicaciones 1-6, o una sal aceptable farmacéuticamente del mismo, caracterizado porque L es (CR^{7a}R^{7b})_m.

10. El compuesto de cualquiera de las reivindicaciones 1-9, o una sal aceptable farmacéuticamente del mismo, caracterizado porque W es N.

11. El compuesto de cualquiera de las reivindicaciones 1-9, o una sal aceptable farmacéuticamente del mismo, caracterizado porque W es CR³.

12. El compuesto de cualquiera de las reivindicaciones 1-11, o una sal aceptable farmacéuticamente del mismo, caracterizado porque X es N.

13. El compuesto de cualquiera de las reivindicaciones 1-11, o una sal aceptable farmacéuticamente del mismo, caracterizado porque X es CR⁴.

14. El compuesto de cualquiera de las reivindicaciones 1-13, o una sal aceptable farmacéuticamente del mismo, caracterizado porque Y es N.
15. El compuesto de cualquiera de las reivindicaciones 1-13, o una sal aceptable farmacéuticamente del mismo, caracterizado porque Y es CR⁵.
16. El compuesto de cualquiera de las reivindicaciones 1-15, o una sal aceptable farmacéuticamente del mismo, caracterizado porque Z es N.
17. El compuesto de cualquiera de las reivindicaciones 1-15, o una sal aceptable farmacéuticamente del mismo, caracterizado porque Z es CR⁶.
18. El compuesto de cualquiera de las reivindicaciones 1-17, o una sal aceptable farmacéuticamente del mismo, caracterizado porque G es O.
19. El compuesto de cualquiera de las reivindicaciones 1-17, o una sal aceptable farmacéuticamente del mismo, caracterizado porque G es S.
20. El compuesto de cualquiera de las reivindicaciones 1-17, o una sal aceptable farmacéuticamente del mismo, caracterizado porque G es NR^N.
21. El compuesto de cualquiera de las reivindicaciones 1-20, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R¹ es heteroarilo opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre -(C₁₋₄ alquil)_r-Cy¹, halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1}.
22. El compuesto de cualquiera de las reivindicaciones 1-20, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R¹ es NR^AR^B.
23. El compuesto de cualquiera de las reivindicaciones 1-22, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{2a} y R^{2b} se seleccionan en forma independiente

A

entre H y C₁₋₆ alquilo opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alqueno, C₂₋₆ alquino, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, y S(O)₂NR^{c2}R^{d2}.

24. El compuesto de cualquiera de las reivindicaciones 1-23, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R³, R⁴, R⁵, y R⁶ se seleccionan en forma independiente entre H o C₁₋₆ alquilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, y S(O)₂NR^{c3}R^{d3}.

25. El compuesto de cualquiera de las reivindicaciones 1-23, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R³ es C₁₋₆ alquilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, y S(O)₂NR^{c3}R^{d3}.

26. El compuesto de cualquiera de las reivindicaciones 1-23, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R⁴, R⁵, y R⁶ son cada uno H.

27. El compuesto de cualquiera de las reivindicaciones 1-26, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{7a}, R^{7b}, R^{7c}, y R^{7d} son cada uno H.

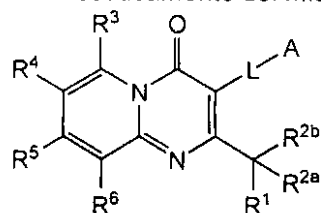
28. El compuesto de cualquiera de las reivindicaciones 1-27, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es heteroarilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre -(C₁₋₄ alquil)_r-Cy¹, halo, C₁₋₆ alquilo,

C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1}.

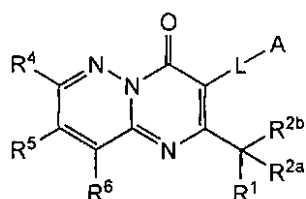
29. El compuesto de cualquiera de las reivindicaciones 1-28, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^B y R^C se seleccionan en forma independiente entre H y C₁₋₆ alquilo.

30. El compuesto de cualquiera de las reivindicaciones 1-29, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A no es fenilo sustituido con la posición 4 con halógeno.

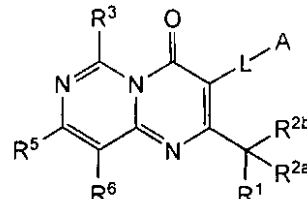
31. El compuesto de cualquiera de las reivindicaciones 1-30, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula Ia, Ib, Ic, Id, Ie, IIa, IIb, o IIc:



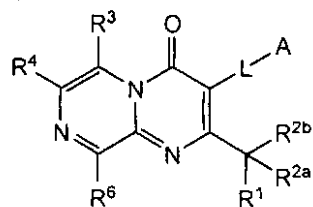
Ia



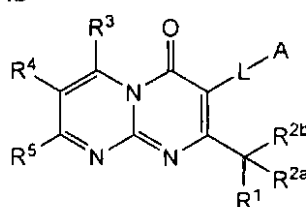
Ib



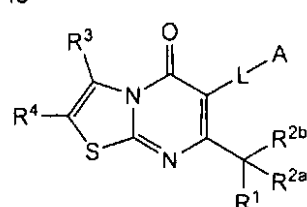
Ic



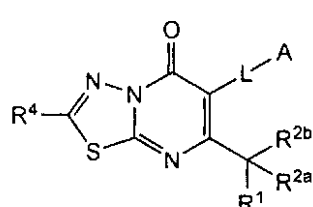
Id



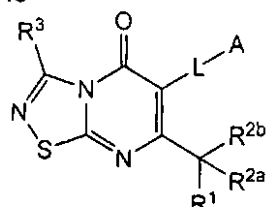
Ie



IIa

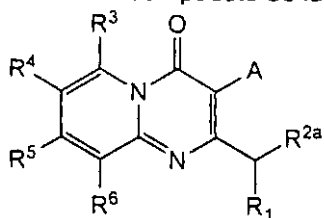


IIb

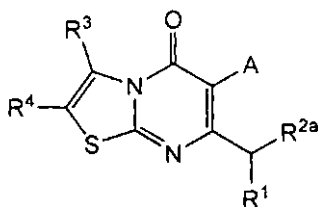


IIc.

32. El compuesto de la reivindicación 1 caracterizado porque es de fórmula If o IId:



If



IId

o una sal aceptable farmacéuticamente del mismo.

33. El compuesto de la reivindicación 32, o una sal aceptable farmacéuticamente del mismo, caracterizado porque:

A es arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d;

R¹ es OR^a, SR^a, S(O)R^a, S(O)₂R^a, NR^aR^b, NR^cC(O)NR^aR^b, NR^cC(O)OR^a, NR^cC(=NR^e)NR^aR^b, NR^cS(O)₂R^a, NR^cS(O)₂NR^cR^a, heterocicloalquilo, o heteroarilo, donde dicho heterocicloalquilo o heteroarilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre -(C₁₋₄ alquil)_r-Cy¹, halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1},

$\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$;

$\text{R}^{2\text{a}}$ es H, halo, OH, CN, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a2} , SR^{a2} , $\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{OC}(\text{O})\text{R}^{\text{b2}}$, $\text{OC}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{S}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})_2\text{R}^{\text{b2}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$;

R^3 , R^4 , R^5 , y R^6 se seleccionan en forma independiente entre H, halo, CN, NO_2 , OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{OC}(\text{O})\text{R}^{\text{b3}}$, $\text{OC}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})\text{R}^{\text{b3}}$, $\text{S}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$;

R^{A} es heteroarilo, heterocicloalquilo, heteroarilalquilo, o heterocicloalquilalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre – $(\text{C}_{1-4}\text{ alquil})\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{OC}(\text{O})\text{R}^{\text{b1}}$, $\text{OC}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$,

$\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$;

R^{B} y R^{C} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(\text{=NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{=NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{E} es H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, o $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

Cy^1 es arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{OC}(\text{O})\text{R}^{\text{b1}}$, $\text{OC}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$;

R^{a} , R^{b} , R^{c} , y R^{d} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(\text{=NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{=NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, y

$S(O)_2NR^{c5}R^{d5}$,

o R^c y R^d junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

R^{a1} , R^{b1} , R^{c1} , y R^{d1} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

o R^{c1} y R^{d1} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

R^{a2} , R^{b2} , R^{c2} , y R^{d2} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo,

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cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

o R^{c2} y R^{d2} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

R^{a3}, R^{b3}, R^{c3}, y R^{d3} se seleccionan en forma independiente entre H, C₁₋₆ alquilo, C₂₋₆ alquénilo, C₂₋₆ alquínilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₂₋₆ alquénilo, C₂₋₆ alquínilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

o R^{c3} y R^{d3} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, halo, C₁₋₆ haloalquilo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5},

$\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{e} y R^{f} se seleccionan en forma independiente entre H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, y $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{a5} , R^{b5} , R^{c5} , y R^{d5} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquénilo, C_{2-6} alquínilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquénilo, C_{2-6} alquínilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre OH, CN, amino, halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} alquiltio, C_{1-6} alquilamino, $\text{di}(\text{C}_{1-6}$ alquil)amino, C_{1-6} haloalquilo, y C_{1-6} haloalcoxi;

o R^{c5} y R^{d5} junto con el átomo de N al cual están unidos forman a un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre OH, CN, amino, halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} alquiltio, C_{1-6} alquilamino, $\text{di}(\text{C}_{1-6}$ alquil)amino, C_{1-6} haloalquilo, y C_{1-6} haloalcoxi; y

r es 0 o 1;

siempre que:

a) en la Fórmula If, cuando A es 3-fluorofenilo; $\text{R}^{2\text{a}}$ es H; R^3 es metilo; y R^4 , R^5 , y R^6 son H; entonces, R^1 no es 4-amino-3-yodo-1H-pirazolo[3,4-d]pirimidin-1-ilo; y

b) en la Fórmula If, cuando A es 1,3-dioxolan-2-ilo; $\text{R}^{2\text{a}}$, R^3 , R^4 , y R^6 son H; entonces, R^1 no es 1-(*tert*-butoxicarbonil)piperidin-4-ilo.

34. El compuesto de la reivindicación 33, o una sal aceptable farmacéuticamente del mismo, caracterizado porque el compuesto tiene la Fórmula If.

35. El compuesto de la reivindicación 33, o una sal aceptable farmacéuticamente del mismo, caracterizado porque el compuesto tiene la Fórmula IId.

36. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es cicloalquilo o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

37. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es arilo o heteroarilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

y $S(O)_2NR^cR^d$.

38. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es arilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$.

39. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es fenilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$.

mk

40. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es fenilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, o C₁₋₆ haloalquilo.

41. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es fenilo.

42. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es heteroarilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

43. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es heteroarilo de 6 miembros opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido

con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

44. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es piridilo opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, o C₁₋₆ haloalquilo.

45. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es heteroarilo de 5 miembros opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

46. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es pirazolilo opcionalmente sustituido con 1 o 2 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, o C₁₋₆ haloalquilo.

47. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R¹ es heteroarilo opcionalmente sustituido con 1, 2,

o 3 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , C(O)R^{b1} , $\text{C(O)NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , OC(O)R^{b1} , $\text{OC(O)NR}^{c1}\text{R}^{d1}$, $\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(O)R}^{b1}$, $\text{NR}^{c1}\text{C(O)OR}^{a1}$, $\text{NR}^{c1}\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S(O)R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, S(O)R^{b1} , $\text{S(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, y $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$.

48. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^1 es heteroarilo bicíclico opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , C(O)R^{b1} , $\text{C(O)NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , OC(O)R^{b1} , $\text{OC(O)NR}^{c1}\text{R}^{d1}$, $\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(O)R}^{b1}$, $\text{NR}^{c1}\text{C(O)OR}^{a1}$, $\text{NR}^{c1}\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S(O)R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, S(O)R^{b1} , $\text{S(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, y $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$.

49. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^1 es purinilo opcionalmente sustituido con $-(C_{1-4} \text{ alquil})_r\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , C(O)R^{b1} , $\text{C(O)NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , OC(O)R^{b1} , $\text{OC(O)NR}^{c1}\text{R}^{d1}$, $\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(O)R}^{b1}$, $\text{NR}^{c1}\text{C(O)OR}^{a1}$, $\text{NR}^{c1}\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S(O)R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, S(O)R^{b1} , $\text{S(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, o $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$.

50. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^1 es OR^A , SR^A , S(O)R^A , $\text{S(O)}_2\text{R}^A$, NR^AR^B , $\text{NR}^C\text{C(O)NR}^A\text{R}^B$, $\text{NR}^C\text{C(O)OR}^A$, $\text{NR}^C\text{C(=NR}^E\text{)NR}^A\text{R}^B$, $\text{NR}^C\text{S(O)}_2\text{R}^A$, o $\text{NR}^C\text{S(O)}_2\text{NR}^C\text{R}^A$.

51. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^1 es NR^AR^B .

52. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es heteroarilo opcionalmente sustituido con 1, 2,

3, 4, o 5 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r-Cy^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, y $S(O)_2NR^{c1}R^{d1}$.

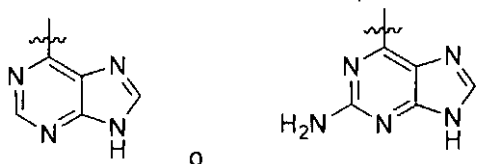
53. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es heteroarilo bicíclico opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r-Cy^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, y $S(O)_2NR^{c1}R^{d1}$.

54. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es purinilo opcionalmente sustituido con 1 o 2 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r-Cy^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, y $S(O)_2NR^{c1}R^{d1}$.

55. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es purinilo opcionalmente sustituido con 1 o 2 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$.

56. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable

farmacéuticamente del mismo, caracterizado porque R^A es:



57. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es heteroarilo bicíclico opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r$, $-Cy^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, y $S(O)_2NR^{c1}R^{d1}$.

58. El compuesto de cualquiera de las reivindicaciones 33-57, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^B y R^C se seleccionan en forma independiente entre H y C_{1-6} alquilo.

59. El compuesto de cualquiera de las reivindicaciones 33-57, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^B y R^C son cada uno H.

60. El compuesto de cualquiera de las reivindicaciones 33-59, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{2a} es H, halo, OH, CN, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, y $S(O)_2NR^{c2}R^{d2}$.

61. El compuesto de cualquiera de las reivindicaciones 33-59, o una sal aceptable

farmacéuticamente del mismo, caracterizado porque R^{2a} es halo, OH, CN, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, y $S(O)_2NR^{c2}R^{d2}$.

62. El compuesto de cualquiera de las reivindicaciones 33-59, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{2a} es H, halo, OH, CN, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo.

63. El compuesto de cualquiera de las reivindicaciones 33-59, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{2a} es metilo o etilo.

64. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, y $S(O)_2NR^{c3}R^{d3}$.

65. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es H, halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$,

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$C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, o C_{1-6} alquilo, donde dicho C_{1-6} alquilo, está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, y $S(O)_2NR^{c3}R^{d3}$.

66. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es H o C_{1-6} alquilo.

67. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es C_{1-6} alquilo.

68. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es metilo.

69. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^4 , R^5 , y R^6 se seleccionan en forma independiente entre H, halo, C_{1-6} alquilo, o C_{1-6} haloalquilo.

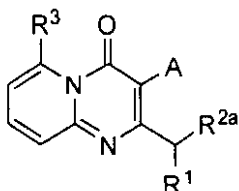
70. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^4 , R^5 , y R^6 son cada uno H.

71. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^4 es H.

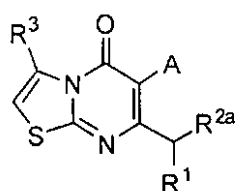
72. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^5 es H.

73. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^6 es H.

74. El compuesto de cualquiera de las reivindicaciones 33-73, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula Ig o IIe:

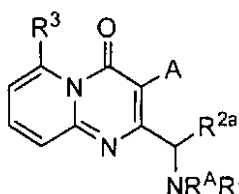


Ig

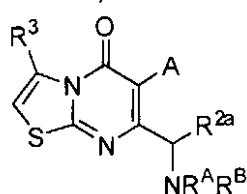


IIf.

75. El compuesto de cualquiera de las reivindicaciones 33-74, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula Ih o IIf:

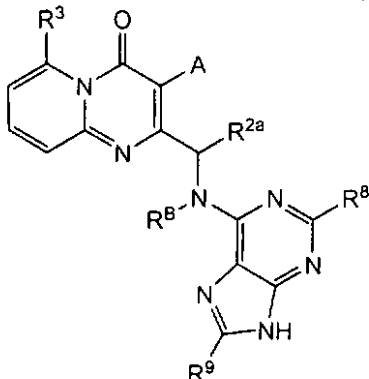


Ih

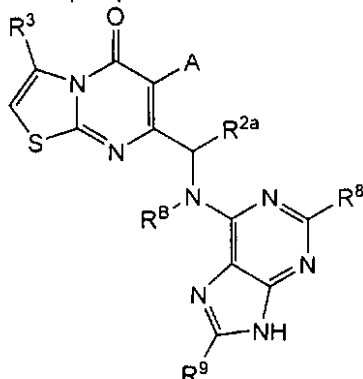


IIf.

76. El compuesto de cualquiera de las reivindicaciones 33-75, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula li o IIg:



li



IIg

donde R⁸ y R⁹ se seleccionan en forma independiente entre H, C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5}.

77. El compuesto de la reivindicación 1, es seleccionado de:

2-[1-(6-amino-9H-purin-9-il)etil]-6-metil-3-fenil-4H-pirido[1,2-a]pirimidin-4-ona;

B

6-metil-3-fenil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
3-(5-fluoropiridin-3-il)-6-metil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
3-(3-fluorofenil)-6-metil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
3-(3,5-difluorofenil)-6-metil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
3-(2-fluoropiridin-3-il)-6-metil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
6-metil-2-[1-(9H-purin-6-ilamino)propil]-3-(1H-pirazol-4-il)-4H-pirido[1,2-a]pirimidin-4-ona;
3-metil-6-fenil-7-[1-(9H-purin-6-ilamino)etil]-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
7-{1-[(2-amino-9H-purin-6-il)amino]etil}-3-metil-6-fenil-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
6-(3-fluorofenil)-3-metil-7-[1-(9H-purin-6-ilamino)etil]-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
7-{1-[(2-amino-9H-purin-6-il)amino]etil}-6-(3-fluorofenil)-3-metil-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
6-(3,5-difluorofenil)-3-metil-7-[1-(9H-purin-6-ilamino)etil]-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
7-{1-[(2-amino-9H-purin-6-il)amino]etil}-6-(3,5-difluorofenil)-3-metil-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
3-metil-7-[1-(9H-purin-6-ilamino)etil]-6-piridin-2-il-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona, o una sal aceptable farmacéuticamente de cualquier de las mencionadas precedentemente.

78 Una composición que comprende un compuesto de conformidad con cualquiera de las reivindicaciones 1-77 o una sal aceptable farmacéuticamente de la misma, y al menos un vehículo aceptable farmacéuticamente.

79. Un método para modular la actividad de una PI3K quinasa caracterizado porque comprende poner en contacto la quinasa con un compuesto de cualquiera de las reivindicaciones 1-77.

80. El método de la reivindicación 79 caracterizado porque la PI3K se selecciona entre el grupo que consiste en PI3K α , PI3K β , PI3K γ , y PI3K δ .

81 El método de la reivindicación 79 caracterizado porque dicha PI3K comprende una mutación.

82 El método de cualquiera de las reivindicaciones 79-81 caracterizado porque dicha modulación

es una inhibición.

83. El método de cualquiera de las reivindicaciones 79-81 caracterizado porque dicho compuesto es un inhibidor selectivo de PI3K δ respecto de uno o más de PI3K α , PI3K β , y PI3K γ .

84. Un método para tratar una enfermedad en un paciente, caracterizado porque dicha enfermedad está asociada con la expresión o actividad anormal de una PI3K quinasa, que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1-77.

85. El método de la reivindicación 84 caracterizado porque dicha enfermedad es osteoartritis, restenosis, aterosclerosis, trastornos de los huesos, artritis, retinopatía diabética, psoriasis, hipertrofia prostática benigna, aterosclerosis, inflamación, angiogénesis, pancreatitis, enfermedad renal, enfermedad inflamatoria del intestino, miastenia gravis, esclerosis múltiple, o síndrome de Sjogren.

86. El método de la reivindicación 84 caracterizado porque la PI3K se selecciona entre el grupo que consiste en PI3K α , PI3K β , PI3K γ , y PI3K δ .

87. El método de la reivindicación 84 caracterizado porque la PI3K es PI3K δ .

88. El método de cualquiera de las reivindicaciones 84-87 caracterizado porque se administra más de uno de dichos compuestos.

89. El método de la reivindicación 88 caracterizado porque el compuesto se administra en combinación con un inhibidor de quinasa que inhibe a una quinasa diferente de una PI3K quinasa.

90. Un método para tratar una enfermedad de base inmune en un paciente, caracterizado porque comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1-77.

91. El método de la reivindicación 90 caracterizado porque dicha enfermedad de base inmune es artritis reumatoide, alergia, asma, glomerulonefritis, lupus, o una inflamación relacionada con cualquiera de las mencionadas anteriormente.

92. Un método para tratar cáncer en un paciente, caracterizado porque comprende administrar a

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dicho paciente una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1-77.

93. El método de la reivindicación 92 caracterizado porque dicho cáncer es cáncer de mama, de próstata, de colon, endometrial, del cerebro, de vejiga, de piel, de útero, de ovarios, de pulmón, pancreático, renal, gástrico, o hematológico.

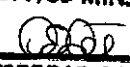
94. El método de la reivindicación 93 caracterizado porque dicho cáncer hematológico es leucemia mieloblástica aguda, leucemia mieloide crónica, o linfoma de células B.

95. Un método para tratar una enfermedad pulmonar en un paciente, caracterizado porque comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1-77.

96. El método de la reivindicación 95 caracterizado porque dicha enfermedad pulmonar es lesión pulmonar aguda (ALI) o síndrome de angustia respiratoria en adultos (ARDS).

Traducido según mi mejor saber y entender, este día 22 de diciembre de 2011, en la ciudad de Bogotá, D.C., por Anita Escobar de Tamayo, Traductora Oficial, Res. 2177 de 1989, Ministerio de Justicia, República de Colombia.

TRADUCTORA OFICIAL
RES. 2177/89 MINJUSTICIA


ANITA ESCOBAR DE TAMAYO



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

November 30, 2011

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

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Certifying Officer

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Electronic Acknowledgement Receipt

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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1	Transmittal of New Application	transmittal.pdf	134036 f23461b9b4ac9ca7e5905867f7ba03f3b717f5c1	no	2
Warnings:					
Information:					
2		application.pdf	584057 b88a82899190e2bd0f0cb2421ff9406e0ec89b25	yes	99
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	69	
	Claims		70	98	
	Abstract		99	99	
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	29623 2735ef528af27fcb6e38c22adb0964a976da0af5	no	2
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. §1.53(c).

INVENTOR(S)					
Given Name (first and middle (if any))		Family Name or Surname		Residence (City and either State or Foreign Country)	
Yun-Long Brian Andrew P.		Li Metcalf Combs		Chadds Ford, PA Moraga, CA Kennett Square, PA	
Additional inventors are being named on the 0 separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
PYRIMIDINONES AS PI3K INHIBITORS					
CORRESPONDENCE ADDRESS					
Direct all correspondence to:					
☒ Customer Number: 26161					
OR					
☐ Firm or Individual Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	
ENCLOSED APPLICATION PARTS (check all that apply)					
☐ Application Data Sheet.		See 37 C.F.R. § 1.76.		☐ CD(s), Number	
☒ Specification		Number of Pages 99		☐ Other (specify):	
☐ Drawing(s)		Number of Sheets			
Application Size Fee: If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$270 (\$135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. § 41(a)(1)(G) and 37 C.F.R. § 1.16(s)					
METHOD OF PAYMENT OF FILING FEES AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT					
☐ Applicant Claims small entity status. See 37 C.F.R. § 1.27.				TOTAL FEE AMOUNT (\$)	
☐ A check or money order is enclosed to cover the filing fees.				220.00	
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Account Number 06-1050 A copy of this form is enclosed for fee processing.					
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
☒ No.					
☐ Yes, the name of the U.S. Government agency and the Government contract number are:					

Respectfully submitted,

Signature: /Christine A. Goddard/ Date: June 29, 2009

Christine A. Goddard, Ph.D. , Reg. No. 46,731

Telephone No: 617-542-5070

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PYRIMIDINONES AS PI3K INHIBITORS

5 FIELD OF THE INVENTION

The present invention provides pyrimidinones that modulate the activity of phosphoinositide 3-kinases (PI3Ks) and are useful in the treatment of diseases related to the activity of PI3Ks including, for example, inflammatory disorders, immune-based disorders, cancer, and other diseases.

10

BACKGROUND OF THE INVENTION

The phosphoinositide 3-kinases (PI3Ks) belong to a large family of lipid signaling kinases that phosphorylate phosphoinositides at the D3 position of the inositol ring (Cantley, Science, 2002, 296(5573):1655-7). PI3Ks are divided into three classes (class I, II, and III) according to their structure, regulation and substrate specificity. Class I PI3Ks, which include PI3K α , PI3K β , PI3K γ , and PI3K δ , are a family of dual specificity lipid and protein kinases that catalyze the phosphorylation of phosphatidylinosito-4,5-bisphosphate (PIP₂) giving rise to phosphatidylinosito-3,4,5-trisphosphate (PIP₃). PIP₃ functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion and migration. All four class I PI3K isoforms exist as heterodimers composed of a catalytic subunit (p110) and a tightly associated regulatory subunit that controls their expression, activation, and subcellular localization. PI3K α , PI3K β , and PI3K δ associate with a regulatory subunit known as p85 and are activated by growth factors and cytokines through a tyrosine kinase-dependent mechanism (Jimenez, et al., J Biol Chem., 2002, 277(44):41556-62) whereas PI3K γ associates with two regulatory subunits (p101 and p84) and its activation is driven by the activation of G-protein-coupled receptors (Brock, et al., J Cell Biol., 2003, 160(1):89-99). PI3K α and PI3K β are ubiquitously expressed. In contrast, PI3K γ and PI3K δ are predominantly expressed in leukocytes (Vanhaesebroeck, et al., Trends Biochem Sci., 2005, 30(4):194-204).

The differential tissue distribution of the PI3K isoforms factors in their distinct biological functions. Genetic ablation of either PI3K α or PI3K β results in embryonic lethality, indicating that PI3K α and PI3K β have essential and non-redundant functions, at least during development

ns

(Vanhaesebroeck, et al., 2005). In contrast, mice which lack PI3K γ and PI3K δ are viable, fertile and have a normal life span although they show an altered immune system. PI3K γ deficiency leads to impaired recruitment of macrophages and neutrophils to sites of inflammation as well as impaired T cell activation (Sasaki, et al., Science, 2000, 287(5455):1040-6). PI3K δ -mutant mice have specific defects in B cell signaling that lead to impaired B cell development and reduced antibody responses after-antigen stimulation (Clayton, et al., J Exp Med. 2002, 196(6):753-63; Jou, et al., Mol Cell Biol. 2002, 22(24):8580-91; Okkenhaug, et al., Science, 2002, 297(5583):1031-4).

The phenotypes of the PI3K γ and PI3K δ -mutant mice suggest that these enzymes may play a role in inflammation and other immune-based diseases and this is borne out in preclinical models. PI3K γ -mutant mice are largely protected from disease in mouse models of rheumatoid arthritis (RA) and asthma (Camps, et al., Nat Med. 2005, 11(9):936-43; Thomas, et al., Eur J Immunol. 2005, 35(4):1283-91). In addition, treatment of wild-type mice with a selective inhibitor of PI3K γ was shown to reduce glomerulonephritis and prolong survival in the MRL-lpr model of systemic lupus nephritis (SLE) and to suppress joint inflammation and damage in models of RA (Barber, et al., Nat Med. 2005, 11(9):933-5; Camps, et al., 2005). Similarly, both PI3K δ -mutant mice and wild-type mice treated with a selective inhibitor of PI3K δ have been shown to have attenuated allergic airway inflammation and hyper-responsiveness in a mouse model of asthma (Ali, et al., Nature. 2004, 431(7011):1007-11; Lee, et al., FASEB J. 2006, 20(3):455-65) and to have attenuated disease in a model of RA (Randis, et al., Eur. J. Immunol., 2008, 38(5):1215-24).

In addition to their potential role in inflammatory diseases, all four class I PI3K isoforms may play a role in cancer. The gene encoding p110 α is mutated frequently in common cancers, including breast, prostate, colon and endometrial (Samuels, et al., Science, 2004, 304(5670):554; Samuels, et al., Curr Opin Oncol. 2006, 18(1):77-82). Eighty percent of these mutations are represented by one of three amino acid substitutions in the helical or kinase domains of the enzyme and lead to a significant upregulation of kinase activity resulting in oncogenic transformation in cell culture and in animal models (Kang, et al., Proc Natl Acad Sci U S A. 2005, 102(3):802-7; Bader, et al., Proc Natl Acad Sci U S A. 2006, 103(5):1475-9). No such mutations have been identified in the other PI3K isoforms although there is evidence that they can contribute to the development and progression of malignancies. Consistent overexpression

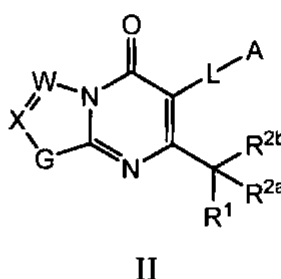
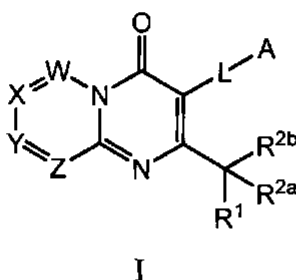
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of PI3K δ is observed in acute myeloblastic leukemia (Sujobert, et al., Blood, 2005, 106(3):1063-6) and inhibitors of PI3K δ can prevent the growth of leukemic cells (Billottet, et al., Oncogene. 2006, 25(50):6648-59). Elevated expression of PI3K γ is seen in chronic myeloid leukemia (Hickey, et al., J Biol Chem. 2006, 281(5):2441-50). Alterations in expression of PI3K β ,
5 PI3K γ and PI3K δ have also been observed in cancers of the brain, colon and bladder (Benistant, et al., Oncogene, 2000, 19(44):5083-90; Mizoguchi, et al., Brain Pathol. 2004, 14(4):372-7; Knobbe, et al., Neuropathol Appl Neurobiol. 2005, 31(5):486-90). Further, these isoforms have all been shown to be oncogenic in cell culture (Kang, et al., 2006).

Thus, new or improved agents which inhibit kinases such as PI3K are continually needed
10 for developing new and more effective pharmaceuticals that are aimed at augmentation or suppression of the immune and inflammatory pathways (such as immunosuppressive agents for organ transplants), as well as agents for the prevention and treatment of autoimmune diseases (e.g., multiple sclerosis, rheumatoid arthritis, asthma, type I diabetes, inflammatory bowel disease, Crohn's disease, autoimmune thyroid disorders, Alzheimer's disease, nephritis), diseases
15 involving a hyperactive inflammatory response (e.g., eczema), allergies, lung diseases, cancer (e.g., prostate, breast, leukemia, multiple myeloma), and some immune reactions (e.g., skin rash or contact dermatitis or diarrhea) caused by other therapeutics. The compounds, compositions, and methods described herein are directed toward these needs and other ends.

20 SUMMARY OF THE INVENTION

The present invention provides, *inter alia*, compounds of Formula I or II:



or pharmaceutically acceptable salts thereof, wherein constituent members are defined herein.

25 The present invention further provides pharmaceutical compositions comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

The present invention further provides methods of modulating an activity of one or more kinases (such as a PI3K) comprising contacting the kinase with a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

The present invention further provides methods of treating a disease or a disorder associated with abnormal kinase expression or activity in a patient by administering to a patient a therapeutically effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt of the same.

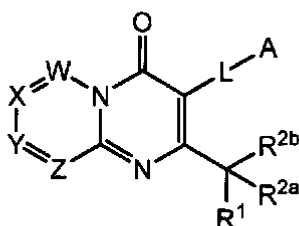
The present invention further provides methods of treating diseases such as immune-based diseases, cancer, and lung diseases in a patient by administering to the patient a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

The present invention further provides a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, for use in therapy.

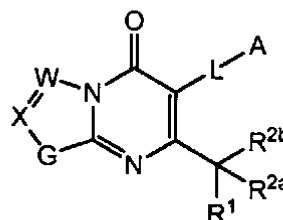
The present invention further provides use of a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, for the production of a medicament for use in therapy.

DETAILED DESCRIPTION

The present invention provides, *inter alia*, compounds that modulate the activity of one or more PI3Ks and are useful, for example, in the treatment of various diseases such as those associated with expression or activity of one or more PI3Ks. The compounds of the invention include those of Formula I or II:



I



II

or pharmaceutically acceptable salts thereof, wherein:

A is C₁₋₁₀ alkyl, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d,

20

$\text{NR}^c\text{S}(\text{O})\text{R}^b$, $\text{NR}^c\text{S}(\text{O})_2\text{R}^b$, $\text{NR}^c\text{S}(\text{O})_2\text{NR}^c\text{R}^d$, $\text{S}(\text{O})\text{R}^b$, $\text{S}(\text{O})\text{NR}^c\text{R}^d$, $\text{S}(\text{O})_2\text{R}^b$, and $\text{S}(\text{O})_2\text{NR}^c\text{R}^d$;
wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or
heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected
from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^a , SR^a ,
5 $\text{C}(\text{O})\text{R}^b$, $\text{C}(\text{O})\text{NR}^c\text{R}^d$, $\text{C}(\text{O})\text{OR}^a$, $\text{OC}(\text{O})\text{R}^b$, $\text{OC}(\text{O})\text{NR}^c\text{R}^d$, $\text{C}(=\text{NR}^e)\text{NR}^c\text{R}^d$, $\text{NR}^c\text{C}(=\text{NR}^e)\text{NR}^c\text{R}^d$,
 NR^cR^d , $\text{NR}^c\text{C}(\text{O})\text{R}^b$, $\text{NR}^c\text{C}(\text{O})\text{OR}^a$, $\text{NR}^c\text{C}(\text{O})\text{NR}^c\text{R}^d$, $\text{NR}^c\text{S}(\text{O})\text{R}^b$, $\text{NR}^c\text{S}(\text{O})_2\text{R}^b$, $\text{NR}^c\text{S}(\text{O})_2\text{NR}^c\text{R}^d$,
 $\text{S}(\text{O})\text{R}^b$, $\text{S}(\text{O})\text{NR}^c\text{R}^d$, $\text{S}(\text{O})_2\text{R}^b$, and $\text{S}(\text{O})_2\text{NR}^c\text{R}^d$;

L is absent, $(\text{CR}^{7a}\text{R}^{7b})_m$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{O}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{S}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{S}(\text{O})$
 $(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{S}(\text{O})_2(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}(\text{CR}^{7a}\text{R}^{7b})_q$,
10 $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{C}(\text{O})\text{NR}^{7c}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{C}(\text{O})\text{O}(\text{CR}^{7a}\text{R}^{7b})_q$,
 $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{C}(=\text{NR}^{7d})\text{NR}^{7c}(\text{CR}^{7a}\text{R}^{7b})_q$, or $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{S}(\text{O})_2(\text{CR}^{7a}\text{R}^{7b})_q$;

W is N or CR^3 ;

X is N or CR^4 ;

Y is N or CR^5 ;

15 Z is N or CR^6 ;

G is O, S, or NR^N ;

R^1 is OR^A , SR^A , $\text{S}(\text{O})\text{R}^A$, $\text{S}(\text{O})_2\text{R}^A$, NR^AR^B , $\text{NR}^C\text{C}(\text{O})\text{NR}^A\text{R}^B$, $\text{NR}^C\text{C}(\text{O})\text{OR}^A$,
 $\text{NR}^C\text{C}(=\text{NR}^E)\text{NR}^A\text{R}^B$, $\text{NR}^C\text{S}(\text{O})_2\text{R}^A$, $\text{NR}^C\text{S}(\text{O})_2\text{NR}^C\text{R}^A$, heterocycloalkyl, or heteroaryl, wherein
said heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents

20 independently selected from $-(\text{C}_{1-4}\text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6}
haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, $\text{OC}(\text{O})\text{R}^{b1}$,
 $\text{OC}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{R}^{b1}$,
 $\text{NR}^{c1}\text{C}(\text{O})\text{OR}^{a1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S}(\text{O})\text{R}^{b1}$, $\text{NR}^{c1}\text{S}(\text{O})_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})\text{R}^{b1}$,
 $\text{S}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, and $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$;

25 R^{2a} and R^{2b} are independently selected from H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl,
 C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl,
heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6}
haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl,
heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3
30 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6}
haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $\text{C}(\text{O})\text{R}^{b2}$, $\text{C}(\text{O})\text{NR}^{c2}\text{R}^{d2}$, $\text{C}(\text{O})\text{OR}^{a2}$, $\text{OC}(\text{O})\text{R}^{b2}$,

OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2},
 NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2},
 S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a 3-, 4-, 5-,
 5 6-, or 7-membered cycloalkyl ring or a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl ring, each
 optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆
 alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2},
 C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2},
 NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2},
 10 NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

R³, R⁴, R⁵, and R⁶ are independently selected from H, halo, CN, NO₂, OR^{a3}, SR^{a3},
 C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3},
 S(O)₂NR^{c3}R^{d3}, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl,
 heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein
 15 said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl,
 heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4,
 or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3},
 C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3},
 NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3},
 20 S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

R^{7a} and R^{7b} are independently selected from H, halo, or C₁₋₄ alkyl;

R^{7c} is H or C₁₋₄ alkyl;

R^{7d} is H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, or C(O)NR^{c5}R^{d5};

R^A is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each
 25 optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)_n,
 Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1},
 SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1},
 NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1},
 NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and
 30 S(O)₂NR^{c1}R^{d1};

30

R^B and R^C are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

10 R^E is H, CN, NO_2 , OR^{a5} , SR^{b5} , $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, or $C(O)NR^{c5}R^{d5}$;
 R^N is H or C_{1-4} alkyl;

Cy^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$,
 15 $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^a , R^b , R^c , and R^d are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$,
 20 $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^c and R^d together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} ,
 30 $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$,

NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5},
S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a1}, R^{b1}, R^{c1}, and R^{d1} are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a2}, R^{b2}, R^{c2}, and R^{d2} are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5},
S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a3}, R^{b3}, R^{c3}, and R^{d3} are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^e and R^f are independently selected from H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, and C(O)NR^{c5}R^{d5};

R^{a5}, R^{b5}, R^{c5}, and R^{d5} are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy;

or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

p is 0, 1, 2, 3, or 4;

q is 0, 1, 2, 3, or 4; and

r is 0 or 1.

5 In some embodiments, the compounds of the invention have Formula I.

In some embodiments, the compounds of the invention have Formula II.

In some embodiments, A is C₁₋₁₀ alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a,
 10 C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a,
 NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b,
 NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆
 alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted
 with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
 15 alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a,
 OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b,
 NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d,
 S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments, A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each
 20 optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆
 alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl,
 heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d,
 NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d,
 NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b,
 25 and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl,
 or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently
 selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂,
 OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d,
 NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b,
 30 NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

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In some embodiments, A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a,
 5 NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a,
 10 OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments, L is absent.

In some embodiments, L is (CR^{7a}R^{7b})_m, (CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q,
 15 (CR^{7a}R^{7b})_pS(O)(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)₂(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q, or (CR^{7a}R^{7b})_pNR^{7c}S(O)₂(CR^{7a}R^{7b})_q.

In some embodiments, L is (CR^{7a}R^{7b})_m.

In some embodiments, W is N.

20 In some embodiments, W is CR³.

In some embodiments, X is N.

In some embodiments, X is CR⁴.

In some embodiments, Y is N.

In some embodiments, Y is CR⁵.

25 In some embodiments, Z is N.

In some embodiments, Z is CR⁶.

In some embodiments, not more than 2 of W, X, Y, or Z are N.

In some embodiments, not more than 3 of W, X, Y, or Z are N.

In some embodiments, one of W and X is N.

30 In some embodiments, G is O.

In some embodiments, G is S.

In some embodiments, G is NR^N .

In some embodiments, R^1 is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from $-(\text{C}_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , $\text{OR}^{\text{a}1}$, $\text{SR}^{\text{a}1}$, $\text{C}(\text{O})\text{R}^{\text{b}1}$, $\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{C}(\text{O})\text{OR}^{\text{a}1}$, $\text{OC}(\text{O})\text{R}^{\text{b}1}$, $\text{OC}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{OR}^{\text{a}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{S}(\text{O})\text{R}^{\text{b}1}$, $\text{S}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{S}(\text{O})_2\text{R}^{\text{b}1}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$.

In some embodiments, R^1 is $\text{NR}^{\text{A}}\text{R}^{\text{B}}$.

In some embodiments, $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ are independently selected from H and C_{1-6} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , $\text{OR}^{\text{a}2}$, $\text{SR}^{\text{a}2}$, $\text{C}(\text{O})\text{R}^{\text{b}2}$, $\text{C}(\text{O})\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{C}(\text{O})\text{OR}^{\text{a}2}$, $\text{OC}(\text{O})\text{R}^{\text{b}2}$, $\text{OC}(\text{O})\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{NR}^{\text{c}2}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{NR}^{\text{c}2}\text{C}(\text{O})\text{R}^{\text{b}2}$, $\text{NR}^{\text{c}2}\text{C}(\text{O})\text{OR}^{\text{a}2}$, $\text{NR}^{\text{c}2}\text{C}(\text{O})\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{NR}^{\text{c}2}\text{S}(\text{O})\text{R}^{\text{b}2}$, $\text{NR}^{\text{c}2}\text{S}(\text{O})_2\text{R}^{\text{b}2}$, $\text{NR}^{\text{c}2}\text{S}(\text{O})_2\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{S}(\text{O})\text{R}^{\text{b}2}$, $\text{S}(\text{O})\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{S}(\text{O})_2\text{R}^{\text{b}2}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$.

In some embodiments, at least one of $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ is other than H.

In some embodiments, R^3 , R^4 , R^5 , and R^6 are independently selected from H or C_{1-6} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $\text{OR}^{\text{a}3}$, $\text{SR}^{\text{a}3}$, $\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{OC}(\text{O})\text{R}^{\text{b}3}$, $\text{OC}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$.

In some embodiments, R^3 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $\text{OR}^{\text{a}3}$, $\text{SR}^{\text{a}3}$, $\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{OC}(\text{O})\text{R}^{\text{b}3}$, $\text{OC}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$.

In some embodiments, R^4 , R^5 , and R^6 are each H.

In some embodiments, $\text{R}^{7\text{a}}$, $\text{R}^{7\text{b}}$, $\text{R}^{7\text{c}}$, and $\text{R}^{7\text{d}}$ are each H.

In some embodiments, R^{A} is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $\text{OR}^{\text{a}5}$, $\text{SR}^{\text{a}5}$, $\text{C}(\text{O})\text{R}^{\text{b}5}$, $\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{C}(\text{O})\text{OR}^{\text{a}5}$, $\text{OC}(\text{O})\text{R}^{\text{b}5}$, $\text{OC}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{R}^{\text{b}5}$,

$\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$.

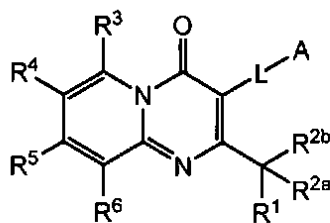
In some embodiments, R^{B} and R^{C} are independently selected from H and C_{1-6} alkyl.

In some embodiments, A is other than phenyl substituted at the 4-position by halogen.

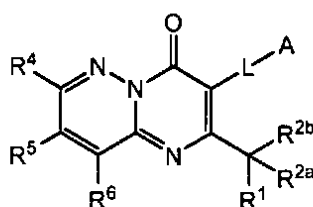
5 In some embodiments, r is 0.

In some embodiments, r is 1.

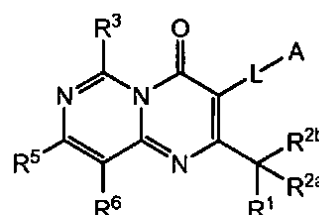
In some embodiments, the compounds of the invention have Formula Ia, Ib, Ic, Id, Ie, IIa, IIb, or IIc:



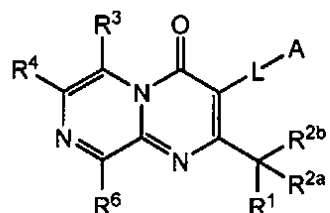
Ia



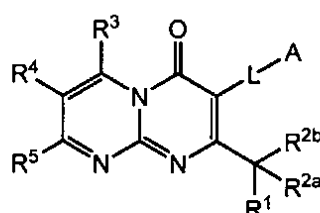
Ib



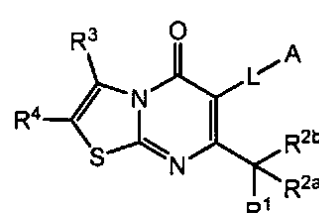
Ic



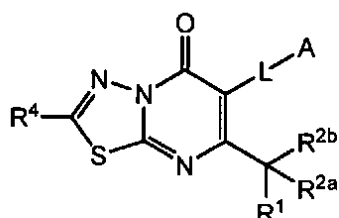
Id



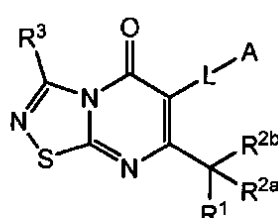
Ie



IIa

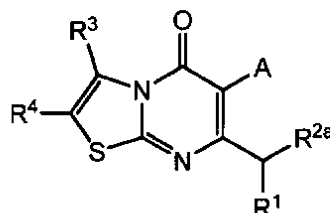
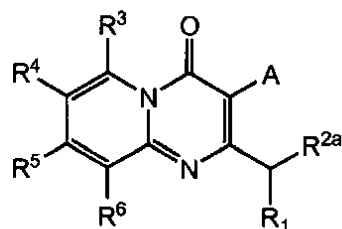


IIb



IIc.

In some embodiments, the compounds of the invention have Formula If or IId:



If

IId.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId:

A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

R¹ is OR^A, SR^A, S(O)R^A, S(O)₂R^A, NR^AR^B, NR^CC(O)NR^AR^B, NR^CC(O)OR^A, NR^CC(=NR^E)NR^AR^B, NR^CS(O)₂R^A, NR^CS(O)₂NR^CR^A, heterocycloalkyl, or heteroaryl, wherein said heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^{2a} is H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2},

$\text{NR}^{\text{c}2}\text{S}(\text{O})\text{R}^{\text{b}2}$, $\text{NR}^{\text{c}2}\text{S}(\text{O})_2\text{R}^{\text{b}2}$, $\text{NR}^{\text{c}2}\text{S}(\text{O})_2\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{S}(\text{O})\text{R}^{\text{b}2}$, $\text{S}(\text{O})\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$, $\text{S}(\text{O})_2\text{R}^{\text{b}2}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}2}\text{R}^{\text{d}2}$;

R^3 , R^4 , R^5 , and R^6 are independently selected from H, halo, CN, NO_2 , $\text{OR}^{\text{a}3}$, $\text{SR}^{\text{a}3}$, $\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $\text{OR}^{\text{a}3}$, $\text{SR}^{\text{a}3}$, $\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{OC}(\text{O})\text{R}^{\text{b}3}$, $\text{OC}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$;

R^{A} is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(\text{C}_{1-4} \text{ alkyl})_r$, Cy^1 , halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , $\text{OR}^{\text{a}1}$, $\text{SR}^{\text{a}1}$, $\text{C}(\text{O})\text{R}^{\text{b}1}$, $\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{C}(\text{O})\text{OR}^{\text{a}1}$, $\text{OC}(\text{O})\text{R}^{\text{b}1}$, $\text{OC}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{OR}^{\text{a}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{S}(\text{O})\text{R}^{\text{b}1}$, $\text{S}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{S}(\text{O})_2\text{R}^{\text{b}1}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$;

R^{B} and R^{C} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $\text{OR}^{\text{a}5}$, $\text{SR}^{\text{a}5}$, $\text{C}(\text{O})\text{R}^{\text{b}5}$, $\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{C}(\text{O})\text{OR}^{\text{a}5}$, $\text{OC}(\text{O})\text{R}^{\text{b}5}$, $\text{OC}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{R}^{\text{b}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{OR}^{\text{a}5}$, $\text{C}(\text{=NR}^{\text{f}})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{=NR}^{\text{f}})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{S}(\text{O})\text{R}^{\text{b}5}$, $\text{S}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{S}(\text{O})_2\text{R}^{\text{b}5}$, $\text{NR}^{\text{c}5}\text{S}(\text{O})_2\text{R}^{\text{b}5}$, $\text{NR}^{\text{c}5}\text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$;

R^{E} is H, CN, NO_2 , $\text{OR}^{\text{a}5}$, $\text{SR}^{\text{a}5}$, $\text{S}(\text{O})_2\text{R}^{\text{b}5}$, $\text{C}(\text{O})\text{R}^{\text{b}5}$, $\text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, or $\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$;

Cy^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

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C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

- 5 R^a, R^b, R^c, and R^d are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

- 15 or R^c and R^d together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

- 20 R^{a1}, R^{b1}, R^{c1}, and R^{d1} are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

- 25 or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5},

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$C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$,
 $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$,
 $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a2} , R^{b2} , R^{c2} , and R^{d2} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$,
 $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$,
 $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a3} , R^{b3} , R^{c3} , and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$,
 $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$,
 $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$,

$\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{e} and R^{f} are independently selected from H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

- 5 R^{a5} , R^{b5} , R^{c5} , and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents
- 10 independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $\text{di}(\text{C}_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;
- or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $\text{di}(\text{C}_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy; and
- 15 r is 0 or 1.

In some embodiments of compounds of Formulas I and Ia-If, when A is 3-fluorophenyl; $\text{R}^{2\text{a}}$ is H; R^3 is methyl; and R^4 , R^5 , and R^6 are H; then R^1 is other than 4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl.

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In some embodiments of compounds of Formulas I and Ia-If, when A is 1,3-dioxolan-2-yl; $\text{R}^{2\text{a}}$, R^3 , R^4 , and R^6 are H; then R^1 is other than 1-(tert-butoxycarbonyl)piperidin-4-yl.

In some embodiments of compounds of Formulas I and Ia-If, R^1 is other than a substituted or unsubstituted pyrazolo[3,4-d]pyrimidin-1-yl group.

25 In some embodiments of compounds of Formulas I and Ia-If, R^1 is other than a substituted or unsubstituted piperidinyl group.

In some embodiments, the compound has Formula Ia.

In some embodiments, the compound has Formula Ib.

In some embodiments, the compound has Formula Ic.

30 In some embodiments, the compound has Formula Id.

In some embodiments, the compound has Formula Ie.

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In some embodiments, the compound has Formula If.

In some embodiments, the compound has Formula IIa.

In some embodiments, the compound has Formula IIb.

In some embodiments, the compound has Formula IIc.

5 In some embodiments, the compound has Formula IId.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a,
 10 OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5
 15 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is aryl or
 20 heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b,
 25 and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b,
 30 NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

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In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is phenyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl,

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heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is 6-membered heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is pyridyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is 5-membered heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

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- and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is pyrazolyl optionally substituted with 1 or 2 substituents independently selected from halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

- 10 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

- 20 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is bicyclic heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

- 25 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is purinyl optionally substituted with $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, or $S(O)_2NR^{c1}R^{d1}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is OR^A , SR^A , $S(O)R^A$, $S(O)_2R^A$, NR^AR^B , $NR^CC(O)NR^AR^B$, $NR^CC(O)OR^A$, $NR^CC(=NR^E)NR^AR^B$, $NR^CS(O)_2R^A$, or $NR^CS(O)_2NR^CR^A$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^1 is NR^AR^B .

- 5 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r$, Cy^1 , halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

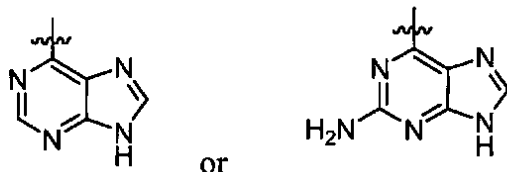
- 15 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r$, Cy^1 , halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

- 20 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r$, Cy^1 , halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

- 25 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

- 30 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is:

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In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from –

5 (C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}.

10 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^B and R^C are independently selected from H and C₁₋₆ alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^B and R^C are each H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is H, halo,

15 OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}.

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In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl is optionally substituted with 1, 2, or 3 substituents

25 independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}.

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In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is C_{1-6} alkyl.

5 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is methyl or ethyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and
 10 heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$,
 15 $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is H, halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, or C_{1-6} alkyl, wherein said C_{1-6} alkyl, is optionally substituted with
 20 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$.

25 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is H or C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is methyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^4 , R^5 , and R^6 are independently selected from H, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

30 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^4 , R^5 , and R^6 are each H.

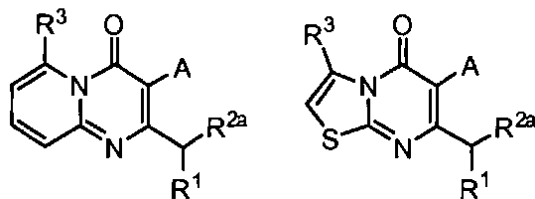
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In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^4 is H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^5 is H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^6 is H.

In some embodiments, the compounds of the invention have Formula Ig or IIe:

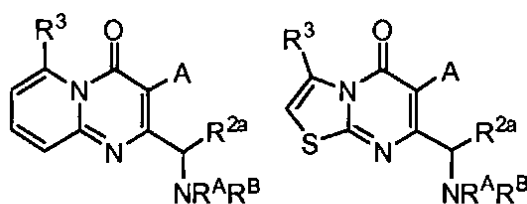


Ig

IIe.

In some embodiments of compounds of Formulas Ig and IIe, R^1 is according to any of the previously recited embodiments for R^1 .

In some embodiments, the compounds of the invention have Formula Ih or IIf:

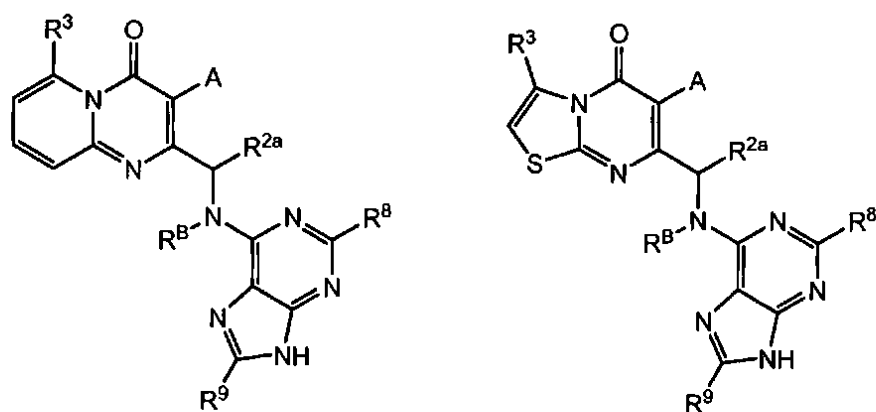


Ih

IIf.

In some embodiments, of compounds of Formulas Ih and IIf, R^A is according to any of the previously recited embodiments for R^A .

In some embodiments, the compounds of the invention have Formula II or IIg:



II

IIg.

wherein R^8 and R^9 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$,

$\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$.

In some embodiments, R^8 and R^9 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, and $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$.

In some embodiments, R^8 and R^9 are independently selected from H and C_{1-6} alkyl.

In some embodiments of compounds of Formulas Ig-Ii and Ile-IIg, A is according to any of the previously recited embodiments for A.

In some embodiments of compounds of Formulas Ig-Ii and Ile-IIg, R^3 is according to any of the previously recited embodiments for R^3 .

In some embodiments of compounds of Formulas Ig-Ii and Ile-IIg, R^{2a} is according to any of the previously recited embodiments for R^{2a} .

In some embodiments of compounds of Formulas Ig-Ii and Ile-IIg, R^B is according to any of the previously recited embodiments for R^B .

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

At various places in the present specification, linking substituents are described. It is specifically intended that each linking substituent include both the forward and backward forms of the linking substituent. For example, $-\text{NR}(\text{CR}'\text{R}'')_n-$ includes both $-\text{NR}(\text{CR}'\text{R}'')_n-$ and $-(\text{CR}'\text{R}'')_n\text{NR}-$. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-

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membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

As used herein, the term "alkyl" is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. Example alkyl groups include methyl (Me), ethyl (Et), propyl (e.g., n-propyl and isopropyl), butyl (e.g., n-butyl, isobutyl, sec-butyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, sec-pentyl, neopentyl), and the like. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms.

As used herein, "alkenyl" refers to an alkyl group having one or more carbon-carbon double bonds. Example alkenyl groups include ethenyl, propenyl, cyclohexenyl, and the like.

As used herein, "alkynyl" refers to an alkyl group having one or more carbon-carbon triple bonds. Example alkynyl groups include ethynyl, propynyl, and the like.

As used herein, "haloalkyl" refers to an alkyl group having one or more halogen substituents. Example haloalkyl groups include CF₃, C₂F₅, CHF₂, CCl₃, CHCl₂, C₂Cl₅, and the like.

As used herein, "halosulfanyl" refers to a sulfur group having one or more halogen substituents. Example halosulfanyl groups include pentahalosulfanyl groups such as SF₅.

As used herein, "aryl" refers to monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms.

As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl, alkenyl, and alkynyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) groups and spirocycles. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido. Cycloalkyl groups also include cycloalkylidenes. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norbornyl, adamantyl, and the like. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclopentene, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can

be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring.

As used herein, "heteroaryl" refers to an aromatic heterocycle having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (*e.g.*, having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrol, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. Examples of bicyclic heteroaryl groups include without limitation, purinyl, indolyl, and the like. In some embodiments, any ring-forming N in a heteroaryl moiety can be substituted by oxo. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 4 to about 14, 9 to about 10, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, "heterocycloalkyl" refers to non-aromatic heterocycles having one or more ring-forming heteroatoms such as an O, N, or S atom. Heterocycloalkyl groups include monocyclic and polycyclic (*e.g.*, having 2, 3 or 4 fused rings) systems as well as spirocycles. Example "heterocycloalkyl" groups include morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxole, benzo-1,4-dioxane, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, and the like. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the nonaromatic heterocyclic ring, for example phthalimidyl, naphthalimidyl, and benzo derivatives of heterocycles. The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. The heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20



carbon atoms. In some embodiments, the heterocycloalkyl group contains 3 to about 14, 4 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. In some embodiments, the heterocycloalkyl group contains 0 to 3 double or triple bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double or triple bonds.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

As used herein, "arylalkyl" refers to alkyl substituted by aryl and "cycloalkylalkyl" refers to alkyl substituted by cycloalkyl. An example arylalkyl group is benzyl.

As used herein, "heteroarylalkyl" refers to alkyl substituted by heteroaryl and "heterocycloalkylalkyl" refers to alkyl substituted by heterocycloalkyl.

As used herein, "amino" refers to NH_2 .

As used herein, "alkoxy" refers to an -O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), t-butoxy, and the like.

As used herein, "haloalkoxy" refers to an -O-(haloalkyl) group.

As used herein, "alkylthio" refers to an -S-alkyl group. Example alkylthio groups include meththio, ethylthio, propylthio (e.g., n-propylthio and isopropylthio), and the like.

As used herein, "alkylamino" refers to an -NH-alkyl group. Example alkylamino groups include methylamino, ethylamino, propylamino (e.g., n-propylamino and isopropylamino), and the like.

As used herein, "di(alkyl)amino" refers to an -N(alkyl)₂ group. Example di(alkyl)amino groups include dimethylamino, diethylamino, dipropylamino (e.g., di(n-propyl)amino and di(isopropyl)amino), and the like.

It should be further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare

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optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β -camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α -methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

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The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g. hydrates and solvates) or can be isolated.

5 In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 10 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound 15 medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, e.g. a reaction temperature, that is 20 about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or 25 base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of 30 the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by

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reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's*
5 *Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

Synthesis

10 Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable
15 solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step
20 can be selected by the skilled artisan.

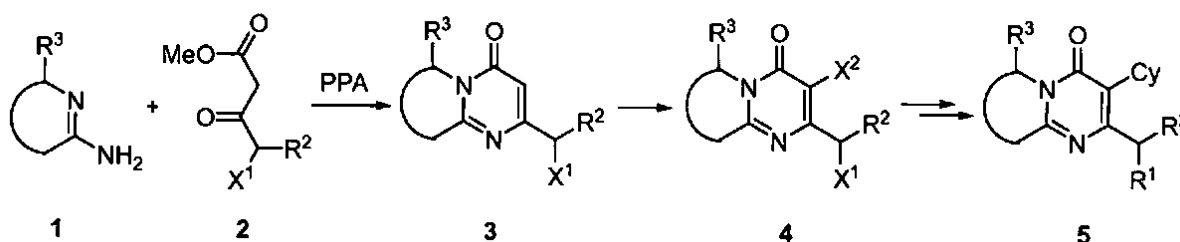
Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective*
25 *Groups in Organic Synthesis*, 3rd Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ¹H or ¹³C), infrared spectroscopy, spectrophotometry (e.g., UV-
30 visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

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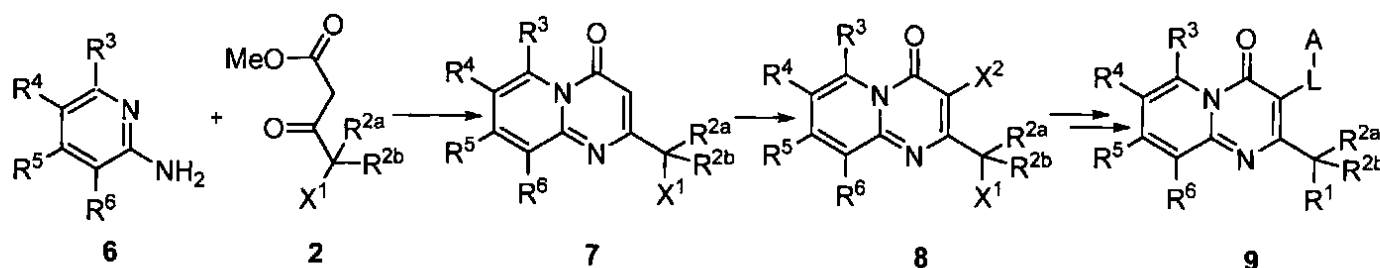
Example synthetic methods for preparing compounds of the invention are provided in the Schemes below. For instance, compounds of the invention can be prepared by the general synthetic procedure shown in Scheme 1. Heteroaryl compounds of formula 1 can react with 4-halo-3-oxo-pentanoates 2 in the presence of polyphosphoric acid (PPA) to provide the compounds of formula 3 via a cyclocondensation reaction. These can be subjected to halogenation reaction under suitable conditions, to provide halogenated compounds 4. Compounds of formula 4 can be transformed to the compounds of formula 5 through any variation of a sequence of steps. X^1 can be replaced with either an azide, an amine, or a heterocyclic group through an S_N2 displacement and eventually transformed to the R^1 group. X^2 can be converted to a desired cyclic moiety (Cy) through any of the standard cross-coupling reactions, known to one skilled in the art, e.g., using boronic acid derivatives of the desired cyclic moiety.

Scheme 1



As shown in Scheme 2, the pyrido[1,2-a]pyrimidin-4-ones of the invention can be prepared by cyclocondensation of aminopyrimidines 6 with a β -keto ester 2. Halogenation of the resultant pyridopyrimidinones 7 under suitable conditions (such as NBS or bromine) provides compounds of formula 8. The latter can be transformed to the compounds of formula 9 through an S_N2 substitution of X^1 with a heterocycle R^1 followed by a coupling reaction of X^2 with L-A moiety (such as a Negishi coupling of organozinc reagent; a Suzuki or Stille coupling of an arylboronic acid or arylstanne, respectively). Alternatively, X^1 can be replaced with either an amine or an azide which can be reduced to amine. The amine can then be subjected to coupling reaction with a R^1 moiety to give compounds of formula 9.

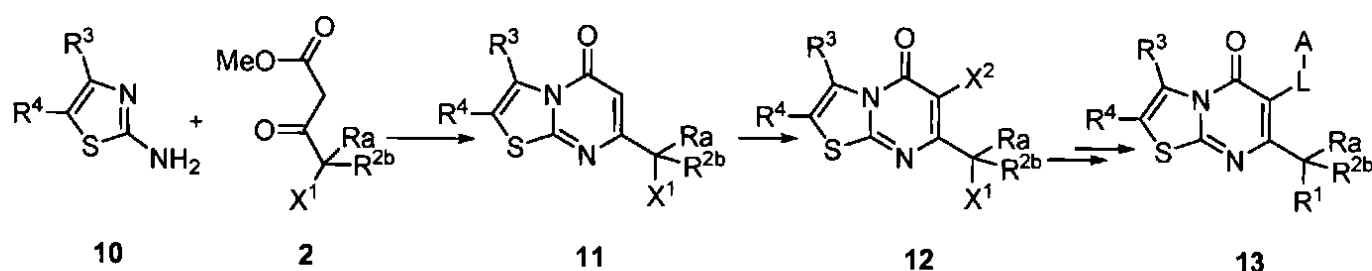
Scheme 2



The thiazolo[3,2-a]pyrimidin-5-ones of the invention can be prepared according to

- 5 Scheme 3. 2-Aminothiazole 10 condensed with a β -keto ester 2 provides thiazolopyrimidinone 11. Compounds of formula 11 can be converted to compounds of formula 13 through any variations of a sequence of steps as described above.

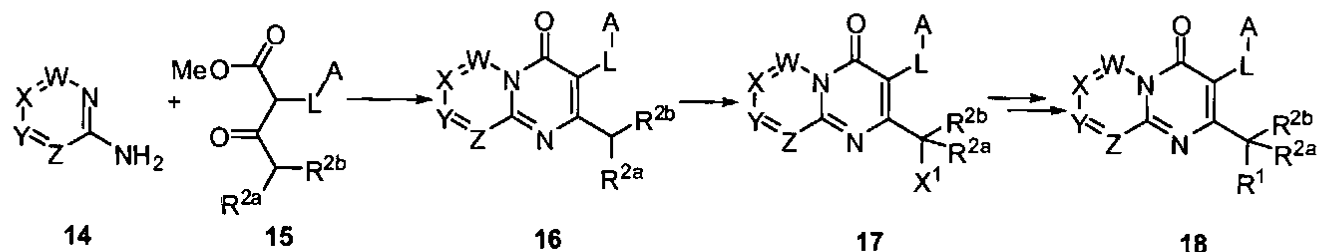
Scheme 3



Alternatively, compounds of the invention can be synthesized by reacting amino heterocycles 14 with an α -substituted β -keto ester 15 shown in Scheme 4. The cyclocondensation derivatives 16 can then be subjected to halogenation (such as NBS or bromine) or oxidation (such as SeO_2) to afford halogen compounds 17 ($X^1 = \text{halogen}$), or alcohol compounds 17 ($X = \text{OH}$), respectively. Compounds of formula 17 can then be transformed to compounds of formula 18 through any variations of a sequence of steps. X^1 can be coupled directly with a heterocycles under any of the cross coupling conditions know to one skilled in the art (such as Buchwald-Hartwig cross coupling conditions) or converted to a halogen then the latter can be coupled with a heterocycles through $\text{S}_\text{N}2$ substitutions.

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Scheme 4



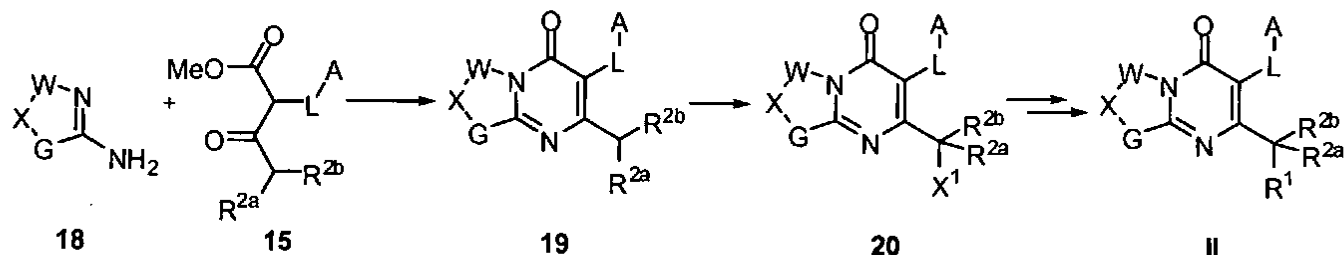
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Compounds of Formula II of the invention can be prepared according to Scheme 5.

Amino heterocycles 19 condensed with α-substituted β-ketone ester 15 affords compounds of formula 20. The latter can be transformed to compounds of Formula II through any variation of steps described above.

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Scheme 5



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It should be noted that in all of the Schemes described herein, if there are functional groups present on a substituent group, further modification can be made if appropriate and desired. For example, a CN group can be hydrolyzed to afford an amide group; a carboxylic acid can be converted to an ester, which in turn can be reduced to an alcohol, which in turn can be further modified. In another example, an OH group can be converted into a better leaving group such as mesylate, which in turn is suitable for nucleophilic substitution, such as by CN. Furthermore, an OH group can be subjected to Mitsunobu reaction conditions with phenol, or heteroaryl alcohol, to afford aryl or heteroaryl ether compounds. One skilled in the art will recognize further modifications.

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It should be further noted that the reaction sequences described above can be modified to suit different target molecules. For instance, Cy-boronic acid can be reacted with 4 to generate the Suzuki product first. The X¹ group of the Suzuki product can then be further functionalized with a nucleophilic reagent such as an azide or a heterocyclic amine.

5

Methods

The compounds of the invention can modulate activity of one or more of various kinases including, for example, phosphoinositide 3-kinases (PI3Ks). The term "modulate" is meant to refer to an ability to increase or decrease the activity of one or more members of the PI3K family. Accordingly, the compounds of the invention can be used in methods of modulating a PI3K by contacting the PI3K with any one or more of the compounds or compositions described herein. In some embodiments, compounds of the present invention can act as inhibitors of one or more PI3Ks. In further embodiments, the compounds of the invention can be used to modulate activity of a PI3K in an individual in need of modulation of the receptor by administering a modulating amount of a compound of the invention, or a pharmaceutically acceptable salt thereof. In some embodiments, modulating is inhibiting.

Given that cancer cell growth and survival is impacted by multiple signaling pathways, the present invention is useful for treating disease states characterized by drug resistant kinase mutants. In addition, different kinase inhibitors, exhibiting different preferences in the kinases which they modulate the activities of, may be used in combination. This approach could prove highly efficient in treating disease states by targeting multiple signaling pathways, reduce the likelihood of drug-resistance arising in a cell, and reduce the toxicity of treatments for disease.

Kinases to which the present compounds bind and/or modulate (e.g., inhibit) include any member of the PI3K family. In some embodiments, the PI3K is PI3K α , PI3K β , PI3K γ , or PI3K δ . In some embodiments, the PI3K is PI3K γ or PI3K δ . In some embodiments, the PI3K is PI3K γ . In some embodiments, the PI3K is PI3K δ . In some embodiments, the PI3K includes a mutation. A mutation can be a replacement of one amino acid for another, or a deletion of one or more amino acids. In such embodiments, the mutation can be present in the kinase domain of the PI3K.

In some embodiments, more than one compound of the invention is used to inhibit the activity of one kinase (e.g., PI3K γ or PI3K δ).

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In some embodiments, more than one compound of the invention is used to inhibit more than one kinase, such as at least two kinases (e.g., PI3K γ and PI3K δ).

In some embodiments, one or more of the compounds is used in combination with another kinase inhibitor to inhibit the activity of one kinase (e.g., PI3K γ or PI3K δ).

5 In some embodiments, one or more of the compounds is used in combination with another kinase inhibitor to inhibit the activities of more than one kinase (e.g., PI3K γ or PI3K δ), such as at least two kinases..

The compounds of the invention can be selective. By "selective" is meant that the compound binds to or inhibits a kinase with greater affinity or potency, respectively, compared
10 to at least one other kinase. In some embodiments, the compounds of the invention are selective inhibitors of PI3K γ or PI3K δ over PI3K α and/or PI3K β . In some embodiments, the compounds of the invention are selective inhibitors of PI3K δ (e.g., over PI3K α , PI3K β and PI3K γ). In some
embodiments, the compounds of the invention are selective inhibitors of PI3K γ (e.g., over
PI3K α , PI3K β and PI3K δ). In some embodiments, selectivity can be at least about 2-fold, 5-
15 fold, 10-fold, at least about 20-fold, at least about 50-fold, at least about 100-fold, at least about 200-fold, at least about 500-fold or at least about 1000-fold. Selectivity can be measured by methods routine in the art. In some embodiments, selectivity can be tested at the K_m ATP concentration of each enzyme. In some embodiments, the selectivity of compounds of the invention can be determined by cellular assays associated with particular PI3K kinase activity.

20 Another aspect of the present invention pertains to methods of treating a kinase (such as PI3K)-associated disease or disorder in an individual (e.g., patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of one or more compounds of the present invention or a pharmaceutical composition thereof. A PI3K-
associated disease can include any disease, disorder or condition that is directly or indirectly
25 linked to expression or activity of the PI3K, including overexpression and/or abnormal activity levels. In some embodiments, the disease can be linked to Akt (protein kinase B), mammalian target of rapamycin (mTOR), or phosphoinositide-dependent kinase 1 (PDK1). In some
embodiments, the mTOR-related disease can be inflammation, atherosclerosis, psoriasis, restenosis, benign prostatic hypertrophy, bone disorders, pancreatitis, angiogenesis, diabetic
30 retinopathy, atherosclerosis, arthritis, immunological disorders, kidney disease, or cancer. A PI3K-associated disease can also include any disease, disorder or condition that can be

prevented, ameliorated, or cured by modulating PI3K activity. In some embodiments, the disease is characterized by the abnormal activity of PI3K. In some embodiments, the disease is characterized by mutant PI3K. In such embodiments, the mutation can be present in the kinase domain of the PI3K.

5 Examples of PI3K-associated diseases include immune-based diseases involving the system including, for example, rheumatoid arthritis, allergy, asthma, glomerulonephritis, lupus, or inflammation related to any of the above.

 Further examples of PI3K-associated diseases include cancers such as breast, prostate, colon, endometrial, brain, bladder, skin, uterus, ovary, lung, pancreatic, renal, gastric, or
10 hematological cancer.

 In some embodiments, the hematological cancer is acute myeloblastic leukemia (AML) or chronic myeloid leukemia (CML), or B cell lymphoma.

 Further examples of PI3K-associated diseases include lung diseases such as acute lung injury (ALI) and adult respiratory distress syndrome (ARDS).

15 Further examples of PI3K-associated diseases include osteoarthritis, restenosis, atherosclerosis, bone disorders, arthritis, diabetic retinopathy, psoriasis, benign prostatic hypertrophy, atherosclerosis, inflammation, angiogenesis, pancreatitis, kidney disease, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, or Sjogren's syndrome, and the like.

20 As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a PI3K with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having a PI3K, as well as, for example, introducing a
● compound of the invention into a sample containing a cellular or purified preparation containing
25 the PI3K.

 As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

 As used herein, the phrase "therapeutically effective amount" refers to the amount of
30 active compound or pharmaceutical agent that elicits the biological or medicinal response that is

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being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treating" or "treatment" refers to one or more of (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

Combination Therapies

One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, as well as Bcr-Abl, Flt-3, EGFR, HER2, JAK, c-MET, VEGFR, PDGFR, cKit, IGF-1R, RAF and FAK kinase inhibitors such as, for example, those described in WO 2006/056399, or other agents such as, therapeutic antibodies can be used in combination with the compounds of the present invention for treatment of PI3K-associated diseases, disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

Example antibodies for use in combination therapy include but are not limited to Trastuzumab (e.g. anti-HER2), Ranibizumab (e.g. anti-VEGF-A), Bevacizumab (trade name Avastin, e.g. anti-VEGF), Panitumumab (e.g. anti-EGFR), Cetuximab (e.g. anti-EGFR), Rituxan (anti-CD20) and antibodies directed to c-MET.

One or more of the following agents may be used in combination with the compounds of the present invention and are presented as a non limiting list: a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec™, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide,

- Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin,
- 5 Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycorformycin, Mitomycin-C, L-Asparaginase, Teniposide 17.alpha.-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate,
- 10 Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrozole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Fulvestrant,
- 15 Ifosfomide, Rituximab, C225, Campath, Clofarabine, cladribine, aphidicolon, rituxan, sunitinib, dasatinib, tezacitabine, Sml1, fludarabine, pentostatin, triapine, didox, trimidox, amidox, 3-AP, and MDL-101,731.

Example chemotherapeutics include proteasome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin,

20 cyclophosphamide, vincristine, etoposide, carmustine, and the like.

Example steroids include corticosteroids such as dexamethasone or prednisone.

Example Bcr-Abl inhibitors include the compounds, and pharmaceutically acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No. 5,521,184, WO 04/005281, and U.S. Ser. No. 60/578,491.

- 25 Example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 03/037347, WO 03/099771, and WO 04/046120.

Example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444.

- 30 Example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402.

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In some embodiments, the compounds of the invention can be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients resistant to imatinib or other kinase inhibitors.

In some embodiments, the compounds of the invention can be used in combination with a
5 chemotherapeutic in the treatment of cancer, such as multiple myeloma, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without exacerbation of its toxic effects. Examples of additional pharmaceutical agents used in the treatment of multiple myeloma, for example, can include, without limitation, melphalan, melphalan plus prednisone [MP], doxorubicin, dexamethasone, and Velcade (bortezomib).

10 Further additional agents used in the treatment of multiple myeloma include Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors. Additive or synergistic effects are desirable outcomes of combining a PI3K inhibitor of the present invention with an additional agent. Furthermore, resistance of multiple myeloma cells to agents such as dexamethasone may be reversible upon treatment with the PI3K inhibitor of the present invention. The agents can be combined with the present
15 compound in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with the compounds of the invention where the dexamethasone is administered intermittently as opposed to continuously.

20 In some further embodiments, combinations of the compounds of the invention with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone marrow transplant or stem cell transplant.

Pharmaceutical Formulations and Dosage Forms

25 When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated.

Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous
30 membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or

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parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the invention or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.* about 40 mesh.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art, *e.g.*, see International App. No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium

silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1000 mg (1 g), more usually about 100 to about 500 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

In some embodiments, the compounds or compositions of the invention contain from about 5 to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 to about 10, about 10 to about 15, about 15 to about 20, about 20 to about 25, about 25 to about 30, about 30 to about 35, about 35 to about 40, about 40 to about 45, or about 45 to about 50 mg of the active ingredient.

In some embodiments, the compounds or compositions of the invention contain from about 50 to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 to about 100, about 100 to about 150, about 150 to about 200, about 200 to about 250, about 250 to about 300, about 350 to about 400, or about 450 to about 500 mg of the active ingredient.

In some embodiments, the compounds or compositions of the invention contain from about 500 to about 1000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 to about 550, about 550 to about 600, about 600 to about 650, about 650 to about 700, about 700 to about 750, about 750 to about 800, about 800 to about 850, about 850 to about 900, about 900 to about 950, or about 950 to about 1000 mg of the active ingredient.

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The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal

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respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, for example, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, e.g. glycerinmonostearate, PEG-glycerinmonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, for example, glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2, or at least about 5 wt % of the compound of the invention. The topical formulations can be suitably packaged in tubes of, for example, 100 g which are optionally associated with instructions for the treatment of the select indication, e.g., psoriasis or other skin condition.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain

of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 $\mu\text{g/kg}$ to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compositions of the invention can further include one or more additional pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or immunosuppressant, examples of which are listed hereinabove.

Labeled Compounds and Assay Methods

Another aspect of the present invention relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating PI3K in tissue samples, including human, and for identifying PI3K ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes PI3K assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present

invention include but are not limited to ^2H (also written as D for deuterium), ^3H (also written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{82}Br , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I and ^{131}I . The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro*

5 PI3K labeling and competition assays, compounds that incorporate ^3H , ^{14}C , ^{82}Br , ^{125}I , ^{131}I , ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C , ^{18}F , ^{125}I , ^{123}I , ^{124}I , ^{131}I , ^{75}Br , ^{76}Br or ^{77}Br will generally be most useful.

It is understood that a "radio-labeled" or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from

10 the group consisting of ^3H , ^{14}C , ^{125}I , ^{35}S and ^{82}Br .

The present invention can further include synthetic methods for incorporating radio-isotopes into compounds of the invention. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the compounds of invention.

15 A labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind a PI3K by monitoring its concentration variation when contacting with the PI3K, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to reduce binding of another

20 compound which is known to bind to a PI3K (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the PI3K directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the

25 standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

Kits

The present invention also includes pharmaceutical kits useful, for example, in the

30 treatment or prevention of PI3K-associated diseases or disorders, such as cancer, which include one or more containers containing a pharmaceutical composition comprising a therapeutically

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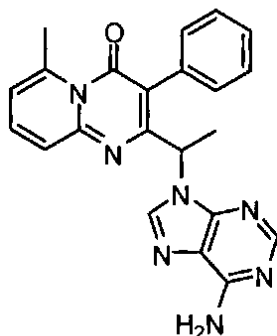
effective amount of a compound of the invention. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to be PI3K inhibitors according to at least one assay described herein.

EXAMPLES

The example compounds below containing one or more chiral centers were obtained in racemate form or as isomeric mixtures, unless otherwise specified.

Example 1. 2-[1-(6-amino-9H-purin-9-yl)ethyl]-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one



Step 1. methyl 4-chloro-3-oxopentanoate

To a solution of 3-oxopentanoic acid, methyl ester (Aldrich, 26.0 mL, 207.2 mmol) in methylene chloride (300 mL) was added in portions, N,N,N-trimethyl(phenyl) methanaminium dichloriodanuide (75.71 g, 217.5 mmol). The reaction mixture was stirred at room temperature (rt) for 2 h, then washed with saturated sodium thiosulfate, brine, dried over magnesium sulfate and concentrated. The crude product was used directly in next step (23 g, 67.4%).



Step 2. 2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a manually stirred polyphosphoric acid (30 g, 200 mmol) in a 200 mL beaker was added 6-methyl-2-pyridinamine (Aldrich, 4.7 g, 43 mmol), followed by methyl 4-chloro-3-oxopentanoate (8.584 g, 52.15 mmol). The mixture was heated with stirring at 110 °C for 5 h. After being cooled, the dark slurry was transferred on to 100 g of ice. The pH of the mixture was adjusted to 6-7 with 10% sodium hydroxide. The mixture was extracted with methylene chloride. The combined organic layers were washed with water, brine, dried over magnesium sulfate and evaporated to dryness. The residue was purified on silica gel, eluting with 0-10% methanol in methylene chloride, to yield the desired product (3.16 g, 32.7%). LCMS calculated for $C_{11}H_{12}ClN_2O(M+H)^+$: $m/z = 223.1$; Found: 223.2.

Step 3. 3-bromo-2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a stirred solution of 2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (3.16 g, 14.2 mmol) in methylene chloride (30 mL) was added drop-wise bromine (0.804 mL, 15.6 mmol) in methylene chloride (7 mL). The reaction mixture was stirred at rt for 2 h. The product precipitated out and collected by filtration (2.42 g, 56.6%). LCMS calculated for $C_{11}H_{11}BrClN_2O(M+H)^+$: $m/z = 301.0$; Found: 301.1.

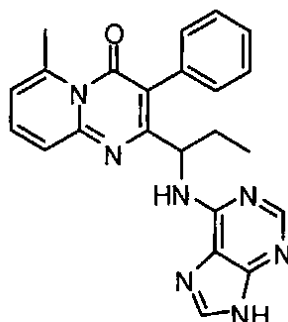
Step 4. 2-[1-(6-amino-9H-purin-9-yl)ethyl]-3-bromo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 3-bromo-2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (1.24 g, 4.11 mmol), adenine (Sigma, 1.08 g, 8.04 mmol), and potassium carbonate (1.11 g, 8.04 mmol) in *N,N*-dimethylformamide (20 mL) was stirred at rt overnight. The suspension was then poured into water and extracted with methylene chloride. The combined organic layers were washed with water, brine, and then the organic layers dried and evaporated to dryness. The residue was chromatographed on silica gel, eluting with 0 to 10% MeOH in methylene chloride, to provide the desired product (176 mg, 10.7%). LCMS calculated for $C_{16}H_{15}BrN_7O(M+H)^+$: $m/z = 400.1$; Found: 400.1. ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.44 (1H, s), 8.07 (1H, s), 7.67 (1H, dd, $J = 8.7$ and 7.2 Hz), 7.30 (1H, br d, $J = 8.7$ Hz), 7.20 (2H, s), 6.99 (1H, br d, $J = 7.2$ Hz), 6.15 (1H, q, $J = 7.2$ Hz), 2.91 (3H, s), 1.84 (3H, d, $J = 7.2$ Hz) ppm.

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Step 5. 2-[1-(6-amino-9H-purin-9-yl)ethyl]-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 2-[1-(6-amino-9H-purin-9-yl)ethyl]-3-bromo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.030 g, 0.075 mmol) and phenylboronic acid (11.0 mg, 0.0899 mmol) in 1,4-dioxane (0.6 mL) was added a 1 M solution of sodium carbonate (9.53 mg, 0.0899 mmol) in water (0.089 mL) and tetrakis(triphenylphosphine)palladium (0) (4.33 mg, 0.00375 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on RP-HPLC at pH 10 (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH₄OH) to provide the desired product. LCMS calculated for C₂₂H₂₀N₇O(M+H)⁺: m/z = 398.2; Found: 398.3. ¹H NMR (DMSO-d₆, 300 MHz) δ 8.37 (1H, s), 7.97 (1H, s), 7.56 (1H, dd, J = 8.7 and 6.6 Hz), 7.41–7.36 (5H, m), 7.26 (1H, br d, J = 9.0 Hz), 7.09 (2H, br s), 6.85 (1H, br d, J = 7.2 Hz), 5.59 (1H, q, J = 7.2 Hz), 2.80 (3H, s), 1.64 (3H, d, J = 7.2 Hz) ppm.

Example 2. 6-methyl-3-phenyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one**Step 1. methyl 4-bromo-3-oxohexanoate**

Under a nitrogen atmosphere, a solution of bromine (8.61 mL, 167 mmol) in chloroform (20 mL) was added drop-wise over a period of 2 h to a solution of methyl 3-oxohexanoate (Fluka, 24.1 g, 167 mmol) in chloroform (147 mL), at 0 °C (ice bath). The reaction mixture was stirred for 30 min at 0 °C and then allowed to warm to rt overnight. While stirring, a stream of air was bubbled through the solution for 1 h. The reaction mixture was dried over sodium sulfate and the solvent evaporated under reduced pressure to provide the desired compound.

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Step 2. 2-(1-bromopropyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a manually stirred polyphosphoric acid (80 g, 800 mmol) in a 1000 mL beaker at rt was added 6-methyl-2-pyridinamine (15 g, 140 mmol), followed by methyl 4-bromo-3-oxohexanoate (37.3 g, 167 mmol). The mixture was heated with stirring at 110 °C for 5 h. After cooling, the dark slurry was transferred into 300 g of ice. The pH of the mixture was adjust to 6-7 with 10% sodium hydroxide. The precipitate was collected by filtration under reduced pressure, washed with water, and air dried to yield the desired product (25.4 g, 64.8%). LCMS calculated for $C_{12}H_{14}BrN_2O(M+H)^+$: $m/z = 281.0$; Found: 281.2. ^1H NMR (DMSO- d_6 , 300 MHz) δ 7.66 (1H, d, $J = 9.0$ and 6.9 Hz), 7.39 (1H, d, $J = 9.0$ Hz), 6.90 (1H, d, $J = 6.9$ Hz), 6.33 (1H, s), 4.91 (1H, t, $J = 7.5$ Hz), 2.91 (3H, s), 2.15 (2H, qd, $J = 7.5$ and 7.5 Hz), 0.93 (3H, t, $J = 7.5$ Hz) ppm.

Step 3. 2-(1-bromopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 2-(1-bromopropyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (3.46 g, 12.3 mmol) and *N*-iodosuccinimide (4.15 g, 18.4 mmol) in acetonitrile (100 mL) was stirred at 80 °C, under nitrogen, overnight. After removal of acetonitrile in vacuum, the resulting solid was dissolved in methylene chloride, washed with water, saturated $Na_2S_2O_3$, saturated sodium bicarbonate, and brine; and then the organic layers dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure to provide the desired product (4.53 g, 90.4%). LCMS calculated for $C_{12}H_{13}BrIN_2O(M+H)^+$: $m/z = 406.9$; Found: 407.1.

Step 4. 2-(1-azidopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 2-(1-bromopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (4.50 g, 11.0 mmol) and sodium azide (3.59 g, 55.3 mmol) in was stirred at rt for 2 h. After diluting with ethyl acetate, the mixture was washed with water, brine, dried over sodium sulfate, and evaporated under reduced pressure to provide the crude product, which was used directly in next step (3.35 g, 82.1%). LCMS calculated for $C_{12}H_{13}IN_5O(M+H)^+$: $m/z = 370.0$; Found: 370.2.

Step 5. 2-(1-azidopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 2-(1-azidopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.11 g, 0.29 mmol) and phenylboronic acid (42.9 mg, 0.352 mmol) in 1,4-dioxane (2 mL) was

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added a 1 M solution of sodium carbonate (37.3 mg, 0.352 mmol) in water (0.35 mL) and tetrakis(triphenylphosphine)palladium (0) (16.9 mg, 0.0147 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on silica gel, eluting with 0 to 40% EtOAc in hexane, to provide the desired product (50 mg, 53.4%). LCMS calculated for C₁₈H₁₈N₅O(M+H)⁺: m/z = 320.2; Found: 320.3.

Step 6. 2-(1-aminopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

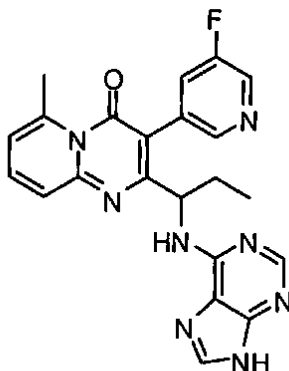
To a stirred solution of 2-(1-azidopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.030 g, 0.094 mmol) in tetrahydrofuran (0.24 mL) and water (0.06 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.11 mL) at rt and the mixture was stirred at rt for 1 h. To the mixture was added methylene chloride and the mixture was washed with brine, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The crude residue was used directly in next step. LCMS calculated for C₁₈H₂₀N₃O(M+H)⁺: m/z = 294.2; Found: 294.3.

Step 7. 6-methyl-3-phenyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 6-bromo-9H-purine (Aldrich, 0.0152 g, 0.07656 mmol), 2-(1-aminopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.019 g, 0.064 mmol), and *N,N*-diisopropylethylamine (0.0134 mL, 0.07666 mmol) in ethanol (0.5 mL) was refluxed under nitrogen overnight. The mixture was cooled and purified on RP-HPLC at pH 10 (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH₄OH) to provide the product as the free base. LCMS calculated for C₂₃H₂₂N₇O(M+H)⁺: m/z = 412.2; Found: 412.4. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.07 (2H, m), 7.60 (1H, dd, *J* = 9.0 and 6.9 Hz), 7.39–7.32 (7H, m), 7.00 (1H, m), 6.85 (1H, br d, *J* = 6.9 Hz), 5.13 (1H, m), 2.81 (3H, s), 1.72 (2H, m), 0.65 (3H, t, *J* = 7.2 Hz) ppm.

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Example 3. 3-(5-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



Step 1. 2-(1-aminopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

- 5 To a stirred solution of 2-(1-azidopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (3.10 g, 8.40 mmol) in tetrahydrofuran (20 mL) and water (6.06 mL) was added a 1.0 M solution of trimethylphosphine in tetrahydrofuran (0.1 mmol) at rt and stirred for 1 h. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride.
- 10 The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (2.58 g, 89.5%). LCMS calculated for $C_{12}H_{15}IN_3O(M+H)^+$: $m/z = 344.0$; Found: 344.2.

Step 2. 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

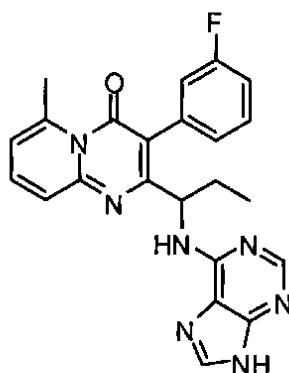
- 15 A mixture of 6-bromo-9H-purine (1.65 g, 0.008270 mol), 2-(1-aminopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (2.58 g, 0.00752 mol), and *N,N*-diisopropylethylamine (1.571 mL, 0.009022 mol) in ethanol (60 mL) was refluxed under nitrogen overnight. The mixture was concentrated and the resulting residue was purified on silica gel, eluting with 0 to 10% methanol in methylene chloride, to provide the desired product (2.86 g, 82.5%). LCMS
- 20 calculated for $C_{17}H_{17}IN_7O(M+H)^+$: $m/z = 462.1$; Found: 462.2. ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.31 (2H, m), 8.19 (1H, s), 8.15 (1H, s), 7.69 (1H, dd, $J = 8.7$ and 6.9 Hz), 7.44 (1H, d, $J = 8.7$ Hz), 6.99 (1H, d, $J = 6.9$ Hz), 5.69 (1H, m), 2.89 (3H, s), 1.91 (2H, m), 0.95 (3H, t, $J = 7.2$ Hz) ppm.

- 25 *Step 3. 3-(5-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-*

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a]pyrimidin-4-one

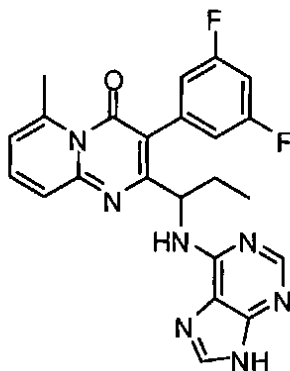
To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (0.030 g, 0.065 mmol) and (5-fluoropyridin-3-yl)boronic acid (Combi-Blocks, 11.0 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on RP-HPLC at pH 10 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH₄OH) to provide the desired product. LCMS calculated for C₂₂H₂₀FN₈O(M+H)⁺: m/z = 431.2; Found: 431.3.

Example 4. 3-(3-fluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and (3-fluorophenyl)boronic acid (Aldrich, 10.9 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on RP-HPLC at pH 10 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH₄OH) to provide the desired product. LCMS calculated for C₂₃H₂₁FN₇O(M+H)⁺: m/z = 430.2; Found: 430.3. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.11 (2H, m), 7.65 (1H, m), 7.45 (2H, m), 7.24 (4H, m), 7.08 (1H, m), 6.91 (1H, m), 5.17 (1H, m), 2.87

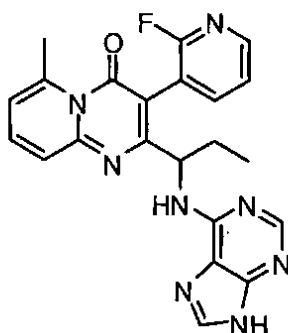
(3H, s), 1.79 (2H, m), 0.72 ((3H, t, $J = 7.2$ Hz) ppm. ^{19}F NMR (DMSO- d_6 , 282 MHz) δ -114 ppm.

Example 5. 3-(3,5-difluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

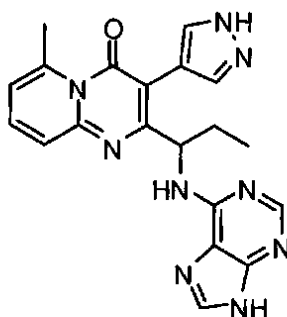


To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and (3,5-difluorophenyl)boronic acid (Aldrich, 12.3 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO_4 , and concentrated. The residue was purified on RP-HPLC at pH 10 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to provide the desired product. LCMS calculated for $\text{C}_{23}\text{H}_{20}\text{F}_2\text{N}_7\text{O}(\text{M}+\text{H})^+$: $m/z = 448.2$; Found: 448.3. ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.06 (2H, m), 7.61 (1H, m), 7.38 (1H, m), 7.14 (5H, m), 6.88 (1H, m), 5.08 (1H, m), 2.83 (3H, s), 1.75 (2H, m), 0.70 ((3H, t, $J = 7.8$ Hz) ppm. ^{19}F NMR (DMSO- d_6 , 282 MHz) δ -111 ppm.

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Example 6. 3-(2-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and (2-fluoropyridin-3-yl)boronic acid (Alfa Aesar, 11.0 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on RP-HPLC at pH 2 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to provide the desired product as a TFA salt. LCMS calculated for free base C₂₂H₂₀FN₈O(M+H)⁺: m/z = 431.2; Found: 431.3.

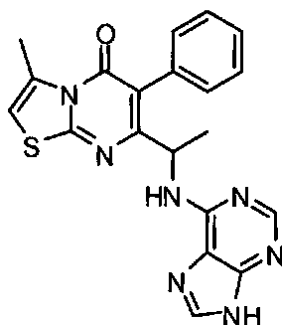
Example 7. 6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-3-(1H-pyrazol-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (Aldrich, 15.1 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and

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tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on RP-HPLC at pH 2 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to provide the desired product as a TFA salt. LCMS calculated for free base C₂₀H₂₀N₉O(M+H)⁺: m/z = 402.2; Found: 402.1.

Example 8. 3-methyl-6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



Step 1. methyl 4-bromo-3-oxopentanoate

Under a nitrogen atmosphere, a solution of bromine (8.61 mL, 167 mmol) in chloroform (20 mL, 200 mmol) was added dropwise over a period of 2 h to a solution of 3-oxopentanoic acid, methyl ester (Aldrich, 21.0 mL, 167 mmol) in chloroform (147 mL, 1840 mmol), at 0 °C (ice bath). The reaction mixture was stirred for 30 min at 0 °C and then allowed to stand at rt overnight. While stirring, a stream of air was bubbled through the solution for 1 h. After drying over sodium sulfate, the solvent was evaporated under reduced pressure leaving the desired compound.

Step 2. 7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a manually stirred polyphosphoric acid (80 g, 800 mmol) in a 1000 mL beaker was added 4-methyl-1,3-thiazol-2-amine (Aldrich, 16 g, 140 mmol), followed by methyl 4-bromo-3-oxopentanoate (34.9 g, 167 mmol). The mixture was heated with stirring at 110 °C for 5 h. After cooling, the dark slurry was transferred into 300 g of ice. The pH of the mixture was adjust to 6-7 with 10% sodium hydroxide. The aqueous layer was discarded and the dark oil layer was diluted with methylene chloride and washed with 1 N NaOH, brine, dried over

magnesium sulfate, and evaporated to dryness to yield the desired product (16.2 g, 42.6%).

LCMS calculated for $C_9H_{10}BrN_2OS(M+H)^+$: $m/z = 273.0$; Found: 273.1.

Step 2. 6-bromo-7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

- 5 A mixture of 7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (16.2 g, 59.3 mmol) and *N*-bromosuccinimide (15.8 g, 89.0 mmol) in acetonitrile (500 mL) was stirred at 80 °C, under nitrogen, overnight. After removal of acetonitrile in vacuum, the resulting solid was dissolved in methylene chloride, washed with water, saturated $Na_2S_2O_3$, saturated sodium bicarbonate, and brine; and then the organic layers dried over sodium sulfate and filtered. The
10 filtrate was concentrated under reduced pressure to provide the desired product (19.5 g, 93.4%). LCMS calculated for $C_9H_9Br_2N_2OS(M+H)^+$: $m/z = 350.9$; Found: 351.0.

Step 3. 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

- 15 A mixture of 6-bromo-7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (11.1 g, 31.5 mmol) and sodium azide (6.15 g, 94.6 mmol) in dimethyl formamide (DMF) (100 mL) was stirred at rt for 2 h. After diluting with EtOAc, the mixture was washed with water, brine, dried over sodium sulfate, and evaporated under reduced pressure. The crude residue was purified on silica gel, eluting with 0 to 80% EtOAc in hexane, to provide the product (8.68 g, 87.6%). LCMS calculated for $C_9H_9BrN_3OS(M+H)^+$: $m/z = 314.0$; Found: 313.9. ^1H
20 NMR (DMSO- d_6 , 300 MHz) δ 7.15 (1H, s), 4.83 (1H, q, $J = 6.6$ Hz), 2.69 (3H, s), 1.48 (3H, d, $J = 6.6$ Hz) ppm.

Step 4. 7-(1-azidoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

- 25 To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.100 g, 0.318 mmol) and phenylboronic acid (46.6 mg, 0.382 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (40.5 mg, 0.382 mmol) in water (0.38 mL) and tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0159 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel,
30 eluting with 0 to 50% EtOAc in hexane, to provide the desired product (44 mg, 44.4%). LCMS calculated for $C_{15}H_{14}N_5OS(M+H)^+$: $m/z = 312.1$; Found: 312.3.



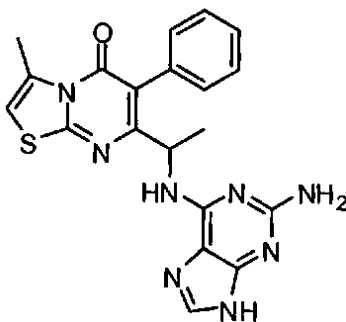
Step 5. 7-(1-aminoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a stirred solution of 7-(1-azidoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.044 g, 0.14 mmol) in tetrahydrofuran (0.4 mL) and water (0.102 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.17 mL) at rt and the mixture was stirred at rt for 1 h. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (36 mg, 89.3%). LCMS calculated for $C_{15}H_{16}N_3OS(M+H)^+$: $m/z = 286.1$; Found: 286.0.

Step 6. 3-methyl-6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

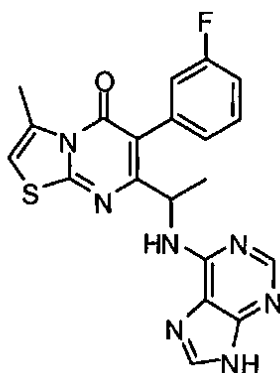
A mixture of 6-bromo-9H-purine (0.01504 g, 0.0076 mmol), 7-(1-aminoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.018 g, 0.063 mmol), and *N,N*-diisopropylethylamine (0.013 mL, 0.0076 mol) in ethanol (0.5 mL) was refluxed under nitrogen overnight. The mixture was concentrated under reduced pressure and the residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for free base $C_{20}H_{18}N_7OS(M+H)^+$: $m/z = 404.1$; Found: 404.3. ^1H NMR (DMSO- d_6 , 300 MHz) for a TFA salt: δ 8.54 (2H, m), 8.41 (2H, m), 7.44–7.36 (5H, m), 7.08 (1H, d, $J = 1.2$ Hz), 5.21 (1H, m), 2.64 (3H, s), 1.38 (3H, d, $J = 6.6$ Hz) ppm.

Example 9. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



A mixture of 2-amino-6-bromopurine (Aldrich, 0.01618 g, 0.007558 mmol), 7-(1-aminoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 8, step 5; 0.018 g, 0.063 mmol), and *N,N*-diisopropylethylamine (0.01318 mL, 0.007569 mmol) in ethanol (0.5 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resulting residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{19}N_8OS(M+H)^+$: $m/z = 419.1$; Found: 419.3. ^1H NMR (DMSO- d_6 , 300 MHz) for TFA salt: δ 8.74 (1H, m), 8.16 (1H, s), 7.46–7.33 (6H, m), 7.14–7.11 (3H, m), 5.20 (1H, m), 2.66 (3H, d, $J = 1.5$ Hz), 1.32 (3H, d, $J = 6.6$ Hz) ppm.

Example 10. 6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



Step 1. 7-(1-azidoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 8, step 3; 0.100 g, 0.318 mmol) and (3-fluorophenyl)boronic acid (53.4 mg, 0.382 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (40.5 mg, 0.382 mmol) in water (0.38 mL) and tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0159 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel, eluting with 0 to 50% EtOAc in hexane, to provide the desired product (35 mg, 33.4%). LCMS calculated for $C_{15}H_{13}FN_5OS(M+H)^+$: $m/z = 330.1$; Found: 330.2.

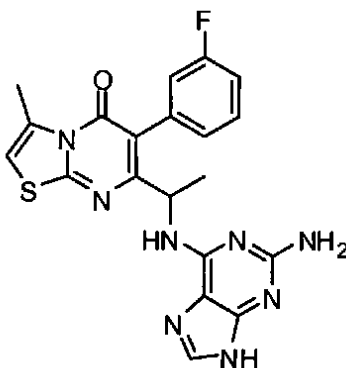
Step 2. 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a stirred solution of 7-(1-azidoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.037 g, 0.11 mmol) in tetrahydrofuran (0.3 mL) and water (0.0811 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.13 mmol) at rt and stirred for 1 h. To the mixture was added EtOAc and was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (31 mg, 90.9%). LCMS calculated for $C_{15}H_{15}FN_3OS(M+H)^+$: $m/z = 304.1$; Found: 304.3.

Step 3. 6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-9H-purine (0.01258 g, 0.006320 mmol), 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.016 g, 0.053 mmol), and *N,N*-diisopropylethylamine (0.011 mL, 0.006329 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resulting residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{17}FN_7OS(M+H)^+$: $m/z = 422.1$; Found: 422.3. ^1H NMR (DMSO- d_6 , 300 MHz) for TFA salt: δ 8.55 (2H, m), 8.40 (2H, m), 7.48 (1H, m), 7.25–7.22 (3H, m), 7.09 (1H, s), 5.19 (1H, m), 2.64 (3H, d, $J = 0.9$ Hz), 1.40 (3H, d, $J = 6.6$ Hz) ppm. ^{19}F NMR (DMSO- d_6 , 282 MHz) for TFA salt: δ -74.2, -114.0 ppm.

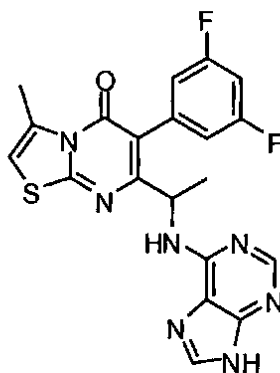
Example 11. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



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A mixture of 2-amino-6-bromopurine (0.01353 g, 0.006320 mmol), 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 10, step 2; 0.016 g, 0.053 mmol), and *N,N*-diisopropylethylamine (0.01102 mL, 0.006329 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resultant residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{18}FN_8OS(M+H)^+$: $m/z = 437.1$; Found: 437.3. ^1H NMR (DMSO- d_6 , 300 MHz) for TFA salt: δ 8.74 (1H, m), 8.16 (1H, s), 7.46 (1H, m), 7.20–7.13 (7H, m), 5.18 (1H, m), 2.66 (3H, s), 1.33 (3H, d, $J = 6.9$ Hz) ppm. ^{19}F NMR (DMSO- d_6 , 282 MHz) for TFA salt: δ -74.0, -114.0 ppm.

Example 12. 6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



Step 1. 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.10 g, 0.318 mmol) and (3,5-difluorophenyl)boronic acid (60.3 mg, 0.382 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (40.5 mg, 0.382 mmol) in water (0.38 mL) and tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0159 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel, eluting with 0 to 40% EtOAc in hexane, to provide the desired product (42 mg, 38.0%). LCMS calculated for $C_{15}H_{12}F_2N_5OS(M+H)^+$: $m/z = 348.1$; Found: 348.2.

Step 2. 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-

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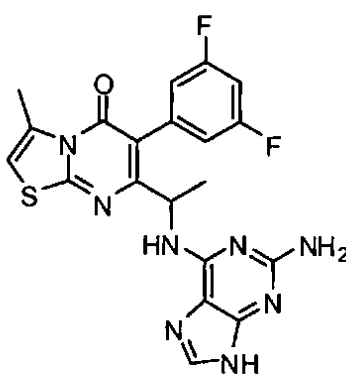
one

To a stirred solution of 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.042 g, 0.12 mmol) in tetrahydrofuran (0.3 mL) and water (0.0873 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.14 mmol) at rt and stirred for 1 h. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate, and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (36 mg, 92.7%). LCMS calculated for $C_{15}H_{14}F_2N_3OS(M+H)^+$: $m/z = 322.1$; Found: 322.3.

Step 3. 6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-9H-purine (0.01258 g, 0.006320 mmol), 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.017 g, 0.053 mmol), and *N,N*-diisopropylethylamine (0.011 mL, 0.006329 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was concentrated under reduced pressure and the resultant residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{16}F_2N_7OS(M+H)^+$: $m/z = 440.1$; Found: 440.3. ^1H NMR (DMSO- d_6 , 300 MHz) for TFA salt: δ 8.55 (1H, m), 8.39 (2H, m), 7.29 (1H, m), 7.15–7.11 (3H, m), 5.17 (1H, m), 2.64 (3H, d, $J = 1.2$ Hz), 1.42 (3H, d, $J = 6.9$ Hz) ppm.

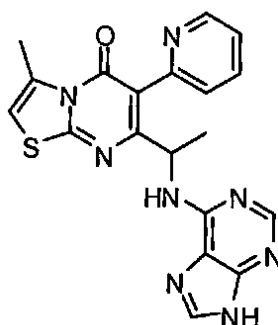
Example 13. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



B

A mixture of 2-amino-6-bromopurine (0.01436 g, 0.006712 mmol), 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 12, step 2; 0.018 g, 0.056 mmol), and *N,N*-diisopropylethylamine (0.01171 mL, 0.006722 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resultant residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{17}F_2N_8OS(M+H)^+$: $m/z = 455.1$; Found: 455.3. ^1H NMR (DMSO- d_6 , 300 MHz) for TFA salt: δ 8.74 (1H, m), 8.16 (1H, s), 7.26–7.06 (6H, m), 5.16 (1H, m), 2.66 (3H, d, $J = 1.2$ Hz), 1.36 (3H, d, $J = 6.9$ Hz) ppm.

Example 14. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



Step 1. 7-(1-azidoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 2-(tributylstannyl)pyridine (Aldrich, 0.176 g, 0.382 mmol), 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 8, step 3; 0.10 g, 0.318 mmol), and tetrakis(triphenylphosphine)palladium (0) (0.0184 g, 0.0159 mmol) in 1,4-dioxane (0.5 mL) was heated at 65 °C overnight. After being cooled and quenched with saturated ammonium chloride, the resulting mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried and evaporated to dryness. The residue was purified on silica gel, eluting with 0 to 100% EtOAc in hexane, to provide the desired product (13 mg, 13%). LCMS calculated for $C_{14}H_{13}N_6OS(M+H)^+$: $m/z = 313.1$; Found: 313.0.

Step 2. 7-(1-aminoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a stirred solution of 7-(1-azidoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.012 g, 0.039 mmol) in tetrahydrofuran (0.1 mL) and water (0.0285 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.047 mmol) at rt and stirred for 1 h.

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To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step. LCMS

5 calculated for $C_{14}H_{15}N_4OS(M+H)^+$: $m/z = 287.1$; Found: 287.0.

Step 3. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-9H-purine (9.300 mg, 0.004673 mmol), 7-(1-aminoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (11 mg, 0.039 mmol), and *N,N*-diisopropylethylamine (8.152 μ L, 0.004680 mmol) in ethanol (0.3 mL) was refluxed under nitrogen overnight. The mixture was concentrated under reduced pressure and the residue was purified on RP-HPLC (eluting with a gradient of methanol/water containing 1% TFA) to provide the product as a TFA salt. LCMS calculated for $C_{19}H_{17}N_8OS(M+H)^+$: $m/z = 405.1$; Found:

10
15 405.3.

Example A: PI3K Enzyme Assay

Materials: [γ - ^{33}P]ATP (10 mCi/mL) was purchased from Perkin-Elmer (Waltham, MA). Lipid kinase substrate, consisting of 1:19 molar ratio of phosphoinositol-4,5-bisphosphate (PIP2) with phosphoserine (PS), was purchased from Invitrogen (Carlsbad, CA). PI3K isoforms α , β , δ and γ were purchased from Millipore (Bedford, MA). ATP, NaCl, $MgCl_2$, DTT, EDTA and CHAPS were purchased from Sigma-Aldrich (St. Louis, MO). HEPES 1 M, pH 7.0 stock buffer was purchased from Thermo Fisher Scientific (Pittsburgh, PA).

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The kinase reaction was conducted in clear-bottom 96-well plate from Thermo Fisher Scientific in a final volume of 40 μ L. Inhibitors were first diluted serially in DMSO and added to the plate wells before the addition of other reaction components. The final concentration of DMSO in the assay was 2.5%. The PI3K assays were carried out at room temperature in 50 mM HEPES, pH 7.4, 5 mM $MgCl_2$, NaCl 50mM, 5 mM DTT and CHAPS 0.03%. The reaction mixture was prepared containing 20 μ M PIP2:PS, kinase and varying concentration of inhibitors.

25
30 Reactions were initiated by the addition of ATP containing 0.6 μ Ci [γ - ^{33}P]ATP to a final concentration of 200 μ M. The final concentration of PI3K isoforms α , β , δ and γ in the assay

20

were 0.34, 2.0, 0.76 and 13.7 nM respectively. Reactions were incubated for 60 min and terminated by the addition of 170 μ L of 1 M potassium phosphate pH 8.0, 30 mM EDTA quench buffer. A 180 μ L aliquot of the reaction solution was then transferred to 96-well Millipore MultiScreen IP 0.45 μ m PVDF filter plate (The filter plate was prewetted with 200 μ L 100% ethanol, distilled water, and 1 M potassium phosphate pH 8.0, respectively). The filter plate was aspirated on Millipore Manifold under vacuum and washed with 10 $\times$ 200 μ L wash buffer containing 1 M potassium phosphate pH 8.0 and 1 mM ATP. After drying by aspiration and blotting, the plate was air dried in an incubator at 37 $^{\circ}$ C overnight. Packard TopCount adapter (Millipore) was then attached to the plate followed with addition of 120 μ L Microscint 20 scintillation cocktail (Perkin Elmer) in each well. After the plate sealing, the radioactivity of the product was determined by scintillation counting on Topcount (Perkin-Elmer). IC₅₀ determination was performed by fitting the curve of percent control activity versus the log of the inhibitor concentration using the GraphPad Prism 3.0 software. Compounds having and IC₅₀ value of 10 μ M or less are considered active. See Table 1 for data related to compounds of the invention.

Table 1. IC₅₀ data for PI3K δ enzyme assay*

Example	PI3K δ IC ₅₀ (nM)	PI3K α IC ₅₀ (nM)	PI3K β IC ₅₀ (nM)	PI3K γ IC ₅₀ (nM)
1	+++			
2	++			
3	+++			
4	+++			
5	+++			
6	+++			
7	+++			
8	++			
9	+	++++	++++	++
10	+	++++	++++	++++
11	+	++++	++++	+++
12	+			
13	+	++++	++++	+++
14				

* “+” = <50 nM; “++” = 50-100 nM; “+++” = 100-500 nM; “++++” = >500 nM.

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Example B: B cell proliferation assay

To acquire B cells, human PBMC were isolated from the peripheral blood of normal, drug free donors by standard density gradient centrifugation on Ficoll-Hypaque (GE Healthcare, Piscataway, NJ) and incubated with anti-CD19 microbeads (Miltenyi Biotech, Auburn, CA). The B cells were then purified by positive immunosorting using an autoMacs (Miltenyi Biotech) according to the manufacture's instruction.

The purified B cells (2×10^5 /well/200 μ L) were cultured in 96-well ultra-low binding plates (Corning, Corning, NY) in RPMI1640, 10% FBS and goat F(ab')₂ anti-human IgM (10 μ g/ml) (Invitrogen, Carlsbad, CA), in the presence of different amount of test compounds, for three days. [³H]-thymidine (1 μ Ci/well) (PerkinElmer, Boston, MA) in PBS was then added to the B cell cultures for an additional 12 hrs before the incorporated radioactivity was separated by filtration with water through GF/B filters (Packard Bioscience, Meriden, CT) and measured by liquid scintillation counting with a TopCount (Packard Bioscience). Compounds having and IC₅₀ value of 10 μ M or less are considered active. See Table 2 for data related to compounds of the invention.

Table 2. IC₅₀ data for B cell proliferation assay*

Example	B cell IC ₅₀ (nM)
1	+
2	+++
3	+
4	+
5	+
6	++
7	++++
8	+
9	+
10	+
11	+
12	+
13	+
14	

* “+” = <50 nM; “++” = 50-100 nM; “+++” = 100-500 nM; “++++” = >500 nM.

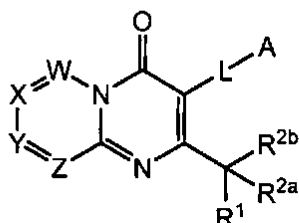
Example C: Akt phosphorylation assay

Ramos cells (B lymphocyte from Burkitts lymphoma) were obtained from ATCC (Manassas, VA) and maintained in RPMI1640 and 10% FBS. The cells (3×10^7 cells /tube/3 mL in RPMI) were incubated with different amounts of test compounds for 2 hrs at 37 °C and then stimulated with goat F(ab')₂ anti-human IgM (5 µg/ml) (Invitrogen) for 17 min. in a 37 °C water bath. The stimulated cells were spun down at 4 °C with centrifugation and whole cell extracts prepared using 300 µL lysis buffer (Cell Signaling Technology, Danvers, MA). The resulting lysates were sonicated and supernatants were collected. The phosphorylation level of Akt in the supernatants were analyzed by using PathScan phospho-Akt1 (Ser473) sandwich ELISA kits (Cell Signaling Technology) according to the manufacture's instruction.

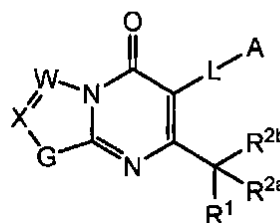
Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A compound of Formula I or II:



I



II

or a pharmaceutically acceptable salt thereof, wherein:

A is C₁₋₁₀ alkyl, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

L is absent, (CR^{7a}R^{7b})_m, (CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)₂(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q, or (CR^{7a}R^{7b})_pNR^{7c}S(O)₂(CR^{7a}R^{7b})_q;

W is N or CR³;

X is N or CR⁴;

Y is N or CR⁵;

Z is N or CR⁶;

G is O, S, or NR^N;

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R^1 is OR^A , SR^A , $S(O)R^A$, $S(O)_2R^A$, NR^AR^B , $NR^CC(O)NR^AR^B$, $NR^CC(O)OR^A$, $NR^CC(=NR^E)NR^AR^B$, $NR^CS(O)_2R^A$, $NR^CS(O)_2NR^CR^A$, heterocycloalkyl, or heteroaryl, wherein said heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r-Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^{2a} and R^{2b} are independently selected from H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl ring or a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl ring, each optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^3 , R^4 , R^5 , and R^6 are independently selected from H, halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4,

or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$;

R^{7a} and R^{7b} are independently selected from H, halo, or C_{1-4} alkyl;

R^{7c} is H or C_{1-4} alkyl;

R^{7d} is H, CN, NO_2 , OR^{a5} , SR^{b5} , $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, or $C(O)NR^{c5}R^{d5}$;

R^A is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r$, Cy^1 , halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^B and R^C are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{b5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^E is H, CN, NO_2 , OR^{a5} , SR^{b5} , $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, or $C(O)NR^{c5}R^{d5}$;

R^N is H or C_{1-4} alkyl;

Cy^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

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R^a , R^b , R^c , and R^d are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^c and R^d together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a2} , R^{b2} , R^{c2} , and R^{d2} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a3} , R^{b3} , R^{c3} , and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^e and R^f are independently selected from H, CN, NO_2 , OR^{a5} , SR^{b5} , $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, and $C(O)NR^{c5}R^{d5}$;

R^{a5} , R^{b5} , R^{c5} , and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $di(C_{1-6} \text{ alkyl})$ amino, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $di(C_{1-6} \text{ alkyl})$ amino, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

p is 0, 1, 2, 3, or 4;

q is 0, 1, 2, 3, or 4; and

r is 0 or 1.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having Formula I.
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having Formula II.
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein A is C_{1-10} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl,

cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

6. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a,

OC(O)R^b , $\text{OC(O)NR}^c\text{R}^d$, $\text{C(=NR}^c\text{)NR}^c\text{R}^d$, $\text{NR}^c\text{C(=NR}^c\text{)NR}^c\text{R}^d$, NR^cR^d , $\text{NR}^c\text{C(O)R}^b$,
 $\text{NR}^c\text{C(O)OR}^a$, $\text{NR}^c\text{C(O)NR}^c\text{R}^d$, $\text{NR}^c\text{S(O)R}^b$, $\text{NR}^c\text{S(O)}_2\text{R}^b$, $\text{NR}^c\text{S(O)}_2\text{NR}^c\text{R}^d$, S(O)R^b , $\text{S(O)NR}^c\text{R}^d$,
 $\text{S(O)}_2\text{R}^b$, and $\text{S(O)}_2\text{NR}^c\text{R}^d$.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein L is absent.

8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein L is $(\text{CR}^{7a}\text{R}^{7b})_m$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{O}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{S}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{S(O)}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{S(O)}_2(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{C(O)NR}^{7c}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{C(O)O}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{C(=NR}^{7d}\text{)NR}^{7c}(\text{CR}^{7a}\text{R}^{7b})_q$, or $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{S(O)}_2(\text{CR}^{7a}\text{R}^{7b})_q$.

9. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein L is $(\text{CR}^{7a}\text{R}^{7b})_m$.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein W is N.

11. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein W is CR^3 .

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein X is N.

13. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein X is CR^4 .

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein Y is N.

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15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein Y is CR⁵.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein Z is N.

17. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein Z is CR⁶.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein G is O.

19. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein G is S.

20. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein G is NR^N.

21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R¹ is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from from $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}.

22. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R¹ is NR^AR^B.

23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are independently selected from H and C₁₋₆ alkyl optionally substituted with

1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}.

24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R³, R⁴, R⁵, and R⁶ are independently selected from H or C₁₋₆ alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}.

25. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R³ is C₁₋₆ alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}.

26. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R⁴, R⁵, and R⁶ are each H.

27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein R^{7a}, R^{7b}, R^{7c}, and R^{7d} are each H.

28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein R^A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1},

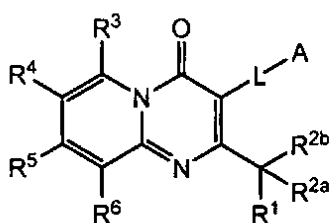
(03}

$\text{NR}^{\text{cl}}\text{C}(\text{O})\text{OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{C}(\text{O})\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{S}(\text{O})\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S}(\text{O})_2\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S}(\text{O})_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S}(\text{O})\text{R}^{\text{bl}}$, $\text{S}(\text{O})\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S}(\text{O})_2\text{R}^{\text{bl}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$.

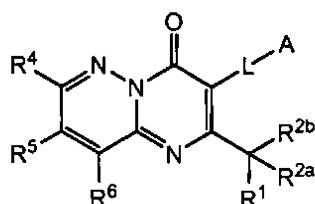
29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^{B} and R^{C} are independently selected from H and C_{1-6} alkyl.

30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein A is other than phenyl substituted at the 4-position by halogen.

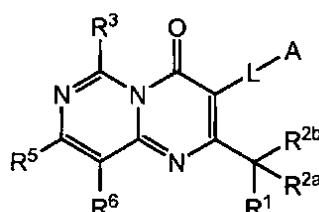
31. The compound of any one of claims 1-30, or a pharmaceutically acceptable salt thereof, having Formula Ia, Ib, Ic, Id, Ie, IIa, IIb, or IIc:



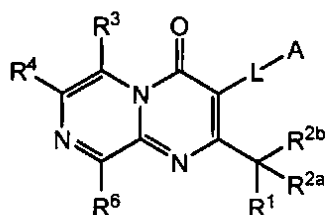
Ia



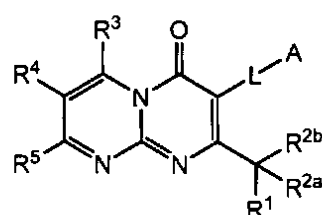
Ib



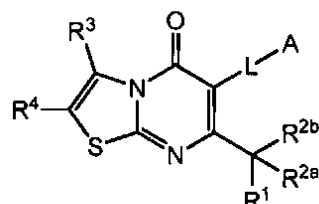
Ic



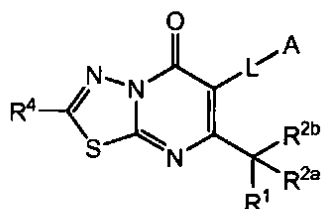
Id



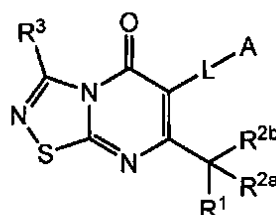
Ie



IIa



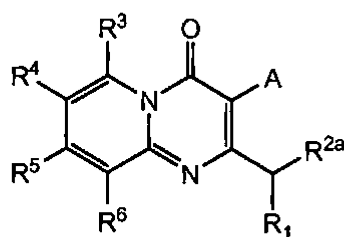
IIb



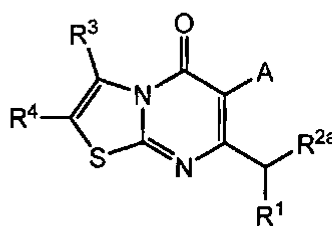
IIc.

32. The compound of claim 1 having Formula If or IId:

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If



IId

or a pharmaceutically acceptable salt thereof.

33. The compound of claim 32, or pharmaceutically acceptable salt thereof, wherein:

A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

R¹ is OR^A, SR^A, S(O)R^A, S(O)₂R^A, NR^AR^B, NR^CC(O)NR^AR^B, NR^CC(O)OR^A, NR^CC(=NR^E)NR^AR^B, NR^CS(O)₂R^A, NR^CS(O)₂NR^CR^A, heterocycloalkyl, or heteroaryl, wherein said heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^{2a} is H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl,

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cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

R³, R⁴, R⁵, and R⁶ are independently selected from H, halo, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)₂NR^{c3}R^{d3}, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

R^A is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)-, Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^B and R^C are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5},

$\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{E} is H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, or $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

Cy^{l} is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{OC}(\text{O})\text{R}^{\text{b1}}$, $\text{OC}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$;

R^{a} , R^{b} , R^{c} , and R^{d} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

or R^{c} and R^{d} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$,

$$\text{NR}^{\text{c}5}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}, \text{S}(\text{O})\text{R}^{\text{b}5}, \text{S}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}, \text{S}(\text{O})_2\text{R}^{\text{b}5}, \text{NR}^{\text{c}5}\text{S}(\text{O})_2\text{R}^{\text{b}5}, \text{NR}^{\text{c}5}\text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{d}5}, \text{and } \text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{d}5};$$

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a2} , R^{b2} , R^{c2} , and R^{d2} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a3} , R^{b3} , R^{c3} , and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$,

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$\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{e} and R^{f} are independently selected from H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{a5} , R^{b5} , R^{c5} , and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $\text{di}(\text{C}_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $\text{di}(\text{C}_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy; and

r is 0 or 1;

provided that:

a) in Formula If, when A is 3-fluorophenyl; $\text{R}^{2\text{a}}$ is H; R^3 is methyl; and R^4 , R^5 , and R^6 are H; then, R^1 is other than 4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl; and

b) in Formula If, when A is 1,3-dioxolan-2-yl; $\text{R}^{2\text{a}}$, R^3 , R^4 , and R^6 are H; then, R^1 is other than 1-(tert-butoxycarbonyl)piperidin-4-yl.

34. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein the compound has Formula If.

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35. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein the compound has Formula II d.

36. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

37. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

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38. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

39. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

40. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

41. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is phenyl.

42. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

43. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is 6-membered heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

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44. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is pyridyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

45. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is 5-membered heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

46. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is pyrazolyl optionally substituted with 1 or 2 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

47. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R¹ is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}.

48. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R¹ is bicyclic heteroaryl optionally substituted with 1, 2, or 3 substituents independently

selected from $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{al} , SR^{al} , C(O)R^{bl} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)OR}^{\text{al}}$, $\text{OC(O)R}^{\text{bl}}$, $\text{OC(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{S(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, S(O)R^{bl} , $\text{S(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, and $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$.

49. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R^1 is purinyl optionally substituted with $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{al} , SR^{al} , C(O)R^{bl} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)OR}^{\text{al}}$, $\text{OC(O)R}^{\text{bl}}$, $\text{OC(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{S(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, S(O)R^{bl} , $\text{S(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, or $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$.

50. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R^1 is OR^{A} , SR^{A} , S(O)R^{A} , $\text{S(O)}_2\text{R}^{\text{A}}$, $\text{NR}^{\text{A}}\text{R}^{\text{B}}$, $\text{NR}^{\text{C}}\text{C(O)NR}^{\text{A}}\text{R}^{\text{B}}$, $\text{NR}^{\text{C}}\text{C(O)OR}^{\text{A}}$, $\text{NR}^{\text{C}}\text{C(=NR}^{\text{E}}\text{)NR}^{\text{A}}\text{R}^{\text{B}}$, $\text{NR}^{\text{C}}\text{S(O)}_2\text{R}^{\text{A}}$, or $\text{NR}^{\text{C}}\text{S(O)}_2\text{NR}^{\text{C}}\text{R}^{\text{A}}$.

51. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R^1 is $\text{NR}^{\text{A}}\text{R}^{\text{B}}$.

52. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^{A} is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{al} , SR^{al} , C(O)R^{bl} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)OR}^{\text{al}}$, $\text{OC(O)R}^{\text{bl}}$, $\text{OC(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{S(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, S(O)R^{bl} , $\text{S(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, and $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$.

53. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^{A} is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{al} , SR^{al} , C(O)R^{bl} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)OR}^{\text{al}}$, $\text{OC(O)R}^{\text{bl}}$,

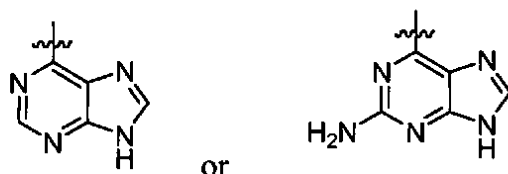
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OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}.

54. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}.

55. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5}.

56. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^A is:



57. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^A is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}.

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58. The compound of any one of claims 33-57, or a pharmaceutically acceptable salt thereof, wherein R^B and R^C are independently selected from H and C_{1-6} alkyl.

59. The compound of any one of claims 33-57, or a pharmaceutically acceptable salt thereof, wherein R^B and R^C are each H.

60. The compound of any one of claims 33-59, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

61. The compound of any one of claims 33-59, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

62. The compound of any one of claims 33-59, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

63. The compound of any one of claims 33-59, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is methyl or ethyl.

64. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$,

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$\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, $\text{OR}^{\text{a}3}$, $\text{SR}^{\text{a}3}$, $\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{OC}(\text{O})\text{R}^{\text{b}3}$, $\text{OC}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$.

65. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is H, halo, CN, NO_2 , $\text{OR}^{\text{a}3}$, $\text{SR}^{\text{a}3}$, $\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, or C_{1-6} alkyl, wherein said C_{1-6} alkyl, is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, $\text{OR}^{\text{a}3}$, $\text{SR}^{\text{a}3}$, $\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{OC}(\text{O})\text{R}^{\text{b}3}$, $\text{OC}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$.

66. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is H or C_{1-6} alkyl.

67. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-6} alkyl.

68. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is methyl.

69. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R^4 , R^5 , and R^6 are independently selected from H, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

70. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R^4 , R^5 , and R^6 are each H.

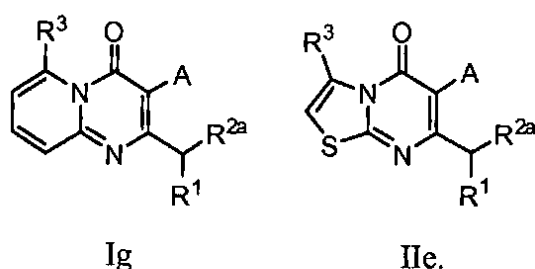
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71. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

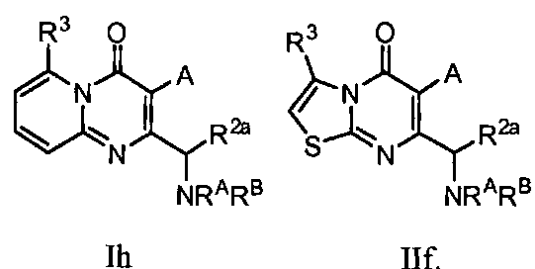
72. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R^5 is H.

73. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R^6 is H.

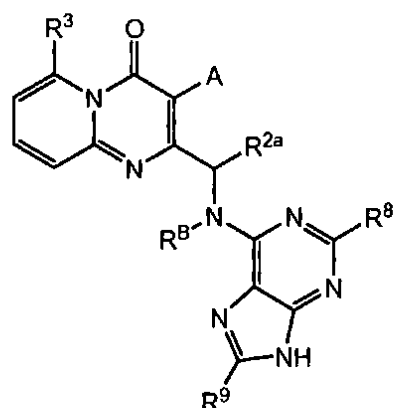
74. The compound of any one of claims 33-73, or a pharmaceutically acceptable salt thereof, having Formula Ig or IIe:



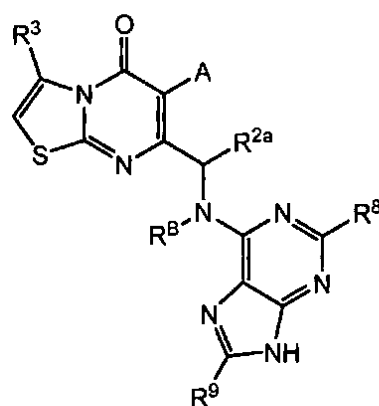
75. The compound of any one of claims 33-74, or a pharmaceutically acceptable salt thereof, having Formula Ih or IIf:



76. The compound of any one of claims 33-75, or a pharmaceutically acceptable salt thereof, having Formula Ii or IIg:



Ii



IIg.

wherein R^8 and R^9 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

77. The compound of claim 1, selected from:

2-[1-(6-amino-9H-purin-9-yl)ethyl]-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one;

6-methyl-3-phenyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

3-(5-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

3-(3-fluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

3-(3,5-difluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

3-(2-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-3-(1H-pyrazol-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one;

3-methyl-6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

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6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one; and

3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one, or a pharmaceutically acceptable salt thereof.

78. A composition comprising a compound according to any one of claims 1-77, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

79. A method of modulating an activity of a PI3K kinase comprising contacting the kinase with a compound of any one of claims 1-77.

80. The method of claim 79 wherein the PI3K is selected from the group consisting of PI3K α , PI3K β , PI3K γ , and PI3K δ .

81. The method of claim 79 wherein said PI3K comprises a mutation.

82. The method of any one of claims 79-81 wherein said modulating is inhibiting.

83. The method of any one of claims 79-81 wherein said compound is a selective inhibitor for PI3K δ over one or more of PI3K α , PI3K β , and PI3K γ .

84. A method of treating a disease in a patient, wherein said disease is associated with abnormal expression or activity of a PI3K kinase, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1-77.

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85. The method of claim 84 wherein said disease is osteoarthritis, restenosis, atherosclerosis, bone disorders, arthritis, diabetic retinopathy, psoriasis, benign prostatic hypertrophy, atherosclerosis, inflammation, angiogenesis, pancreatitis, kidney disease, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, or Sjogren's syndrome.

86. The method of claim 84 wherein the PI3K is selected from the group consisting of PI3K α , PI3K β , PI3K γ , and PI3K δ .

87. The method of claim 84 wherein the PI3K is PI3K δ .

88. The method of any one of claims 84-87 wherein more than one of said compounds is administered.

89. The method of claim 88 wherein the compound is administered in combination with a kinase inhibitor that inhibits a kinase other than a PI3K kinase.

90. A method of treating an immune-based disease in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1-77.

91. The method of claim 90 wherein said immune-based disease is rheumatoid arthritis, allergy, asthma, glomerulonephritis, lupus, or inflammation related to any of the aforementioned.

92. A method of treating a cancer in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of claim 1-77.

93. The method of claim 92 wherein said cancer is breast, prostate, colon, endometrial, brain, bladder, skin, uterus, ovary, lung, pancreatic, renal, gastric, or a hematological cancer.

94. The method of claim 93 wherein said hematological cancer is acute myeloblastic leukemia, chronic myeloid leukemia, or B cell lymphoma.

95. A method of treating a lung disease in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of claim 1-77.

96. The method of claim 95 wherein said lung disease is acute lung injury (ALI) or adult respiratory distress syndrome (ARDS).

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ABSTRACT

The present invention provides pyrimidinones that modulate the activity of phosphoinositide 3-kinases (PI3Ks) and are useful in the treatment of diseases related to the activity of PI3Ks including, for example, inflammatory disorders, immune-based disorders, cancer, and other diseases.

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TRADUCCION OFICIAL No. 2011-12-22-773
DE UN DOCUMENTO ESCRITO EN INGLES

LOS ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS QUE VIEREN ESTOS PRESENTES:
DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

02 de diciembre de 2011

POR EL PRESENTE CERTIFICO QUE ADJUNTO AL PRESENTE SE ENCUENTRA UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS DE AQUELLOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA A CONTINUACION QUE CUMPLIO CON LOS REQUERIMIENTOS PARA QUE SE LE OTORQUE UNA FECHA DE PRESENTACION BAJO 35 USC 111.

NUMERO DE SOLICITUD: 61/259.765

FECHA DE PRESENTACION: 10 de noviembre de 2009

EL CODIGO DEL PAIS Y EL NUMERO DE SU SOLICITUD DE PRIORIDAD, PARA SER USADO PARA PRESENTACION EN EL EXTERIOR BAJO LA CONVENCION DE PARIS, ES US61/259,765

Departamento de Comercio
Oficina de Patentes y Marcas de los
Estados Unidos

Por Autoridad del
Subsecretario de Comercio para
Propiedad Intelectual y Director de la Oficina de
Patentes y Marcas de los Estados Unidos
(firma: ilegible)
N. WILLIAMS
Funcionario que Certifica

Recibo de Reconocimiento Electrónico	
ID EFS:	6423852
Número de Solicitud:	61259765
Número de Solicitud Internacional:	
Número de Confirmación:	1698
Título de la Invención:	PIRIMIDINONAS COMO INHIBIDORES DE PI3K
Primer Inventor Nombrado/Nombre del Solicitante:	Yun-Long Li
Número del Cliente:	26161
Presentador:	Susanne H. Goodson/Joe Farrell
Presentador Autorizado por:	Susanne H. Goodson
Número de Expediente del Apoderado:	20443-0183P02/INCY00096-002
Fecha de Recepción:	10-NOV-2009
Fecha de Presentación:	
Estampilla de Tiempo:	14:06:52
Tipo de Solicitud:	Provisional

Información sobre Pago:	
Presentada con Pago	sí
Tipo de Pago	Cuenta de Depósito
El pago fue exitosamente recibido en RAM	\$220
Número confirmación RAM	8265
Cuenta de Depósito	061050
Usuario Autorizado	

Listas de Archivos:					
Número del Documento	Descripción del Documento	Nombre del Archivo	Tamaño del Archivo (Bytes)/ Message Digest	Multi Partes /.zip	Páginas (si aplica)
1	Transmisión de Nueva Solicitud	transmittal.pdf	50639	no	1
			daa90db120a726551347 6fa17d57173d91a58d16		
Advertencias:					
Información:					
2		application.pdf	6222655	sí	117
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		c55312717289e71eeae		
	Descripción Multipartes/Archivos PDF en .descripción zip			
	Descripción del Documento	Inicio	Final	
	Especificación	1	85	
	Reivindicaciones	86	114	
	Resumen	115	115	
	Dibujos-dibujos con líneas en blanco y negro únicamente	116	117	

Advertencias:					
Información:					
3	Hoja de Trabajo de Derechos (PTO-875)	fee.info.pdf	29752 acf6e7d7b279507c500f5c40 70a6a4065de5b5b8	no	2

Advertencias:	
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Tamaño Total de los Archivos (en bytes):	6303046

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Nuevas Solicitudes Bajo 35 U.S.C. 111

Si se presenta una nueva solicitud y la solicitud incluye los componentes necesarios para una fecha de presentación (ver 37 CFR 1.53(b)-(d) y MPEP 506), un Recibo de Presentación (37 CFR 1.54) será expedido en el curso debido y la fecha mostrada en este Recibo de Reconocimiento establecerá la fecha de presentación de la solicitud.

Fase Nacional de una Solicitud Internacional bajo 35 U.S.C. 371

Si una presentación a tiempo para registrar una solicitud internacional en la fase nacional cumple con las condiciones de 35 U.S.C. 371 y otros requerimientos que aplican se expedirá un Formato PCT/DO/EO/903 que indica aceptación de la solicitud como una presentación de la fase nacional bajo 35 U.S.C. 371 además del Recibo de Presentación, en su curso debido.

Nueva Solicitud Internacional Presentada ante la USPTO como Oficina que Recibe

Si se presenta una nueva solicitud internacional y la solicitud internacional incluye los componentes necesarios para una fecha de presentación internacional (ver Artículo 11 PCT y MPEP 1810), se expedirá una Notificación del Número de la Solicitud Internacional y de la Fecha de Presentación Internacional (Formato PCT/RO/105) en el curso debido, sujeta a las prescripciones relacionadas con la seguridad nacional, y la fecha que aparece en este Recibo de Reconocimiento establecerá la fecha de presentación internacional de la solicitud.

SOLICITUD PROVISIONAL PARA CARATULA DE PATENTE

Esta es una solicitud para presentar una SOLICITUD PROVISIONAL PARA PATENTE bajo 37 C.F.R. §1.53(c).

INVENTOR(ES)		
Nombre (primero y segundo [si aplica])	Apellido	Residencia (Ciudad y Estado o País Extranjero)
Yun-Long Brian Andrew P.	Li Metcalf Combs	Chadds Ford, PA Moraga, CA Kennett Square, PA
Se nombran inventores adicionales en las 0 hojas numeradas separadamente que se adjuntan al presente.		

TITULO DE LA INVENCION (500 caracteres máximo)					
PIRIMIDINONAS COMO INHIBIDORES DE PI3K					
DIRECCION DE CORRESPONDENCIA					
Dirigir toda la correspondencia a: ☒ Número del Cliente 26161 ☐					
☐ Nombre de la Firma o Persona Natural					
Dirección					
Dirección					
Ciudad		Estado		Código Postal	
País		Teléfono		Fax	
PARTES DE LA SOLICITUD QUE SE ADJUNTAN (marque todas las que aplican)					
☐ Hoja Datos de Solicitud.	Ver 37 CFR 1.76	☐ CD(s), Número			
☒ Especificación	Número de Páginas 115	☐ Otros (especificar)			
☐ Dibujo(s)	Número de Hojas 2				
Derechos Tamaño de la Solicitud: Si la especificación y los dibujos exceden 100 hojas de papel, los derechos por el tamaño de la solicitud debidos son \$270 (\$135 para entidad pequeña) por cada por cada 50 hojas o fracción adicional de la misma. Ver 35 U.S.C. §41(a)(1)(G) y 37 CFR §1.16(s).					
MÉTODO DE PAGO DE DERECHOS DE PRESENTACION Y DERECHOS POR EL TAMANO DE LA SOLICITUD PARA ESTA SOLICITUD PROVISIONAL PARA PATENTE					
☐ El Solicitante reivindica estado de entidad pequeña. Ver 37 C.F.R. §1.27.					
☐ Se adjunta un cheque o giro postal para cubrir los derechos de presentación.		SUMA TOTAL DERECHOS			
☐ Pago con tarjeta de crédito. Se adjunta formato PTO-2038		220.00			
☒ El Director por el presente está autorizado para cobrar derechos de presentación o acreditar cualquier sobrepago a la Cuenta de Depósito Número: 06-1050. Se adjunta una copia de esta forma para procesamiento de derechos.					

Presentado respetuosamente,

Firma: /Christine A. Goddard/ Fecha: 10 de noviembre de 2009

Susanne H. Goodson, Ph.D., Reg. No. 58,450

Teléfono No: (302) 652-5070

Expediente No: 20443-0183P02 / INCY0096-002

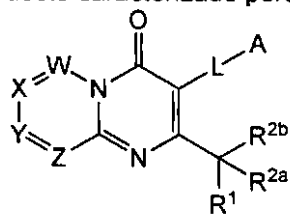
Fecha de Depósito: 29 de junio de 2009

CERTIFICADO DE ENVIO POR CORREO POR ARCHIVO EFS-WEB

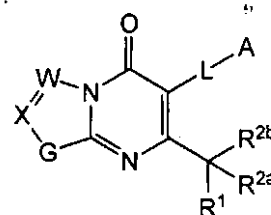
Por el presente certifico que este papel fue presentado ante la Oficina de Patentes y Marcas usando el sistema EFS-WEB en esta fecha: 10 de noviembre de 2009

Lo que se reivindica es:

1. Un compuesto caracterizado porque es de Fórmula I o II:



I



II

o una sal aceptable farmacéuticamente del mismo, donde:

A es C₁₋₁₀ alquilo, arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d;

L se encuentra ausente o es (CR^{7a}R^{7b})_m, (CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O) (CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)₂(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q, o (CR^{7a}R^{7b})_pNR^{7c}S(O)₂(CR^{7a}R^{7b})_q;

W es N o CR³;

X es N o CR⁴;

Y es N o CR⁵;

Z es N o CR⁶;

G es O, S, o NR^N;

R¹ es OR^A, SR^A, S(O)R^A, S(O)₂R^A, NR^AR^B, NR^CC(O)NR^AR^B, NR^CC(O)OR^A, NR^CC(=NR^E)NR^AR^B, NR^CS(O)₂R^A, NR^CS(O)₂NR^CR^A, heterocicloalquilo, o heteroarilo, donde dicho heterocicloalquilo o heteroarilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre -(C₁₋₄ alquil)-Cy¹, halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1};

R^{2a} y R^{2b} se seleccionan en forma independiente entre H, halo, OH, CN, C₁₋₆ alquilo, C₁₋₆ haloalquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₁₋₆ haloalquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, y S(O)₂NR^{c2}R^{d2};

o R^{2a} y R^{2b} junto con el átomo de carbono al cual se encuentran unidos forman un anillo cicloalquilo de 3, 4, 5, 6 o 7 miembros o un anillo heterocicloalquilo de 3, 4, 5, 6, o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre

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halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, y S(O)₂NR^{c2}R^{d2};

R³, R⁴, R⁵, y R⁶ se seleccionan en forma independiente entre H, halo, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)₂NR^{c3}R^{d3}, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, y S(O)₂NR^{c3}R^{d3};

R^{7a} y R^{7b} se seleccionan en forma independiente entre H, halo, o C₁₋₄ alquilo;

R^{7c} es H o C₁₋₄ alquilo;

R^{7d} es H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, o C(O)NR^{c5}R^{d5};

R^A es heteroarilo, heterocicloalquilo, heteroarilalquilo, o heterocicloalquilalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre – (C₁₋₄ alquil)-Cy¹, halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1};

R^B y R^C se seleccionan en forma independiente entre H, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y

heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

R^E es H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, o C(O)NR^{c5}R^{d5};

R^N es H o C₁₋₄ alquilo;

Cy¹ es arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1};

R^a, R^b, R^c, y R^d se seleccionan en forma independiente entre H, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

o R^c y R^d junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o

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heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

R^{a1} , R^{b1} , R^{c1} , y R^{d1} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

o R^{c1} y R^{d1} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

R^{a2} , R^{b2} , R^{c2} , y R^{d2} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en

forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

o R^{c2} y R^{d2} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

R^{a3}, R^{b3}, R^{c3}, y R^{d3} se seleccionan en forma independiente entre H, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

o R^{c3} y R^{d3} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, halo, C₁₋₆ haloalquilo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, y S(O)₂NR^{c5}R^{d5};

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R^e y R^f se seleccionan en forma independiente entre H, CN, NO_2 , OR^{a5} , SR^{b5} , $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, y $C(O)NR^{c5}R^{d5}$;

R^{a5} , R^{b5} , R^{c5} , y R^{d5} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre OH, CN, amino, halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} alquiltio, C_{1-6} alquilamino, $di(C_{1-6}$ alquil)amino, C_{1-6} haloalquilo, y C_{1-6} haloalcoxi;

o R^{c5} y R^{d5} junto con el átomo de N al cual están unidos forman a un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre OH, CN, amino, halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} alquiltio, C_{1-6} alquilamino, $di(C_{1-6}$ alquil)amino, C_{1-6} haloalquilo, y C_{1-6} haloalcoxi;

m es 1, 2, 3, 4, 5, 6, 7, 8, 9, o 10;

p es 0, 1, 2, 3, o 4;

q es 0, 1, 2, 3, o 4; y

r es 0 o 1.

2. El compuesto de la reivindicación 1, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula I.
3. El compuesto de la reivindicación 1, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula II.
4. El compuesto de cualquiera de las reivindicaciones 1-3, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es C_{1-10} alquilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a , SR^a ,

$C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$,
 $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$,
 $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo,
 C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2,
3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6}
alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$,
 $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$,
 $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$.

5. El compuesto de cualquiera de las reivindicaciones 1-3, o una sal aceptable farmacéuticamente
del mismo, caracterizado porque A es arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno
opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre
halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo,
heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$,
 $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$,
 $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y
 $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o
heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma
independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN,
 NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$,
 $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$,
 $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$.

6. El compuesto de cualquiera de las reivindicaciones 1-3, o una sal aceptable farmacéuticamente
del mismo, caracterizado porque A es arilo o heteroarilo, cada uno opcionalmente sustituido con 1, 2, 3,
4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6}
alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a ,

SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$.

7. El compuesto de cualquiera de las reivindicaciones 1-6, o una sal aceptable farmacéuticamente del mismo, caracterizado porque L se encuentra ausente.

8. El compuesto de cualquiera de las reivindicaciones 1-6, o una sal aceptable farmacéuticamente del mismo, caracterizado porque L es $(CR^{7a}R^{7b})_m$, $(CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(O)(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pS(O)_2(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q$, $(CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q$, o $(CR^{7a}R^{7b})_pNR^{7c}S(O)_2(CR^{7a}R^{7b})_q$.

9. El compuesto de cualquiera de las reivindicaciones 1-6, o una sal aceptable farmacéuticamente del mismo, caracterizado porque L es $(CR^{7a}R^{7b})_m$.

10. El compuesto de cualquiera de las reivindicaciones 1-9, o una sal aceptable farmacéuticamente del mismo, caracterizado porque W es N.

11. El compuesto de cualquiera de las reivindicaciones 1-9, o una sal aceptable farmacéuticamente del mismo, caracterizado porque W es CR^3 .

12. El compuesto de cualquiera de las reivindicaciones 1-11, o una sal aceptable farmacéuticamente del mismo, caracterizado porque X es N.

13. El compuesto de cualquiera de las reivindicaciones 1-11, o una sal aceptable farmacéuticamente del mismo, caracterizado porque X es CR^4 .

14. El compuesto de cualquiera de las reivindicaciones 1-13, o una sal aceptable farmacéuticamente del mismo, caracterizado porque Y es N.
15. El compuesto de cualquiera de las reivindicaciones 1-13, o una sal aceptable farmacéuticamente del mismo, caracterizado porque Y es CR⁵.
16. El compuesto de cualquiera de las reivindicaciones 1-15, o una sal aceptable farmacéuticamente del mismo, caracterizado porque Z es N.
17. El compuesto de cualquiera de las reivindicaciones 1-15, o una sal aceptable farmacéuticamente del mismo, caracterizado porque Z es CR⁶.
18. El compuesto de cualquiera de las reivindicaciones 1-17, o una sal aceptable farmacéuticamente del mismo, caracterizado porque G es O.
19. El compuesto de cualquiera de las reivindicaciones 1-17, o una sal aceptable farmacéuticamente del mismo, caracterizado porque G es S.
20. El compuesto de cualquiera de las reivindicaciones 1-17, o una sal aceptable farmacéuticamente del mismo, caracterizado porque G es NR^N.
21. El compuesto de cualquiera de las reivindicaciones 1-20, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R¹ es heteroarilo opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquilo})_r\text{-Cy}^1$, halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1}.
22. El compuesto de cualquiera de las reivindicaciones 1-20, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R¹ es NR^AR^B.
23. El compuesto de cualquiera de las reivindicaciones 1-22, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{2a} y R^{2b} se seleccionan en forma independiente

entre H y C₁₋₆ alquilo opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alqueno, C₂₋₆ alquino, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, y S(O)₂NR^{c2}R^{d2}.

24. El compuesto de cualquiera de las reivindicaciones 1-23, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R³, R⁴, R⁵, y R⁶ se seleccionan en forma independiente entre H o C₁₋₆ alquilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, y S(O)₂NR^{c3}R^{d3}.

25. El compuesto de cualquiera de las reivindicaciones 1-23, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R³ es C₁₋₆ alquilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C₁₋₆ alquilo, C₁₋₆ haloalquilo, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, y S(O)₂NR^{c3}R^{d3}.

26. El compuesto de cualquiera de las reivindicaciones 1-23, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R⁴, R⁵, y R⁶ son cada uno H.

27. El compuesto de cualquiera de las reivindicaciones 1-26, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{7a}, R^{7b}, R^{7c}, y R^{7d} son cada uno H.

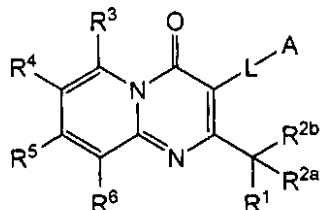
28. El compuesto de cualquiera de las reivindicaciones 1-27, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es heteroarilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre -(C₁₋₄ alquil)_r-Cy¹, halo, C₁₋₆ alquilo,

C₂₋₆ alquenoilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, y S(O)₂NR^{c1}R^{d1}.

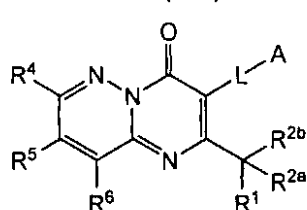
29. El compuesto de cualquiera de las reivindicaciones 1-28, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^B y R^C se seleccionan en forma independiente entre H y C₁₋₆ alquilo.

30. El compuesto de cualquiera de las reivindicaciones 1-29, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A no es fenilo sustituido con la posición 4 con halógeno.

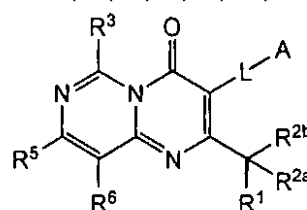
31. El compuesto de cualquiera de las reivindicaciones 1-30, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula Ia, Ib, Ic, Id, Ie, IIa, IIb, o IIc:



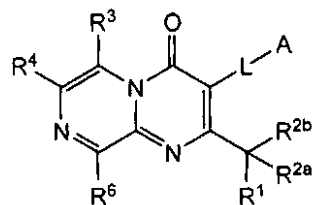
Ia



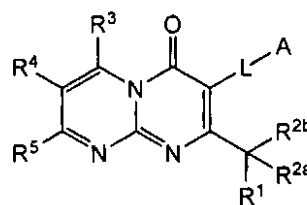
Ib



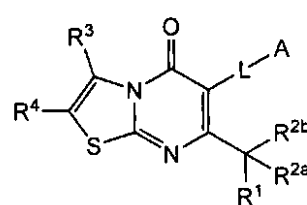
Ic



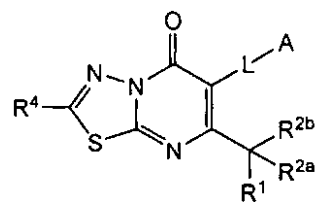
Id



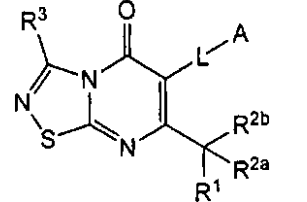
Ie



IIa



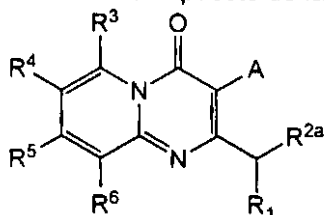
IIb



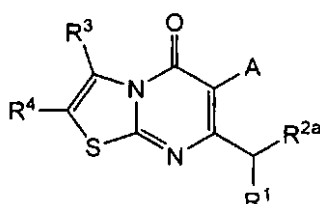
IIc.

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32. El compuesto de la reivindicación 1 caracterizado porque es de fórmula If o IId:



If



IId

o una sal aceptable farmacéuticamente del mismo.

33. El compuesto de la reivindicación 32, o una sal aceptable farmacéuticamente del mismo, caracterizado porque:

A es arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d;

R¹ es OR^A, SR^A, S(O)R^A, S(O)₂R^A, NR^AR^B, NR^CC(O)NR^AR^B, NR^CC(O)OR^A, NR^CC(=NR^E)NR^AR^B, NR^CS(O)₂R^A, NR^CS(O)₂NR^CR^A, heterocicloalquilo, o heteroarilo, donde dicho heterocicloalquilo o heteroarilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre -(C₁₋₄ alquil)-Cy¹, halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1},

$\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$;

$\text{R}^{2\text{a}}$ es H, halo, OH, CN, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a2} , SR^{a2} , $\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{OC}(\text{O})\text{R}^{\text{b2}}$, $\text{OC}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{S}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})_2\text{R}^{\text{b2}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$;

R^3 , R^4 , R^5 , y R^6 se seleccionan en forma independiente entre H, halo, CN, NO_2 , OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{OC}(\text{O})\text{R}^{\text{b3}}$, $\text{OC}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})\text{R}^{\text{b3}}$, $\text{S}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$;

R^{A} es heteroarilo, heterocicloalquilo, heteroarilalquilo, o heterocicloalquilalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre – $(\text{C}_{1-4}\text{ alquil})_r\text{Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{OC}(\text{O})\text{R}^{\text{b1}}$, $\text{OC}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$,

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$\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{S}(\text{O})\text{R}^{\text{b}1}$, $\text{S}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{S}(\text{O})_2\text{R}^{\text{b}1}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$;

R^{B} y R^{C} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, $\text{OR}^{\text{a}5}$, $\text{SR}^{\text{a}5}$, $\text{C}(\text{O})\text{R}^{\text{b}5}$, $\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{C}(\text{O})\text{OR}^{\text{a}5}$, $\text{OC}(\text{O})\text{R}^{\text{b}5}$, $\text{OC}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{R}^{\text{b}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{OR}^{\text{a}5}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{S}(\text{O})\text{R}^{\text{b}5}$, $\text{S}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{S}(\text{O})_2\text{R}^{\text{b}5}$, $\text{NR}^{\text{c}5}\text{S}(\text{O})_2\text{R}^{\text{b}5}$, $\text{NR}^{\text{c}5}\text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$;

R^{E} es H, CN, NO_2 , $\text{OR}^{\text{a}5}$, $\text{SR}^{\text{b}5}$, $\text{S}(\text{O})_2\text{R}^{\text{b}5}$, $\text{C}(\text{O})\text{R}^{\text{b}5}$, $\text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, o $\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$;

Cy^1 es arilo, heteroarilo, cicloalquilo, o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , $\text{OR}^{\text{a}1}$, $\text{SR}^{\text{a}1}$, $\text{C}(\text{O})\text{R}^{\text{b}1}$, $\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{C}(\text{O})\text{OR}^{\text{a}1}$, $\text{OC}(\text{O})\text{R}^{\text{b}1}$, $\text{OC}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{OR}^{\text{a}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{S}(\text{O})\text{R}^{\text{b}1}$, $\text{S}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{S}(\text{O})_2\text{R}^{\text{b}1}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$;

R^{a} , R^{b} , R^{c} , y R^{d} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, $\text{OR}^{\text{a}5}$, $\text{SR}^{\text{a}5}$, $\text{C}(\text{O})\text{R}^{\text{b}5}$, $\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{C}(\text{O})\text{OR}^{\text{a}5}$, $\text{OC}(\text{O})\text{R}^{\text{b}5}$, $\text{OC}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{R}^{\text{b}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(\text{O})\text{OR}^{\text{a}5}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{NR}^{\text{c}5}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{S}(\text{O})\text{R}^{\text{b}5}$, $\text{S}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, $\text{S}(\text{O})_2\text{R}^{\text{b}5}$, $\text{NR}^{\text{c}5}\text{S}(\text{O})_2\text{R}^{\text{b}5}$, $\text{NR}^{\text{c}5}\text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{d}5}$, y

$S(O)_2NR^{c5}R^{d5}$;

o R^c y R^d junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

R^{a1} , R^{b1} , R^{c1} , y R^{d1} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

o R^{c1} y R^{d1} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$;

R^{a2} , R^{b2} , R^{c2} , y R^{d2} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, arilo,

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cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$.

o R^{c2} y R^{d2} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$.

R^{a3} , R^{b3} , R^{c3} , y R^{d3} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$.

o R^{c3} y R^{d3} junto con el átomo de N al cual están unidos forman un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, halo, C_{1-6} haloalquilo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$.

$\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, y $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{a} y R^{f} se seleccionan en forma independiente entre H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, y $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{a5} , R^{b5} , R^{c5} , y R^{d5} se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenido, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenido, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre OH, CN, amino, halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} alquiltio, C_{1-6} alquilamino, $\text{di}(\text{C}_{1-6}$ alquil)amino, C_{1-6} haloalquilo, y C_{1-6} haloalcoxi;

o R^{c5} y R^{d5} junto con el átomo de N al cual están unidos forman a un grupo heterocicloalquilo o heteroarilo de 3, 4, 5, 6 o 7 miembros, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre OH, CN, amino, halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} alquiltio, C_{1-6} alquilamino, $\text{di}(\text{C}_{1-6}$ alquil)amino, C_{1-6} haloalquilo, y C_{1-6} haloalcoxi; y

r es 0 o 1;

siempre que:

a) en la Fórmula If, cuando A es 3-fluorofenilo; $\text{R}^{2\text{a}}$ es H; R^3 es metilo; y R^4 , R^5 , y R^6 son H; entonces, R^1 no es 4-amino-3-yodo-1H-pirazolo[3,4-d]pirimidin-1-ilo; y

b) en la Fórmula If, cuando A es 1,3-dioxolan-2-ilo; $\text{R}^{2\text{a}}$, R^3 , R^4 , y R^6 son H; entonces, R^1 no es 1-(*tert*-butoxicarbonil)piperidin-4-ilo.

34. El compuesto de la reivindicación 33, o una sal aceptable farmacéuticamente del mismo, caracterizado porque el compuesto tiene la Fórmula If.

35. El compuesto de la reivindicación 33, o una sal aceptable farmacéuticamente del mismo, caracterizado porque el compuesto tiene la Fórmula IId.

36. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es cicloalquilo o heterocicloalquilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

37. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es arilo o heteroarilo, cada uno opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b.

y $S(O)_2NR^cR^d$.

38. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es arilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$.

39. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es fenilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$; donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, y $S(O)_2NR^cR^d$.

40. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es fenilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, o C₁₋₆ haloalquilo.

41. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es fenilo.

42. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es heteroarilo opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

43. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es heteroarilo de 6 miembros opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido

con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

44. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es piridilo opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, o C₁₋₆ haloalquilo.

45. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es heteroarilo de 5 miembros opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d; donde dicho C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, C₂₋₆ alquenilo, C₂₋₆ alquinilo, C₁₋₆ haloalquilo, halosulfanilo, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, y S(O)₂NR^cR^d.

46. El compuesto de cualquiera de las reivindicaciones 33-35, o una sal aceptable farmacéuticamente del mismo, caracterizado porque A es pirazolilo opcionalmente sustituido con 1 o 2 sustituyentes seleccionados en forma independiente entre halo, C₁₋₆ alquilo, o C₁₋₆ haloalquilo.

47. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R¹ es heteroarilo opcionalmente sustituido con 1, 2,

o 3 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , C(O)R^{b1} , $\text{C(O)NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , OC(O)R^{b1} , $\text{OC(O)NR}^{c1}\text{R}^{d1}$, $\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(O)R}^{b1}$, $\text{NR}^{c1}\text{C(O)OR}^{a1}$, $\text{NR}^{c1}\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S(O)R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, S(O)R^{b1} , $\text{S(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, y $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$.

48. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^1 es heteroarilo bicíclico opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , C(O)R^{b1} , $\text{C(O)NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , OC(O)R^{b1} , $\text{OC(O)NR}^{c1}\text{R}^{d1}$, $\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(O)R}^{b1}$, $\text{NR}^{c1}\text{C(O)OR}^{a1}$, $\text{NR}^{c1}\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S(O)R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, S(O)R^{b1} , $\text{S(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, y $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$.

49. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^1 es purinilo opcionalmente sustituido con $-(C_{1-4} \text{ alquil})_r\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alqueno, C_{2-6} alquino, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , C(O)R^{b1} , $\text{C(O)NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , OC(O)R^{b1} , $\text{OC(O)NR}^{c1}\text{R}^{d1}$, $\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(=NR}^e\text{)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C(O)R}^{b1}$, $\text{NR}^{c1}\text{C(O)OR}^{a1}$, $\text{NR}^{c1}\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S(O)R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, S(O)R^{b1} , $\text{S(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, o $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$.

50. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^1 es OR^A , SR^A , S(O)R^A , $\text{S(O)}_2\text{R}^A$, NR^AR^B , $\text{NR}^C\text{C(O)NR}^A\text{R}^B$, $\text{NR}^C\text{C(O)OR}^A$, $\text{NR}^C\text{C(=NR}^E\text{)NR}^A\text{R}^B$, $\text{NR}^C\text{S(O)}_2\text{R}^A$, o $\text{NR}^C\text{S(O)}_2\text{NR}^C\text{R}^A$.

51. El compuesto de cualquiera de las reivindicaciones 33-46, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^1 es NR^AR^B .

52. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es heteroarilo opcionalmente sustituido con 1, 2,

3, 4, o 5 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, $\text{OC}(\text{O})\text{R}^{b1}$, $\text{OC}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{R}^{b1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{OR}^{a1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S}(\text{O})\text{R}^{b1}$, $\text{NR}^{c1}\text{S}(\text{O})_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})\text{R}^{b1}$, $\text{S}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, y $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$.

53. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es heteroarilo bicíclico opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, $\text{OC}(\text{O})\text{R}^{b1}$, $\text{OC}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{R}^{b1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{OR}^{a1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S}(\text{O})\text{R}^{b1}$, $\text{NR}^{c1}\text{S}(\text{O})_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})\text{R}^{b1}$, $\text{S}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, y $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$.

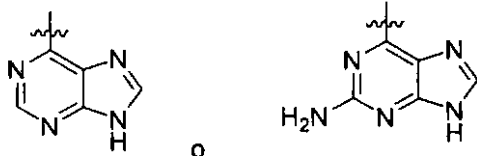
54. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es purinilo opcionalmente sustituido con 1 o 2 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r\text{-Cy}^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, $\text{OC}(\text{O})\text{R}^{b1}$, $\text{OC}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C}(=\text{NR}^e)\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{R}^{b1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{OR}^{a1}$, $\text{NR}^{c1}\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{NR}^{c1}\text{S}(\text{O})\text{R}^{b1}$, $\text{NR}^{c1}\text{S}(\text{O})_2\text{R}^{b1}$, $\text{NR}^{c1}\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})\text{R}^{b1}$, $\text{S}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, y $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$.

55. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es purinilo opcionalmente sustituido con 1 o 2 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, $\text{NR}^{c5}\text{R}^{d5}$, $\text{NR}^{c5}\text{C}(\text{O})\text{R}^{b5}$, $\text{NR}^{c5}\text{C}(\text{O})\text{NR}^{c5}\text{R}^{d5}$, $\text{NR}^{c5}\text{C}(\text{O})\text{OR}^{a5}$, $\text{NR}^{c5}\text{C}(=\text{NR}^f)\text{NR}^{c5}\text{R}^{d5}$, $\text{NR}^{c5}\text{S}(\text{O})_2\text{R}^{b5}$, $\text{NR}^{c5}\text{S}(\text{O})_2\text{NR}^{c5}\text{R}^{d5}$, y $\text{S}(\text{O})_2\text{NR}^{c5}\text{R}^{d5}$.

56. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable

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farmacéuticamente del mismo, caracterizado porque R^A es:



57. El compuesto de cualquiera de las reivindicaciones 33-51, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^A es heteroarilo bicíclico opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre $-(C_{1-4} \text{ alquil})_r$, $-Cy^1$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, y $S(O)_2NR^{c1}R^{d1}$.

58. El compuesto de cualquiera de las reivindicaciones 33-57, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^B y R^C se seleccionan en forma independiente entre H y C_{1-6} alquilo.

59. El compuesto de cualquiera de las reivindicaciones 33-57, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^B y R^C son cada uno H.

60. El compuesto de cualquiera de las reivindicaciones 33-59, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{2a} es H, halo, OH, CN, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, y $S(O)_2NR^{c2}R^{d2}$.

61. El compuesto de cualquiera de las reivindicaciones 33-59, o una sal aceptable

farmacéuticamente del mismo, caracterizado porque R^{2a} es halo, OH, CN, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo, donde dicho C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo está opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados en forma independiente entre halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{1-6} haloalquilo, halosulfanilo, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, y $S(O)_2NR^{c2}R^{d2}$.

62. El compuesto de cualquiera de las reivindicaciones 33-59, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{2a} es H, halo, OH, CN, C_{1-6} alquilo, C_{1-6} haloalquilo, C_{2-6} alquenilo, o C_{2-6} alquinilo.

63. El compuesto de cualquiera de las reivindicaciones 33-59, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^{2a} es metilo o etilo.

64. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilalquilo, donde dicho C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, o heterocicloalquilalquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, y $S(O)_2NR^{c3}R^{d3}$.

65. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es H, halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$,

$C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, o C_{1-6} alquilo, donde dicho C_{1-6} alquilo, está opcionalmente sustituido con 1, 2, 3, 4, o 5 sustituyentes seleccionados en forma independiente entre halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, y $S(O)_2NR^{c3}R^{d3}$.

66. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es H o C_{1-6} alquilo.

67. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es C_{1-6} alquilo.

68. El compuesto de cualquiera de las reivindicaciones 33-63, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^3 es metilo.

69. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^4 , R^5 , y R^6 se seleccionan en forma independiente entre H, halo, C_{1-6} alquilo, o C_{1-6} haloalquilo.

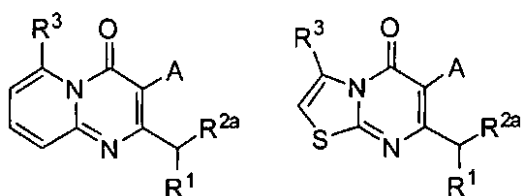
70. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^4 , R^5 , y R^6 son cada uno H.

71. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^4 es H.

72. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^5 es H.

73. El compuesto de cualquiera de las reivindicaciones 33-68, o una sal aceptable farmacéuticamente del mismo, caracterizado porque R^6 es H.

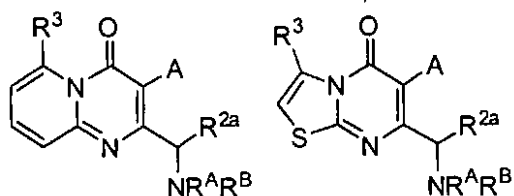
74. El compuesto de cualquiera de las reivindicaciones 33-73, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula Ig o Iie:



Ig

IIe.

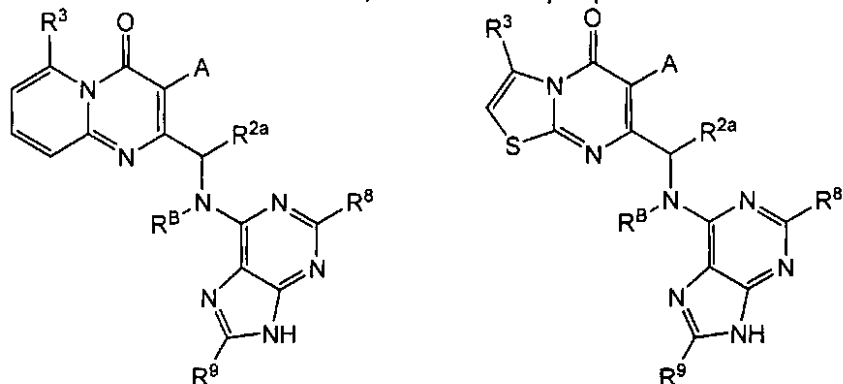
75. El compuesto de cualquiera de las reivindicaciones 33-74, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula Ih o IIf:



Ih

IIf.

76. El compuesto de cualquiera de las reivindicaciones 33-75, o una sal aceptable farmacéuticamente del mismo, caracterizado porque es de fórmula Ii o IIg:



Ii

IIg

donde R^8 y R^9 se seleccionan en forma independiente entre H, C_{1-6} alquilo, C_{1-6} haloalquilo, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, y $S(O)_2NR^{c5}R^{d5}$.

77. El compuesto de la reivindicación 1, es seleccionado de:

2-[1-(6-amino-9H-purin-9-il)etil]-6-metil-3-fenil-4H-pirido[1,2-a]pirimidin-4-ona;

6-metil-3-fenil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
 3-(5-fluoropiridin-3-il)-6-metil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
 3-(3-fluorofenil)-6-metil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
 3-(3,5-difluorofenil)-6-metil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
 3-(2-fluoropiridin-3-il)-6-metil-2-[1-(9H-purin-6-ilamino)propil]-4H-pirido[1,2-a]pirimidin-4-ona;
 6-metil-2-[1-(9H-purin-6-ilamino)propil]-3-(1H-pirazol-4-il)-4H-pirido[1,2-a]pirimidin-4-ona;
 3-metil-6-fenil-7-[1-(9H-purin-6-ilamino)etil]-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
 7-{1-[(2-amino-9H-purin-6-il)amino]etil}-3-metil-6-fenil-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
 6-(3-fluorofenil)-3-metil-7-[1-(9H-purin-6-ilamino)etil]-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
 7-{1-[(2-amino-9H-purin-6-il)amino]etil}-6-(3-fluorofenil)-3-metil-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
 6-(3,5-difluorofenil)-3-metil-7-[1-(9H-purin-6-ilamino)etil]-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;
 7-{1-[(2-amino-9H-purin-6-il)amino]etil}-6-(3,5-difluorofenil)-3-metil-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona;

3-metil-7-[1-(9H-purin-6-ilamino)etil]-6-piridin-2-il-5H-[1,3]tiazolo[3,2-a]pirimidin-5-ona, o una sal aceptable farmacéuticamente de cualquier de las mencionadas precedentemente.

78. El compuesto de la reivindicación 1, caracterizado porque el compuesto es (S)-7-(1-(9H-purin-6-ilamino)etil)-6-(3-fluorofenil)-3-metil-5H-tiazolo[3,2-a]pirimidin-5-ona; o una sal aceptable farmacéuticamente del mismo.

79. Una composición que comprende un compuesto de conformidad con cualquiera de las reivindicaciones 1-78, o una sal aceptable farmacéuticamente de la misma, y al menos un vehículo aceptable farmacéuticamente.

80. Un método para modular la actividad de una PI3K quinasa caracterizado porque comprende poner en contacto la quinasa con un compuesto de cualquiera de las reivindicaciones 1-78, o una sal del mismo farmacéuticamente aceptable.

81. El método de la reivindicación 80 caracterizado porque la PI3K se selecciona entre el grupo que consiste en PI3K α , PI3K β , PI3K γ , y PI3K δ .
82. El método de la reivindicación 80 caracterizado porque dicha PI3K comprende una mutación.
83. El método de cualquiera de las reivindicaciones 80-82 caracterizado porque dicha modulación es una inhibición.
84. El método de cualquiera de las reivindicaciones 80-82 caracterizado porque dicho compuesto es un inhibidor selectivo de PI3K δ respecto de uno o más de PI3K α , PI3K β , y PI3K γ .
85. Un método para tratar una enfermedad en un paciente, caracterizado porque dicha enfermedad está asociada con la expresión o actividad anormal de una PI3K quinasa, que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1-78, o una sal del mismo farmacéuticamente aceptable.
86. El método de la reivindicación 85 caracterizado porque dicha enfermedad es osteoartritis, restenosis, aterosclerosis, trastornos de los huesos, artritis, retinopatía diabética, psoriasis, hipertrofia prostática benigna, aterosclerosis, inflamación, angiogénesis, pancreatitis, enfermedad renal, enfermedad inflamatoria del intestino, miastenia gravis, esclerosis múltiple, o síndrome de Sjogren.
87. El método de la reivindicación 85 caracterizado porque la PI3K se selecciona entre el grupo que consiste en PI3K α , PI3K β , PI3K γ , y PI3K δ .
88. El método de la reivindicación 85 caracterizado porque la PI3K es PI3K δ .
89. El método de cualquiera de las reivindicaciones 85-88 caracterizado porque se administra más de uno de dichos compuestos.
90. El método de la reivindicación 89 caracterizado porque el compuesto se administra en combinación con un inhibidor de quinasa que inhibe a una quinasa diferente de una PI3K quinasa.
91. Un método para tratar una enfermedad de base inmune en un paciente, caracterizado porque comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1-78, o una sal del mismo farmacéuticamente aceptable.

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92. El método de la reivindicación 91 caracterizado porque dicha enfermedad de base inmune es artritis reumatoide, alergia, asma, glomerulonefritis, lupus, o una inflamación relacionada con cualquiera de las mencionadas anteriormente.

93. Un método para tratar cáncer en un paciente, caracterizado porque comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1-78, o una sal del mismo farmacéuticamente aceptable.

94. El método de la reivindicación 93 caracterizado porque dicho cáncer es cáncer de mama, de próstata, de colon, endometrial, del cerebro, de vejiga, de piel, de útero, de ovarios, de pulmón, pancreático, renal, gástrico, o hematológico.

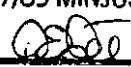
95. El método de la reivindicación 94 caracterizado porque dicho cáncer hematológico es leucemia mieloblástica aguda, leucemia mieloide crónica, o linfoma de células B.

96. Un método para tratar una enfermedad pulmonar en un paciente, caracterizado porque comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1-78, o una sal del mismo farmacéuticamente aceptable.

97. El método de la reivindicación 96 caracterizado porque dicha enfermedad pulmonar es lesión pulmonar aguda (ALI) o síndrome de angustia respiratoria en adultos (ARDS).

Traducido según mi mejor saber y entender, este día 22 de diciembre de 2011, en la ciudad de Bogotá, D.C., por Anita Escobar de Tamayo, Traductora Oficial, Res. 2177 de 1989, Ministerio de Justicia, República de Colombia.

TRADUCTORA OFICIAL
RES. 2177/89 MINJUSTICIA


ANITA ESCOBAR DE TAMAYO



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

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December 02, 2011

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APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.**

APPLICATION NUMBER: 61/259,765

FILING DATE: November 10, 2009

**THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY
APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS
CONVENTION, IS US61/259,765**

**By Authority of the
Under Secretary of Commerce for Intellectual Property
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N. Williams
N. WILLIAMS

Certifying Officer

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Electronic Acknowledgement Receipt

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Confirmation Number:	1698
Title of Invention:	PYRIMIDINONES AS PI3K INHIBITORS
First Named Inventor/Applicant Name:	Yun-Long Li
Customer Number:	26161
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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1	Transmittal of New Application	transmittal.pdf	50639 daa90db120a7265513476fa17d57173d91a58d16	no	1
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Information:					
2		application.pdf	6222655 4d5e03fd7ee832bcab1ac55312717289e71eeae	yes	117
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	85	
	Claims		86	114	
	Abstract		115	115	
	Drawings-only black and white line drawings		116	117	
Warnings:					
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Warnings:					
Information:					
Total Files Size (in bytes):			6303046		
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. §1.53(c).

INVENTOR(S)					
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)			
Yun-Long Brian W. Andrew P.	Li Metcalf Combs	Chadds Ford, PA Moraga, CA Kennett Square, PA			
Additional inventors are being named on the <u>0</u> separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
PYRIMIDINONES AS PI3K INHIBITORS					
CORRESPONDENCE ADDRESS					
Direct all correspondence to:					
☒ Customer Number: 26161					
OR					
☐ Firm or Individual Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	
ENCLOSED APPLICATION PARTS (check all that apply)					
☐ Application Data Sheet. See 37 C.F.R. § 1.76. ☐ CD(s), Number					
☒ Specification Number of Pages <u>115</u> ☐ Other (specify):					
☒ Drawing(s) Number of Sheets <u>2</u>					
Application Size Fee: If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$270 (\$135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. § 41(a)(1)(G) and 37 C.F.R. § 1.16(s)					
METHOD OF PAYMENT OF FILING FEES AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT					
☐ Applicant Claims small entity status. See 37 C.F.R. § 1.27.					
☐ A check or money order is enclosed to cover the filing fees.					
☐ Payment by credit card. Form PTO-2038 is attached.					
☒ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit					
Account Number <u>06-1050</u> A copy of this form is enclosed for fee processing. TOTAL FEE AMOUNT (\$) 220.00					
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government. ☒ No. ☐ Yes, the name of the U.S. Government agency and the Government contract number are:					

Respectfully submitted,

Signature:



Date: November 10, 2009

Susanne H. Goodson, Ph.D., Reg. No. 58,450

Telephone No: (302) 652-5070

Docket No: 20443-0183P02 / INCY0096-002

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PYRIMIDINONES AS PI3K INHIBITORS

5 FIELD OF THE INVENTION

The present invention provides pyrimidinones that modulate the activity of phosphoinositide 3-kinases (PI3Ks) and are useful in the treatment of diseases related to the activity of PI3Ks including, for example, inflammatory disorders, immune-based disorders, cancer, and other diseases.

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BACKGROUND OF THE INVENTION

The phosphoinositide 3-kinases (PI3Ks) belong to a large family of lipid signaling kinases that phosphorylate phosphoinositides at the D3 position of the inositol ring (Cantley, Science, 2002, 296(5573):1655-7). PI3Ks are divided into three classes (class I, II, and III) according to their structure, regulation and substrate specificity. Class I PI3Ks, which include PI3K α , PI3K β , PI3K γ , and PI3K δ , are a family of dual specificity lipid and protein kinases that catalyze the phosphorylation of phosphatidylinosito-4,5-bisphosphate (PIP₂) giving rise to phosphatidylinosito-3,4,5-trisphosphate (PIP₃). PIP₃ functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion and migration. All four class I PI3K isoforms exist as heterodimers composed of a catalytic subunit (p110) and a tightly associated regulatory subunit that controls their expression, activation, and subcellular localization. PI3K α , PI3K β , and PI3K δ associate with a regulatory subunit known as p85 and are activated by growth factors and cytokines through a tyrosine kinase-dependent mechanism (Jimenez, et al., J Biol Chem., 2002, 277(44):41556-62) whereas PI3K γ associates with two regulatory subunits (p101 and p84) and its activation is driven by the activation of G-protein-coupled receptors (Brock, et al., J Cell Biol., 2003, 160(1):89-99). PI3K α and PI3K β are ubiquitously expressed. In contrast, PI3K γ and PI3K δ are predominantly expressed in leukocytes (Vanhaesebroeck, et al., Trends Biochem Sci., 2005, 30(4):194-204).

The differential tissue distribution of the PI3K isoforms factors in their distinct biological functions. Genetic ablation of either PI3K α or PI3K β results in embryonic lethality, indicating that PI3K α and PI3K β have essential and non-redundant functions, at least during development

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(Vanhaesebroeck, et al., 2005). In contrast, mice which lack PI3K γ and PI3K δ are viable, fertile and have a normal life span although they show an altered immune system. PI3K γ deficiency leads to impaired recruitment of macrophages and neutrophils to sites of inflammation as well as impaired T cell activation (Sasaki, et al., Science, 2000, 287(5455):1040-6). PI3K δ -mutant mice have specific defects in B cell signaling that lead to impaired B cell development and reduced antibody responses after antigen stimulation (Clayton, et al., J. Exp. Med. 2002, 196(6):753-63; Jou, et al., Mol. Cell Biol. 2002, 22(24):8580-91; Okkenhaug, et al., Science, 2002, 297(5583):1031-4).

The phenotypes of the PI3K γ and PI3K δ -mutant mice suggest that these enzymes may play a role in inflammation and other immune-based diseases and this is borne out in preclinical models. PI3K γ -mutant mice are largely protected from disease in mouse models of rheumatoid arthritis (RA) and asthma (Camps, et al., Nat Med. 2005, 11(9):936-43; Thomas, et al., Eur. J. Immunol., 2005, 35(4):1283-91). In addition, treatment of wild-type mice with a selective inhibitor of PI3K γ was shown to reduce glomerulonephritis and prolong survival in the MRL-lpr model of systemic lupus nephritis (SLE) and to suppress joint inflammation and damage in models of RA (Barber, et al., Nat Med. 2005, 11(9):933-5; Camps, et al., 2005). Similarly, both PI3K δ -mutant mice and wild-type mice treated with a selective inhibitor of PI3K δ have been shown to have attenuated allergic airway inflammation and hyper-responsiveness in a mouse model of asthma (Ali, et al., Nature. 2004, 431(7011):1007-11; Lee, et al., FASEB J. 2006, 20(3):455-65) and to have attenuated disease in a model of RA (Randis, et al., Eur. J. Immunol., 2008, 38(5):1215-24).

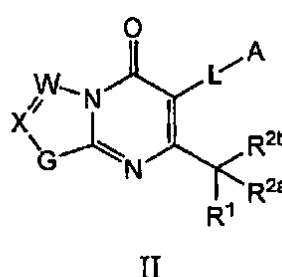
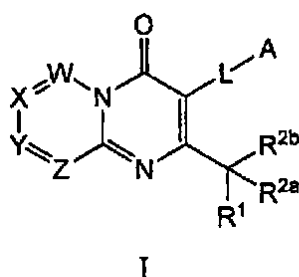
In addition to their potential role in inflammatory diseases, all four class I PI3K isoforms may play a role in cancer. The gene encoding p110 α is mutated frequently in common cancers, including breast, prostate, colon and endometrial (Samuels, et al., Science, 2004, 304(5670):554; Samuels, et al., Curr. Opin. Oncol. 2006, 18(1):77-82). Eighty percent of these mutations are represented by one of three amino acid substitutions in the helical or kinase domains of the enzyme and lead to a significant upregulation of kinase activity resulting in oncogenic transformation in cell culture and in animal models (Kang, et al., Proc. Natl. Acad. Sci. U.S.A. 2005, 102(3):802-7; Bader, et al., Proc. Natl. Acad. Sci. U.S.A. 2006, 103(5):1475-9). No such mutations have been identified in the other PI3K isoforms although there is evidence that they can contribute to the development and progression of malignancies. Consistent overexpression

of PI3K δ is observed in acute myeloblastic leukemia (Sujobert, et al., Blood, 2005, 106(3):1063-6) and inhibitors of PI3K δ can prevent the growth of leukemic cells (Billottet, et al., Oncogene. 2006, 25(50):6648-59). Elevated expression of PI3K γ is seen in chronic myeloid leukemia (Hickey, et al., J. Biol. Chem. 2006, 281(5):2441-50). Alterations in expression of PI3K β , PI3K γ and PI3K δ have also been observed in cancers of the brain, colon and bladder (Benistant, et al., Oncogene, 2000, 19(44):5083-90; Mizoguchi, et al., Brain Pathol. 2004, 14(4):372-7; Knobbe, et al., Neuropathol. Appl. Neurobiol. 2005, 31(5):486-90). Further, these isoforms have all been shown to be oncogenic in cell culture (Kang, et al., 2006).

Thus, new or improved agents which inhibit kinases such as PI3K are continually needed for developing new and more effective pharmaceuticals that are aimed at augmentation or suppression of the immune and inflammatory pathways (such as immunosuppressive agents for organ transplants), as well as agents for the prevention and treatment of autoimmune diseases (e.g., multiple sclerosis, rheumatoid arthritis, asthma, type I diabetes, inflammatory bowel disease, Crohn's disease, autoimmune thyroid disorders, Alzheimer's disease, nephritis), diseases involving a hyperactive inflammatory response (e.g., eczema), allergies, lung diseases, cancer (e.g., prostate, breast, leukemia, multiple myeloma), and some immune reactions (e.g., skin rash or contact dermatitis or diarrhea) caused by other therapeutics. The compounds, compositions, and methods described herein are directed toward these needs and other ends.

SUMMARY OF THE INVENTION

The present invention provides, *inter alia*, compounds of Formula I or II:



or pharmaceutically acceptable salts thereof, wherein constituent members are defined herein.

The present invention further provides pharmaceutical compositions comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

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The present invention further provides methods of modulating an activity of one or more kinases (such as a PI3K) comprising contacting the kinase with a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

The present invention further provides methods of treating a disease or a disorder associated with abnormal kinase expression or activity in a patient by administering to a patient a therapeutically effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt of the same.

The present invention further provides methods of treating diseases such as immune-based diseases, cancer, and lung diseases in a patient by administering to the patient a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

The present invention further provides a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, for use in therapy.

The present invention further provides use of a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, for the production of a medicament for use in therapy.

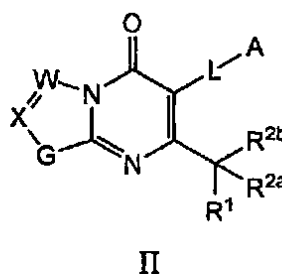
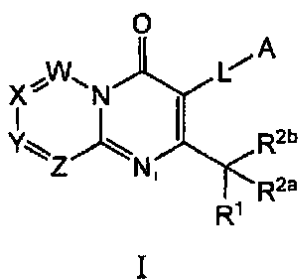
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. X-ray crystal structure of Example 15, step 5.

Figure 2. X-ray crystal structure lattice of Example 15, step 5.

DETAILED DESCRIPTION

The present invention provides, *inter alia*, compounds that modulate the activity of one or more PI3Ks and are useful, for example, in the treatment of various diseases such as those associated with expression or activity of one or more PI3Ks. The compounds of the invention include those of Formula I or II:



or pharmaceutically acceptable salts thereof, wherein:

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A is C₁₋₁₀ alkyl, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d,
 5 NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;
 wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a,
 10 C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

L is absent, (CR^{7a}R^{7b})_m, (CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)
 (CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)₂(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q,
 15 (CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q,
 (CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q, or (CR^{7a}R^{7b})_pNR^{7c}S(O)₂(CR^{7a}R^{7b})_q;

W is N or CR³;

X is N or CR⁴;

Y is N or CR⁵;

20 Z is N or CR⁶;

G is O, S, or NR^N;

R¹ is OR^A, SR^A, S(O)R^A, S(O)₂R^A, NR^AR^B, NR^CC(O)NR^AR^B, NR^CC(O)OR^A,
 NR^CC(=NR^E)NR^AR^B, NR^CS(O)₂R^A, NR^CS(O)₂NR^CR^A, heterocycloalkyl, or heteroaryl, wherein
 said heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents
 25 independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1},
 OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1},
 NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1},
 S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

30 R^{2a} and R^{2b} are independently selected from H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl,

heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2},

or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl ring or a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl ring, each optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

R³, R⁴, R⁵, and R⁶ are independently selected from H, halo, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)₂NR^{c3}R^{d3}, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

R^{7a} and R^{7b} are independently selected from H, halo, or C₁₋₄ alkyl;

R^{7c} is H or C₁₋₄ alkyl;

R^{7d} is H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, or C(O)NR^{c5}R^{d5};

R^A is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1},

SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1},
 NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1},
 NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and
 S(O)₂NR^{c1}R^{d1};

5 R^B and R^C are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl,
 cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and
 heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl,
 heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl
 is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl,
 10 C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5},
 OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5},
 NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and
 S(O)₂NR^{c5}R^{d5};

R^E is H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, or C(O)NR^{c5}R^{d5};

15 R^N is H or C₁₋₄ alkyl;

Cy¹ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1,
 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
 C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1},
 OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1},
 20 NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1},
 S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^a, R^b, R^c, and R^d are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
 alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl,
 and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl,
 25 heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl
 is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl,
 C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5},
 OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5},
 NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and
 30 S(O)₂NR^{c5}R^{d5};

or R^c and R^d together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5},
 5 NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a1}, R^{b1}, R^{c1}, and R^{d1} are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl,
 10 heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and
 15 S(O)₂NR^{c5}R^{d5};

or R^{e1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and
 20 S(O)₂NR^{c5}R^{d5};

R^{a2}, R^{b2}, R^{c2}, and R^{d2} are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl,
 25 heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and
 30 S(O)₂NR^{c5}R^{d5};

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or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a3} , R^{b3} , R^{c3} , and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^e and R^f are independently selected from H, CN, NO_2 , OR^{a5} , SR^{b5} , $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, and $C(O)NR^{c5}R^{d5}$;

R^{a5} , R^{b5} , R^{c5} , and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $di(C_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

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or R^{cs} and R^{ds} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

p is 0, 1, 2, 3, or 4;

q is 0, 1, 2, 3, or 4; and

r is 0 or 1.

In some embodiments, the compounds of the invention have Formula I.

In some embodiments, the compounds of the invention have Formula II.

In some embodiments, A is C₁₋₁₀ alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments, A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂,

OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d,
 NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b,
 NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments, A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4,
 5 or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆
 haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a,
 C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a,
 NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b,
 NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆
 10 alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted
 with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
 alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a,
 OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b,
 NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d,
 15 S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments, L is absent.

In some embodiments, L is (CR^{7a}R^{7b})_m, (CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q,
 (CR^{7a}R^{7b})_pS(O)(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)₂(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q,
 (CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q,
 20 (CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q, or (CR^{7a}R^{7b})_pNR^{7c}S(O)₂(CR^{7a}R^{7b})_q.

In some embodiments, L is (CR^{7a}R^{7b})_m.

In some embodiments, W is N.

In some embodiments, W is CR³.

In some embodiments, X is N.

25 In some embodiments, X is CR⁴.

In some embodiments, Y is N.

In some embodiments, Y is CR⁵.

In some embodiments, Z is N.

In some embodiments, Z is CR⁶.

30 In some embodiments, not more than 2 of W, X, Y, or Z are N.

In some embodiments, not more than 3 of W, X, Y, or Z are N.

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In some embodiments, one of W and X is N.

In some embodiments, G is O.

In some embodiments, G is S.

In some embodiments, G is NR^N .

- 5 In some embodiments, R^1 is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from $-(\text{C}_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{OC}(\text{O})\text{R}^{\text{b1}}$, $\text{OC}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$.

In some embodiments, R^1 is $\text{NR}^{\text{A}}\text{R}^{\text{B}}$.

- In some embodiments, $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ are independently selected from H and C_{1-6} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{OC}(\text{O})\text{R}^{\text{b2}}$, $\text{OC}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{S}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})_2\text{R}^{\text{b2}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$.

In some embodiments, at least one of $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ is other than H.

- In some embodiments, R^3 , R^4 , R^5 , and R^6 are independently selected from H or C_{1-6} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{OC}(\text{O})\text{R}^{\text{b3}}$, $\text{OC}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})\text{R}^{\text{b3}}$, $\text{S}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$.

- 25 In some embodiments, R^3 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{OC}(\text{O})\text{R}^{\text{b3}}$, $\text{OC}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})\text{R}^{\text{b3}}$, $\text{S}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$.

- 30 In some embodiments, R^4 , R^5 , and R^6 are each H.

In some embodiments, $\text{R}^{7\text{a}}$, $\text{R}^{7\text{b}}$, $\text{R}^{7\text{c}}$, and $\text{R}^{7\text{d}}$ are each H.

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In some embodiments, R^A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

In some embodiments, R^B and R^C are independently selected from H and C_{1-6} alkyl.

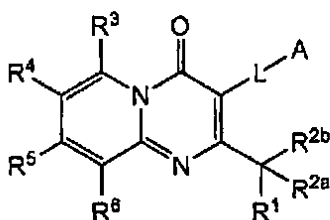
In some embodiments, A is other than phenyl substituted at the 4-position by halogen.

In some embodiments, r is 0.

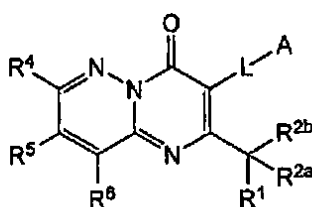
In some embodiments, r is 1.

In some embodiments, the compounds of the invention have Formula Ia, Ib, Ic, Id, Ie, IIa,

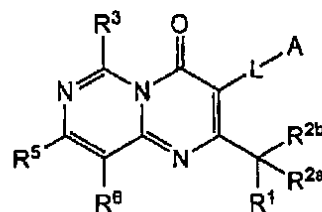
IIb, or IIc:



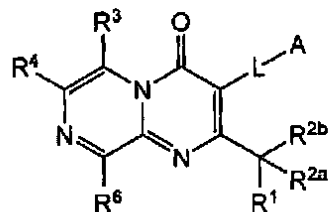
Ia



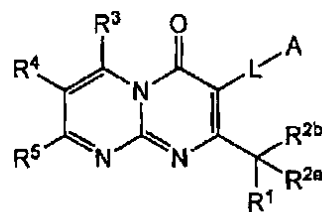
Ib



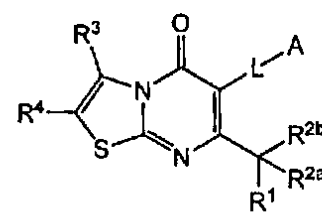
Ic



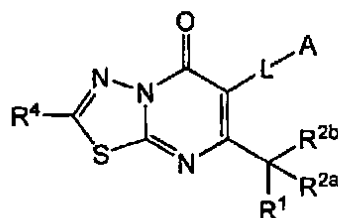
Id



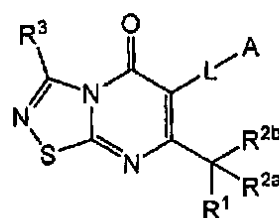
Ie



IIa



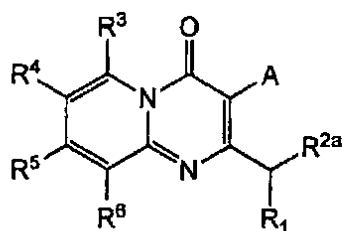
IIb



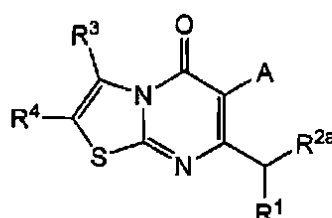
IIc.

In some embodiments, the compounds of the invention have Formula If or IId:

138



If



IId.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId:

- 5 A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;
- 10
- 15

- R¹ is OR^a, SR^a, S(O)R^a, S(O)₂R^a, NR^aR^b, NR^cC(O)NR^aR^b, NR^cC(O)OR^a, NR^cC(=NR^e)NR^aR^b, NR^cS(O)₂R^a, NR^cS(O)₂NR^cR^a, heterocycloalkyl, or heteroaryl, wherein said heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from -(C₁₋₄ alkyl)_x-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};
- 20

- 25 R^{2a} is H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or

heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

R³, R⁴, R⁵, and R⁶ are independently selected from H, halo, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)₂NR^{c3}R^{d3}, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl,

heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

R^A is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^B and R^C are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5},

$\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{E} is H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, or $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

Cy^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{OC}(\text{O})\text{R}^{\text{b1}}$, $\text{OC}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$;

R^{a} , R^{b} , R^{c} , and R^{d} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

or R^{c} and R^{d} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

$$\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}, \text{S}(\text{O})\text{R}^{\text{b5}}, \text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}, \text{S}(\text{O})_2\text{R}^{\text{b5}}, \text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}, \text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}, \text{and } \text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}};$$

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a2} , R^{b2} , R^{c2} , and R^{d2} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a3} , R^{b3} , R^{c3} , and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$,

$\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{e} and R^{f} are independently selected from H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{a5} , R^{b5} , R^{c5} , and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $\text{di}(\text{C}_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $\text{di}(\text{C}_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy; and

r is 0 or 1.

In some embodiments of compounds of Formulas I and Ia-If, when A is 3-fluorophenyl; $\text{R}^{2\text{a}}$ is H; R^3 is methyl; and R^4 , R^5 , and R^6 are H; then R^1 is other than 4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl.

In some embodiments of compounds of Formulas I and Ia-If, when A is 1,3-dioxolan-2-yl; $\text{R}^{2\text{a}}$, R^3 , R^4 , and R^6 are H; then R^1 is other than 1-(tert-butoxycarbonyl)piperidin-4-yl.

In some embodiments of compounds of Formulas I and Ia-If, R^1 is other than a substituted or unsubstituted pyrazolo[3,4-d]pyrimidin-1-yl group.

In some embodiments of compounds of Formulas I and Ia-If, R¹ is other than a substituted or unsubstituted piperidinyl group.

In some embodiments, the compound has Formula Ia.

In some embodiments, the compound has Formula Ib.

5 In some embodiments, the compound has Formula Ic.

In some embodiments, the compound has Formula Id.

In some embodiments, the compound has Formula Ie.

In some embodiments, the compound has Formula If.

In some embodiments, the compound has Formula IIa.

10 In some embodiments, the compound has Formula IIb.

In some embodiments, the compound has Formula IIc.

In some embodiments, the compound has Formula IId.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$.

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In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is phenyl.

- 5 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d,
 10 NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d,
 15 NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

- In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is 6-membered heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5
 20 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is pyridyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is 5-membered heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, A is pyrazolyl optionally substituted with 1 or 2 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R¹ is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R¹ is bicyclic heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1},

NR^{cl}S(O)R^{bl}, NR^{cl}S(O)₂R^{bl}, NR^{cl}S(O)₂NR^{cl}R^{d1}, S(O)R^{bl}, S(O)NR^{cl}R^{d1}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{d1}.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R¹ is purinyl optionally substituted with -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{al}, SR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, OC(O)R^{bl}, OC(O)NR^{cl}R^{d1}, C(=NR^e)NR^{cl}R^{d1}, NR^{cl}C(=NR^e)NR^{cl}R^{d1}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}C(O)NR^{cl}R^{d1}, NR^{cl}S(O)R^{bl}, NR^{cl}S(O)₂R^{bl}, NR^{cl}S(O)₂NR^{cl}R^{d1}, S(O)R^{bl}, S(O)NR^{cl}R^{d1}, S(O)₂R^{bl}, or S(O)₂NR^{cl}R^{d1}.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R¹ is OR^A, SR^A, S(O)R^A, S(O)₂R^A, NR^AR^B, NR^CC(O)NR^AR^B, NR^CC(O)OR^A, NR^CC(=NR^E)NR^AR^B, NR^CS(O)₂R^A, or NR^CS(O)₂NR^CR^A.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R¹ is NR^AR^B.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{al}, SR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, OC(O)R^{bl}, OC(O)NR^{cl}R^{d1}, C(=NR^e)NR^{cl}R^{d1}, NR^{cl}C(=NR^e)NR^{cl}R^{d1}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}C(O)NR^{cl}R^{d1}, NR^{cl}S(O)R^{bl}, NR^{cl}S(O)₂R^{bl}, NR^{cl}S(O)₂NR^{cl}R^{d1}, S(O)R^{bl}, S(O)NR^{cl}R^{d1}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{d1}.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{al}, SR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, OC(O)R^{bl}, OC(O)NR^{cl}R^{d1}, C(=NR^e)NR^{cl}R^{d1}, NR^{cl}C(=NR^e)NR^{cl}R^{d1}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}C(O)NR^{cl}R^{d1}, NR^{cl}S(O)R^{bl}, NR^{cl}S(O)₂R^{bl}, NR^{cl}S(O)₂NR^{cl}R^{d1}, S(O)R^{bl}, S(O)NR^{cl}R^{d1}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{d1}.

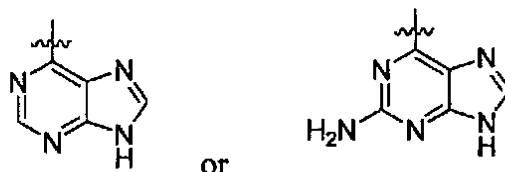
In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{al}, SR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{d1}, C(O)OR^{al}, OC(O)R^{bl}, OC(O)NR^{cl}R^{d1}, C(=NR^e)NR^{cl}R^{d1}, NR^{cl}C(=NR^e)NR^{cl}R^{d1}, NR^{cl}R^{d1}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}C(O)NR^{cl}R^{d1}, NR^{cl}S(O)R^{bl}, NR^{cl}S(O)₂R^{bl}, NR^{cl}S(O)₂NR^{cl}R^{d1}, S(O)R^{bl}, S(O)NR^{cl}R^{d1}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{d1}.

$\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{A} is purinyl optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl, C_{1-6}

haloalkyl, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{A} is:



In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{A} is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(\text{C}_{1-4}\text{ alkyl})_r\text{-Cy}^{\text{l}}$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{OC}(\text{O})\text{R}^{\text{b1}}$, $\text{OC}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{B} and R^{C} are independently selected from H and C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{B} and R^{C} are each H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, $\text{R}^{2\text{a}}$ is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{OC}(\text{O})\text{R}^{\text{b2}}$, $\text{OC}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{S}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})_2\text{R}^{\text{b2}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$.

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In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^{2a} is methyl or ethyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is H, halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, or C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}C(O)OR^{a3}$, $C(=NR^e)NR^{c3}R^{d3}$, $NR^{c3}C(=NR^e)NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is H or C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is C_{1-6} alkyl.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^3 is methyl.

5 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^4 , R^5 , and R^6 are independently selected from H, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

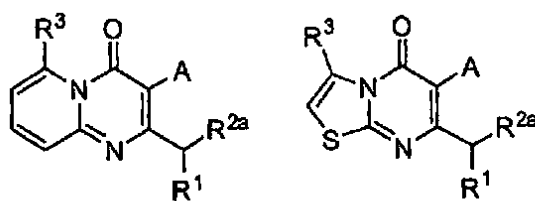
In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^4 , R^5 , and R^6 are each H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^4 is H.

10 In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^5 is H.

In some embodiments of compounds of Formulas I, Ia-If, II, and IIa-IId, R^6 is H.

In some embodiments, the compounds of the invention have Formula Ig or IIe:

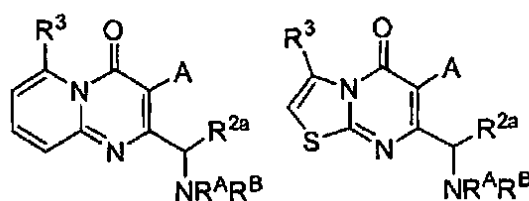


Ig

IIe.

15 In some embodiments of compounds of Formulas Ig and IIe, R^1 is according to any of the previously recited embodiments for R^1 .

In some embodiments, the compounds of the invention have Formula Ih or IIf:

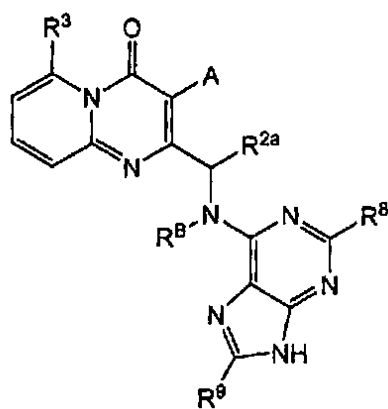


Ih

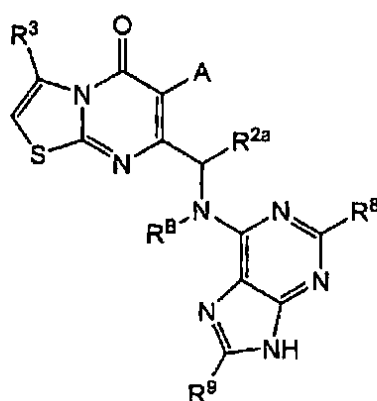
IIf.

20 In some embodiments, of compounds of Formulas Ih and IIf, R^A is according to any of the previously recited embodiments for R^A .

In some embodiments, the compounds of the invention have Formula Ii or IIg:



IIi



IIg.

wherein R^8 and R^9 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

In some embodiments, R^8 and R^9 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}S(O)_2R^{b5}$, and $NR^{c5}S(O)_2NR^{c5}R^{d5}$.

In some embodiments, R^8 and R^9 are independently selected from H and C_{1-6} alkyl.

In some embodiments of compounds of Formulas Ig-IIi and IIe-IIg, A is according to any of the previously recited embodiments for A.

In some embodiments of compounds of Formulas Ig-IIi and IIe-IIg, R^3 is according to any of the previously recited embodiments for R^3 .

In some embodiments of compounds of Formulas Ig-IIi and IIe-IIg, R^{2a} is according to any of the previously recited embodiments for R^{2a} .

In some embodiments of compounds of Formulas Ig-IIi and IIe-IIg, R^B is according to any of the previously recited embodiments for R^B .

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

At various places in the present specification, linking substituents are described. It is specifically intended that each linking substituent include both the forward and backward forms

of the linking substituent. For example, $-NR(CR'R'')_n-$ includes both $-NR(CR'R'')_n-$ and $(CR'R'')_nNR-$. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

As used herein, the term "alkyl" is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. Example alkyl groups include methyl (Me), ethyl (Et), propyl (e.g., n-propyl and isopropyl), butyl (e.g., n-butyl, isobutyl, sec-butyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, sec-pentyl, neopentyl), and the like. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms.

As used herein, "alkenyl" refers to an alkyl group having one or more carbon-carbon double bonds. Example alkenyl groups include ethenyl, propenyl, cyclohexenyl, and the like.

As used herein, "alkynyl" refers to an alkyl group having one or more carbon-carbon triple bonds. Example alkynyl groups include ethynyl, propynyl, and the like.

As used herein, "haloalkyl" refers to an alkyl group having one or more halogen substituents. Example haloalkyl groups include CF_3 , C_2F_5 , CHF_2 , CCl_3 , $CHCl_2$, C_2Cl_5 , and the like.

As used herein, "halosulfanyl" refers to a sulfur group having one or more halogen substituents. Example halosulfanyl groups include pentahalosulfanyl groups such as SF_5 .

As used herein, "aryl" refers to monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms.

As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl, alkenyl, and alkynyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) groups and spirocycles. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido. Cycloalkyl groups also include cycloalkylidenes. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclopentene, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring.

As used herein, "heteroaryl" refers to an aromatic heterocycle having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrol, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. Examples of bicyclic heteroaryl groups include without limitation, purinyl, indolyl, and the like. In some embodiments, any ring-forming N in a heteroaryl moiety can be substituted by oxo. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 4 to about 14, 9 to about 10, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, "heterocycloalkyl" refers to non-aromatic heterocycles having one or more ring-forming heteroatoms such as an O, N, or S atom. Heterocycloalkyl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems as well as spirocycles. Example "heterocycloalkyl" groups include morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxole, benzo-1,4-

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dioxane, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, and the like. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the nonaromatic heterocyclic ring, for example phthalimidyl, naphthalimidyl, and benzo derivatives of heterocycles. The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. The heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heterocycloalkyl group contains 3 to about 14, 4 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. In some embodiments, the heterocycloalkyl group contains 0 to 3 double or triple bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double or triple bonds.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

As used herein, "arylalkyl" refers to alkyl substituted by aryl and "cycloalkylalkyl" refers to alkyl substituted by cycloalkyl. An example arylalkyl group is benzyl.

As used herein, "heteroarylalkyl" refers to alkyl substituted by heteroaryl and "heterocycloalkylalkyl" refers to alkyl substituted by heterocycloalkyl.

As used herein, "amino" refers to NH_2 .

As used herein, "alkoxy" refers to an -O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, *n*-propoxy and isopropoxy), *t*-butoxy, and the like.

As used herein, "haloalkoxy" refers to an -O-(haloalkyl) group.

As used herein, "alkylthio" refers to an -S-alkyl group. Example alkylthio groups include meththio, ethylthio, propylthio (*e.g.*, *n*-propylthio and isopropylthio), and the like.

As used herein, "alkylamino" refers to an -NH-alkyl group. Example alkylamino groups include methylamino, ethylamino, propylamino (*e.g.*, *n*-propylamino and isopropylamino), and the like.

As used herein, "di(alkyl)amino" refers to an $-N(alkyl)_2$ group. Example di(alkyl)amino groups include dimethylamino, diethylamino, dipropylamino (e.g., di(n-propyl)amino and di(isopropyl)amino), and the like.

It should be further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β -camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α -methylbenzylamine (e.g., *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

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Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

The term, “compound,” as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g. hydrates and solvates) or can be isolated.

In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By “substantially isolated” is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof.

Methods for isolating compounds and their salts are routine in the art.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, “ambient temperature” and “room temperature,” as used herein, are understood in the art, and refer generally to a temperature, e.g. a reaction temperature, that is

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about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

Synthesis

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one

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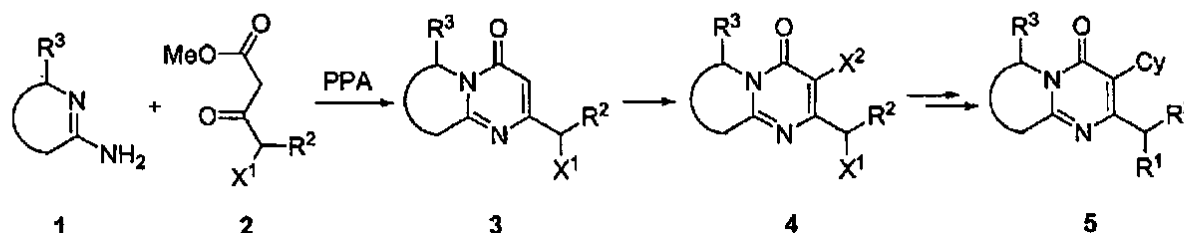
solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ¹H or ¹³C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

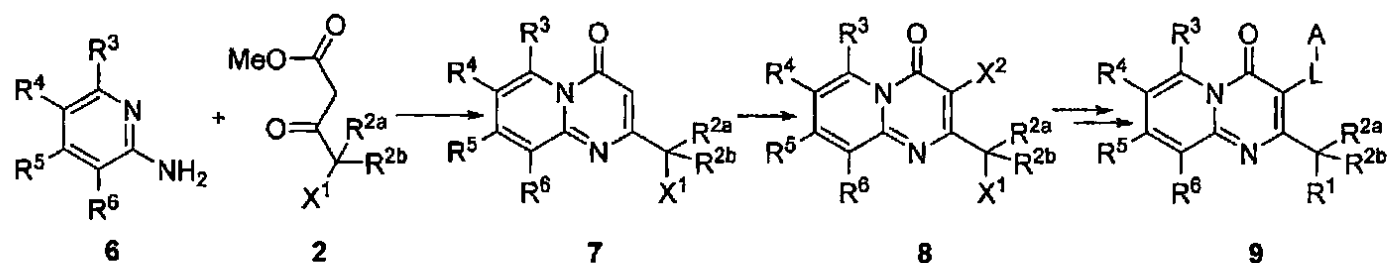
Example synthetic methods for preparing compounds of the invention are provided in the Schemes below. For instance, compounds of the invention can be prepared by the general synthetic procedure shown in Scheme 1. Heteroaryl compounds of formula 1 can react with 4-halo-3-oxo-pentanoates 2 in the presence of polyphosphoric acid (PPA) to provide the compounds of formula 3 via a cyclocondensation reaction. These can be subjected to halogenation reaction under suitable conditions, to provide halogenated compounds 4. Compounds of formula 4 can be transformed to the compounds of formula 5 through any variation of a sequence of steps. X¹ can be replaced with either an azide, an amine, or a heterocyclic group through an S_N2 displacement and eventually transformed to the R¹ group. X² can be converted to a desired cyclic moiety (Cy) through any of the standard cross-coupling reactions, known to one skilled in the art, e.g., using boronic acid derivatives of the desired cyclic moiety.

Scheme 1



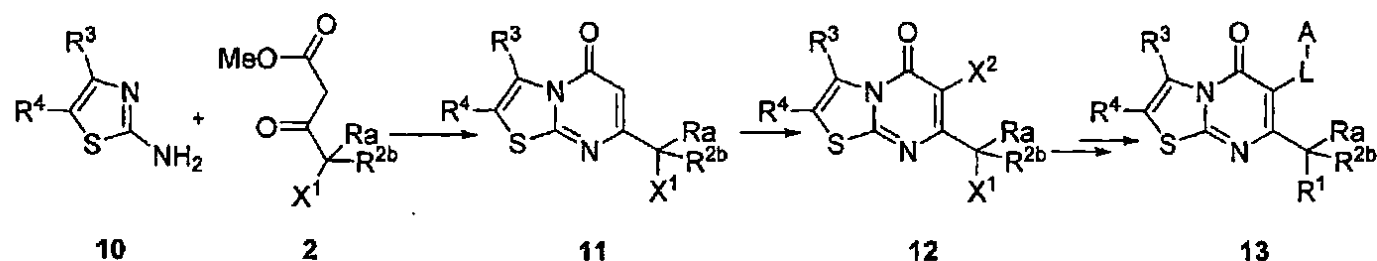
As shown in Scheme 2, the pyrido[1,2-a]pyrimidin-4-ones of the invention can be prepared by cyclocondensation of aminopyrimidines 6 with a β -keto ester 2. Halogenation of the resultant pyridopyrimidinones 7 under suitable conditions (such as NBS or bromine) provides compounds of formula 8. The latter can be transformed to the compounds of formula 9 through an S_N2 substitution of X^1 with a heterocycle R^1 followed by a coupling reaction of X^2 with L-A moiety (such as a Negishi coupling of organozinc reagent; a Suzuki or Stille coupling of an arylboronic acid or arylstanne, respectively). Alternatively, X^1 can be replaced with either an amine or an azide which can be reduced to amine. The amine can then be subjected to coupling reaction with a R^1 moiety to give compounds of formula 9.

Scheme 2



The thiazolo[3,2-a]pyrimidin-5-ones of the invention can be prepared according to Scheme 3. 2-Aminothiazole 10 condensed with a β -keto ester 2 provides thiazolopyrimidinone 11. Compounds of formula 11 can be converted to compounds of formula 13 through any variations of a sequence of steps as described above.

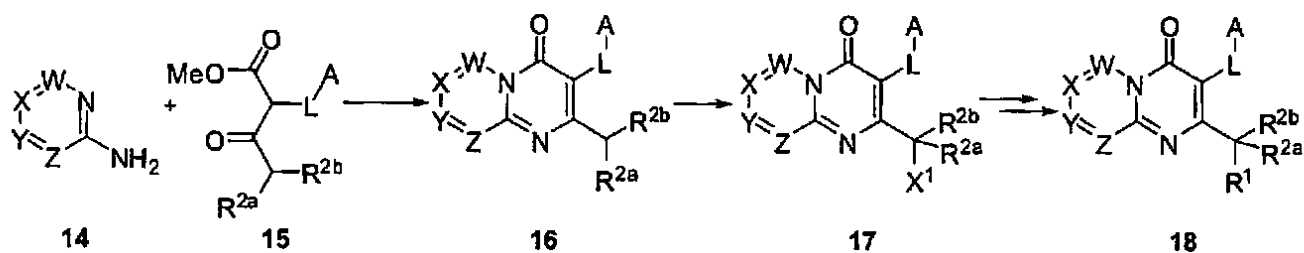
Scheme 3



Alternatively, compounds of the invention can be synthesized by reacting amino heterocycles 14 with an α -substituted β -keto ester 15 shown in Scheme 4. The

cyclocondensation derivatives **16** can then be subjected to halogenation (such as NBS or bromine) or oxidation (such as SeO_2) to afford halogen compounds **17** ($\text{X}^1 = \text{halogen}$), or alcohol compounds **17** ($\text{X} = \text{OH}$), respectively. Compounds of formula **17** can then be transformed to compounds of formula **18** through any variations of a sequence of steps. X^1 can be coupled directly with a heterocycles under any of the cross coupling conditions know to one skilled in the art (such as Buchwald-Hartwig cross coupling conditions) or converted to a halogen then the latter can be coupled with a heterocycles through $\text{S}_{\text{N}}2$ substitutions.

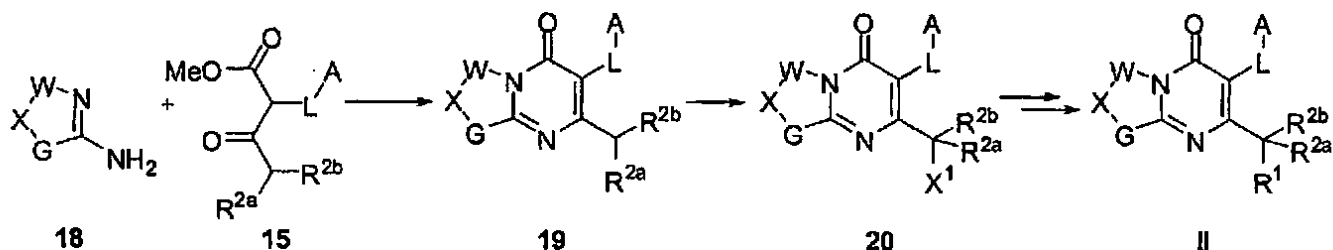
Scheme 4



Compounds of Formula II of the invention can be prepared according to Scheme 5.

Amino heterocycles **19** condensed with α -substituted β -ketone ester **15** affords compounds of formula **20**. The latter can be transformed to compounds of Formula II through any variation of steps described above.

Scheme 5



It should be noted that in all of the Schemes described herein, if there are functional groups present on a substituent group, further modification can be made if appropriate and desired. For example, a CN group can be hydrolyzed to afford an amide group; a carboxylic acid can be

converted to an ester, which in turn can be reduced to an alcohol, which in turn can be further modified. In another example, an OH group can be converted into a better leaving group such as mesylate, which in turn is suitable for nucleophilic substitution, such as by CN. Furthermore, an OH group can be subjected to Mitsunobu reaction conditions with phenol, or heteroaryl alcohol, to afford aryl or heteroaryl ether compounds. One skilled in the art will recognize further modifications.

It should be further noted that the reaction sequences described above can be modified to suit different target molecules. For instance, Cy-boronic acid can be reacted with 4 to generate the Suzuki product first. The X¹ group of the Suzuki product can then be further functionalized with a nucleophilic reagent such as an azide or a heterocyclic amine.

Methods

The compounds of the invention can modulate activity of one or more of various kinases including, for example, phosphoinositide 3-kinases (PI3Ks). The term "modulate" is meant to refer to an ability to increase or decrease the activity of one or more members of the PI3K family. Accordingly, the compounds of the invention can be used in methods of modulating a PI3K by contacting the PI3K with any one or more of the compounds or compositions described herein. In some embodiments, compounds of the present invention can act as inhibitors of one or more PI3Ks. In further embodiments, the compounds of the invention can be used to modulate activity of a PI3K in an individual in need of modulation of the receptor by administering a modulating amount of a compound of the invention, or a pharmaceutically acceptable salt thereof. In some embodiments, modulating is inhibiting.

Given that cancer cell growth and survival is impacted by multiple signaling pathways, the present invention is useful for treating disease states characterized by drug resistant kinase mutants. In addition, different kinase inhibitors, exhibiting different preferences in the kinases which they modulate the activities of, may be used in combination. This approach could prove highly efficient in treating disease states by targeting multiple signaling pathways, reduce the likelihood of drug-resistance arising in a cell, and reduce the toxicity of treatments for disease.

Kinases to which the present compounds bind and/or modulate (e.g., inhibit) include any member of the PI3K family. In some embodiments, the PI3K is PI3K α , PI3K β , PI3K γ , or PI3K δ . In some embodiments, the PI3K is PI3K γ or PI3K δ . In some embodiments, the PI3K is

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PI3K γ . In some embodiments, the PI3K is PI3K δ . In some embodiments, the PI3K includes a mutation. A mutation can be a replacement of one amino acid for another, or a deletion of one or more amino acids. In such embodiments, the mutation can be present in the kinase domain of the PI3K.

5 In some embodiments, more than one compound of the invention is used to inhibit the activity of one kinase (e.g., PI3K γ or PI3K δ).

In some embodiments, more than one compound of the invention is used to inhibit more than one kinase, such as at least two kinases (e.g., PI3K γ and PI3K δ).

10 In some embodiments, one or more of the compounds is used in combination with another kinase inhibitor to inhibit the activity of one kinase (e.g., PI3K γ or PI3K δ).

In some embodiments, one or more of the compounds is used in combination with another kinase inhibitor to inhibit the activities of more than one kinase (e.g., PI3K γ or PI3K δ), such as at least two kinases.

15 The compounds of the invention can be selective. By "selective" is meant that the compound binds to or inhibits a kinase with greater affinity or potency, respectively, compared to at least one other kinase. In some embodiments, the compounds of the invention are selective inhibitors of PI3K γ or PI3K δ over PI3K α and/or PI3K β . In some embodiments, the compounds of the invention are selective inhibitors of PI3K δ (e.g., over PI3K α , PI3K β and PI3K γ). In some
20 embodiments, the compounds of the invention are selective inhibitors of PI3K γ (e.g., over PI3K α , PI3K β and PI3K δ). In some embodiments, selectivity can be at least about 2-fold, 5-fold, 10-fold, at least about 20-fold, at least about 50-fold, at least about 100-fold, at least about 200-fold, at least about 500-fold or at least about 1000-fold. Selectivity can be measured by methods routine in the art. In some embodiments, selectivity can be tested at the K_m ATP
25 concentration of each enzyme. In some embodiments, the selectivity of compounds of the invention can be determined by cellular assays associated with particular PI3K kinase activity.

Another aspect of the present invention pertains to methods of treating a kinase (such as PI3K)-associated disease or disorder in an individual (e.g., patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of one or more
30 compounds of the present invention or a pharmaceutical composition thereof. A PI3K-associated disease can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the PI3K, including overexpression and/or abnormal activity

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levels. In some embodiments, the disease can be linked to Akt (protein kinase B), mammalian target of rapamycin (mTOR), or phosphoinositide-dependent kinase 1 (PDK1). In some embodiments, the mTOR-related disease can be inflammation, atherosclerosis, psoriasis, restenosis, benign prostatic hypertrophy, bone disorders, pancreatitis, angiogenesis, diabetic retinopathy, atherosclerosis, arthritis, immunological disorders, kidney disease, or cancer. A PI3K-associated disease can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating PI3K activity. In some embodiments, the disease is characterized by the abnormal activity of PI3K. In some embodiments, the disease is characterized by mutant PI3K. In such embodiments, the mutation can be present in the kinase domain of the PI3K.

Examples of PI3K-associated diseases include immune-based diseases involving the system including, for example, rheumatoid arthritis, allergy, asthma, glomerulonephritis, lupus, or inflammation related to any of the above.

Further examples of PI3K-associated diseases include cancers such as breast, prostate, colon, endometrial, brain, bladder, skin, uterus, ovary, lung, pancreatic, renal, gastric, or hematological cancer.

In some embodiments, the hematological cancer is acute myeloblastic leukemia (AML) or chronic myeloid leukemia (CML), or B cell lymphoma.

Further examples of PI3K-associated diseases include lung diseases such as acute lung injury (ALI) and adult respiratory distress syndrome (ARDS).

Further examples of PI3K-associated diseases include osteoarthritis, restenosis, atherosclerosis, bone disorders, arthritis, diabetic retinopathy, psoriasis, benign prostatic hypertrophy, atherosclerosis, inflammation, angiogenesis, pancreatitis, kidney disease, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, or Sjogren's syndrome, and the like.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a PI3K with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having a PI3K, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the PI3K.

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As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treating" or "treatment" refers to one or more of (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

Combination Therapies

One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, as well as Bcr-Abl, Flt-3, EGFR, HER2, JAK, c-MET, VEGFR, PDGFR, cKit, IGF-1R, RAF and FAK kinase inhibitors such as, for example, those described in WO 2006/056399, or other agents such as, therapeutic antibodies can be used in combination with the compounds of the present invention for treatment of PI3K-associated diseases, disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

Example antibodies for use in combination therapy include but are not limited to Trastuzumab (e.g. anti-HER2), Ranibizumab (e.g. anti-VEGF-A), Bevacizumab (trade name Avastin, e.g. anti-VEGF), Panitumumab (e.g. anti-EGFR), Cetuximab (e.g. anti-EGFR), Rituxan (anti-CD20) and antibodies directed to c-MET.

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One or more of the following agents may be used in combination with the compounds of the present invention and are presented as a non limiting list: a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methotrexate, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec™, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17.alpha.-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrozole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Fulvestrant, Ifosfomide, Rituximab, C225, Campath, Clofarabine, cladribine, aphidicolon, rituxan, sunitinib, dasatinib, tezacitabine, Sml1, fludarabine, pentostatin, triapine, didox, trimidox, amidox, 3-AP, and MDL-101,731.

Example chemotherapeutics include proteasome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine, etoposide, carmustine, and the like.

Example steroids include corticosteroids such as dexamethasone or prednisone.

Example Bcr-Abl inhibitors include the compounds, and pharmaceutically acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No. 5,521,184, WO 04/005281, and U.S. Ser. No. 60/578,491.

Example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 03/037347, WO 03/099771, and WO 04/046120.

Example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444.

5 Example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402.

10 In some embodiments, the compounds of the invention can be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients resistant to imatinib or other kinase inhibitors.

In some embodiments, the compounds of the invention can be used in combination with a chemotherapeutic in the treatment of cancer, such as multiple myeloma, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without exacerbation of its toxic effects. Examples of additional pharmaceutical agents used in the treatment of multiple myeloma, for example, can include, without limitation, melphalan, melphalan plus prednisone [MP], doxorubicin, dexamethasone, and Velcade (bortezomib). Further additional agents used in the treatment of multiple myeloma include Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors. Additive or synergistic effects are desirable outcomes of combining a PI3K inhibitor of the present invention with an additional agent. Furthermore, resistance of multiple myeloma cells to agents such as dexamethasone may be reversible upon treatment with the PI3K inhibitor of the present invention. The agents can be combined with the present compound in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

25 In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with the compounds of the invention where the dexamethasone is administered intermittently as opposed to continuously.

In some further embodiments, combinations of the compounds of the invention with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone marrow transplant or stem cell transplant.

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Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated.

Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the invention or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active

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compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.* about 40 mesh.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art, *e.g.*, see International App. No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1000 mg (1 g), more usually about 100 to about 500 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

In some embodiments, the compounds or compositions of the invention contain from about 5 to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 to about 10, about 10 to about 15, about 15 to about 20, about 20 to about 25, about 25 to about 30, about 30 to about 35, about 35 to about 40, about 40 to about 45, or about 45 to about 50 mg of the active ingredient.

In some embodiments, the compounds or compositions of the invention contain from about 50 to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 to about 100,

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about 100 to about 150, about 150 to about 200, about 200 to about 250, about 250 to about 300, about 350 to about 400, or about 450 to about 500 mg of the active ingredient.

5 In some embodiments, the compounds or compositions of the invention contain from about 500 to about 1000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 to about 550, about 550 to about 600, about 600 to about 650, about 650 to about 700, about 700 to about 750, about 750 to about 800, about 800 to about 850, about 850 to about 900, about 900 to about 950, or about 950 to about 1000 mg of the active ingredient.

10 The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

15 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient of the present invention.

20 The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

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The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, for example, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, e.g. glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, for example, glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2, or at least about 5 wt % of the compound of the invention. The topical formulations can be suitably packaged in tubes of, for example, 100 g which are optionally associated with instructions for the treatment of the select indication, e.g., psoriasis or other skin condition.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its

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complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 $\mu\text{g/kg}$ to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compositions of the invention can further include one or more additional pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or immunosuppressant, examples of which are listed hereinabove.

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Labeled Compounds and Assay Methods

Another aspect of the present invention relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating PI3K in tissue samples, including human, and for identifying PI3K ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes PI3K assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^2H (also written as D for deuterium), ^3H (also written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{82}Br , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I and ^{131}I . The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* PI3K labeling and competition assays, compounds that incorporate ^3H , ^{14}C , ^{82}Br , ^{125}I , ^{131}I , ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C , ^{18}F , ^{125}I , ^{123}I , ^{124}I , ^{131}I , ^{75}Br , ^{76}Br or ^{77}Br will generally be most useful.

It is understood that a "radio-labeled" or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ^3H , ^{14}C , ^{125}I , ^{35}S and ^{82}Br .

The present invention can further include synthetic methods for incorporating radio-isotopes into compounds of the invention. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the compounds of invention.

A labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind a PI3K by monitoring its concentration variation when contacting with the PI3K, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to reduce binding of another compound which is known to bind to a PI3K (*i.e.*, standard compound). Accordingly, the ability

of a test compound to compete with the standard compound for binding to the PI3K directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

Kits

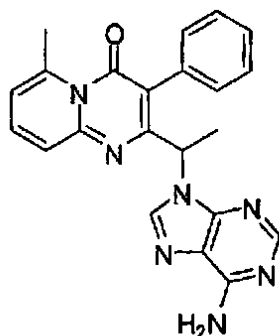
The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of PI3K-associated diseases or disorders, such as cancer, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to be PI3K inhibitors according to at least one assay described herein.

EXAMPLES

The example compounds below containing one or more chiral centers were obtained in racemate form or as isomeric mixtures, unless otherwise specified.

Example 1. 2-[1-(6-amino-9H-purin-9-yl)ethyl]-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one



5 Step 1. methyl 4-chloro-3-oxopentanoate

To a solution of 3-oxopentanoic acid, methyl ester (Aldrich, 26.0 mL, 207.2 mmol) in methylene chloride (300 mL) was added in portions, N,N,N-trimethyl(phenyl) methanaminium dichloroiodanuide (75.71 g, 217.5 mmol). The reaction mixture was stirred at room temperature (rt) for 2 h, then washed with saturated sodium thiosulfate, brine, dried over magnesium sulfate
10 and concentrated. The crude product was used directly in next step (23 g, 67.4%).

Step 2. 2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a manually stirred polyphosphoric acid (30 g, 200 mmol) in a 200 mL beaker was added 6-methyl-2-pyridinamine (Aldrich, 4.7 g, 43 mmol), followed by methyl 4-chloro-3-oxopentanoate (8.584 g, 52.15 mmol). The mixture was heated with stirring at 110 °C for 5 h.
15 After being cooled, the dark slurry was transferred on to 100 g of ice. The pH of the mixture was adjusted to 6-7 with 10% sodium hydroxide. The mixture was extracted with methylene chloride. The combined organic layers were washed with water, brine, dried over magnesium sulfate and evaporated to dryness. The residue was purified on silica gel, eluting with 0-10%
20 methanol in methylene chloride, to yield the desired product (3.16 g, 32.7%). LCMS calculated for $C_{11}H_{12}ClN_2O(M+H)^+$: $m/z = 223.1$; Found: 223.2.

Step 3. 3-bromo-2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a stirred solution of 2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one
25 (3.16 g, 14.2 mmol) in methylene chloride (30 mL) was added drop-wise bromine (0.804 mL, 15.6 mmol) in methylene chloride (7 mL). The reaction mixture was stirred at rt for 2 h. The

product precipitated out and collected by filtration (2.42 g, 56.6%). LCMS calculated for $C_{11}H_{11}BrClN_2O(M+H)^+$: $m/z = 301.0$; Found: 301.1.

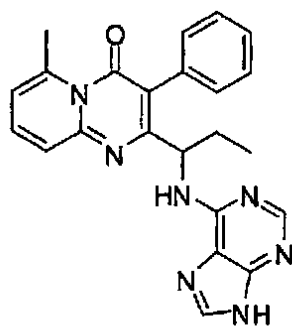
Step 4. 2-[1-(6-amino-9H-purin-9-yl)ethyl]-3-bromo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 3-bromo-2-(1-chloroethyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (1.24 g, 4.11 mmol), adenine (Sigma, 1.08 g, 8.04 mmol), and potassium carbonate (1.11 g, 8.04 mmol) in *N,N*-dimethylformamide (20 mL) was stirred at rt overnight. The suspension was then poured into water and extracted with methylene chloride. The combined organic layers were washed with water, brine, and then the organic layers dried and evaporated to dryness. The residue was chromatographed on silica gel, eluting with 0 to 10% MeOH in methylene chloride, to provide the desired product (176 mg, 10.7%). LCMS calculated for $C_{16}H_{15}BrN_7O(M+H)^+$: $m/z = 400.1$; Found: 400.1. ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.44 (1H, s), 8.07 (1H, s), 7.67 (1H, dd, $J = 8.7$ and 7.2 Hz), 7.30 (1H, br d, $J = 8.7$ Hz), 7.20 (2H, s), 6.99 (1H, br d, $J = 7.2$ Hz), 6.15 (1H, q, $J = 7.2$ Hz), 2.91 (3H, s), 1.84 (3H, d, $J = 7.2$ Hz) ppm.

Step 5. 2-[1-(6-amino-9H-purin-9-yl)ethyl]-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 2-[1-(6-amino-9H-purin-9-yl)ethyl]-3-bromo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.030 g, 0.075 mmol) and phenylboronic acid (11.0 mg, 0.0899 mmol) in 1,4-dioxane (0.6 mL) was added a 1 M solution of sodium carbonate (9.53 mg, 0.0899 mmol) in water (0.089 mL) and tetrakis(triphenylphosphine)palladium (0) (4.33 mg, 0.00375 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on RP-HPLC at pH 10 (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to provide the desired product. LCMS calculated for $C_{22}H_{20}N_7O(M+H)^+$: $m/z = 398.2$; Found: 398.3. ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.37 (1H, s), 7.97 (1H, s), 7.56 (1H, dd, $J = 8.7$ and 6.6 Hz), 7.41–7.36 (5H, m), 7.26 (1H, br d, $J = 9.0$ Hz), 7.09 (2H, br s), 6.85 (1H, br d, $J = 7.2$ Hz), 5.59 (1H, q, $J = 7.2$ Hz), 2.80 (3H, s), 1.64 (3H, d, $J = 7.2$ Hz) ppm.

Example 2. 6-methyl-3-phenyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



Step 1. methyl 4-bromo-3-oxohexanoate

- 5 Under a nitrogen atmosphere, a solution of bromine (8.61 mL, 167 mmol) in chloroform (20 mL) was added drop-wise over a period of 2 h to a solution of methyl 3-oxohexanoate (Fluka, 24.1 g, 167 mmol) in chloroform (147 mL), at 0 °C (ice bath). The reaction mixture was stirred for 30 min at 0 °C and then allowed to warm to rt overnight. While stirring, a stream of air was bubbled through the solution for 1 h. The reaction mixture was dried over sodium sulfate
10 and the solvent evaporated under reduced pressure to provide the desired compound.

Step 2. 2-(1-bromopropyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

- To a manually stirred polyphosphoric acid (80 g, 800 mmol) in a 1000 mL beaker at rt was added 6-methyl-2-pyridinamine (15 g, 140 mmol), followed by methyl 4-bromo-3-oxohexanoate (37.3 g, 167 mmol). The mixture was heated with stirring at 110 °C for 5 h. After
15 cooling, the dark slurry was transferred into 300 g of ice. The pH of the mixture was adjust to 6-7 with 10% sodium hydroxide. The precipitate was collected by filtration under reduced pressure, washed with water, and air dried to yield the desired product (25.4 g, 64.8%). LCMS calculated for $C_{12}H_{14}BrN_2O(M+H)^+$: $m/z = 281.0$; Found: 281.2. ^1H NMR (DMSO- d_6 , 300
20 MHz) δ 7.66 (1H, d, $J = 9.0$ and 6.9 Hz), 7.39 (1H, d, $J = 9.0$ Hz), 6.90 (1H, d, $J = 6.9$ Hz), 6.33 (1H, s), 4.91 (1H, t, $J = 7.5$ Hz), 2.91 (3H, s), 2.15 (2H, qd, $J = 7.5$ and 7.5 Hz), 0.93 (3H, t, $J = 7.5$ Hz) ppm.

Step 3. 2-(1-bromopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

- 25 A mixture of 2-(1-bromopropyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (3.46 g, 12.3 mmol) and *N*-iodosuccinimide (4.15 g, 18.4 mmol) in acetonitrile (100 mL) was stirred at 80 °C,

under nitrogen, overnight. After removal of acetonitrile in vacuum, the resulting solid was dissolved in methylene chloride, washed with water, saturated $\text{Na}_2\text{S}_2\text{O}_3$, saturated sodium bicarbonate, and brine; and then the organic layers dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure to provide the desired product (4.53 g, 90.4%). LCMS calculated for $\text{C}_{12}\text{H}_{13}\text{BrIN}_2\text{O}(\text{M}+\text{H})^+$: $m/z = 406.9$; Found: 407.1.

Step 4. 2-(1-azidopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 2-(1-bromopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (4.50 g, 11.0 mmol) and sodium azide (3.59 g, 55.3 mmol) in DMF was stirred at rt for 2 h. After diluting with ethyl acetate, the mixture was washed with water, brine, dried over sodium sulfate, and evaporated under reduced pressure to provide the crude product, which was used directly in next step (3.35 g, 82.1%). LCMS calculated for $\text{C}_{12}\text{H}_{13}\text{IN}_3\text{O}(\text{M}+\text{H})^+$: $m/z = 370.0$; Found: 370.2.

Step 5. 2-(1-azidopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a mixture of 2-(1-azidopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.11 g, 0.29 mmol) and phenylboronic acid (42.9 mg, 0.352 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (37.3 mg, 0.352 mmol) in water (0.35 mL) and tetrakis(triphenylphosphine)palladium (0) (16.9 mg, 0.0147 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO_4 , and concentrated. The residue was purified on silica gel, eluting with 0 to 40% EtOAc in hexane, to provide the desired product (50 mg, 53.4%). LCMS calculated for $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}(\text{M}+\text{H})^+$: $m/z = 320.2$; Found: 320.3.

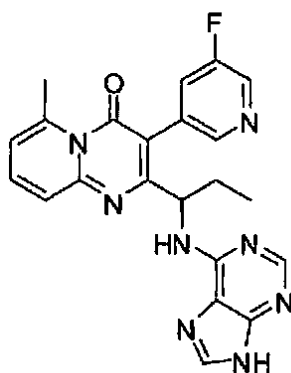
Step 6. 2-(1-aminopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a stirred solution of 2-(1-azidopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.030 g, 0.094 mmol) in tetrahydrofuran (0.24 mL) and water (0.06 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.11 mL) at rt and the mixture was stirred at rt for 1 h. To the mixture was added methylene chloride and the mixture was washed with brine, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The crude residue was used directly in next step. LCMS calculated for $\text{C}_{18}\text{H}_{20}\text{N}_3\text{O}(\text{M}+\text{H})^+$: $m/z = 294.2$; Found: 294.3.

Step 7. 6-methyl-3-phenyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 6-bromo-9H-purine (Aldrich, 0.0152 g, 0.07656 mmol), 2-(1-aminopropyl)-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.019 g, 0.064 mmol), and *N,N*-diisopropylethylamine (0.0134 mL, 0.07666 mmol) in ethanol (0.5 mL) was refluxed under nitrogen overnight. The mixture was cooled and purified on RP-HPLC at pH 10 (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH₄OH) to provide the product as the free base. LCMS calculated for C₂₃H₂₂N₇O(M+H)⁺: m/z = 412.2; Found: 412.4. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.07 (2H, m), 7.60 (1H, dd, *J* = 9.0 and 6.9 Hz), 7.39–7.32 (7H, m), 7.00 (1H, m), 6.85 (1H, br d, *J* = 6.9 Hz), 5.13 (1H, m), 2.81 (3H, s), 1.72 (2H, m), 0.65 (3H, t, *J* = 7.2 Hz) ppm.

Example 3. 3-(5-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



Step 1. 2-(1-aminopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

To a stirred solution of 2-(1-azidopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (3.10 g, 8.40 mmol) in tetrahydrofuran (20 mL) and water (6.06 mL) was added a 1.0 M solution of trimethylphosphine in tetrahydrofuran (0.1 mmol) at rt and stirred for 1 h. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (2.58 g, 89.5%). LCMS calculated for C₁₂H₁₅IN₃O(M+H)⁺: m/z = 344.0; Found: 344.2.

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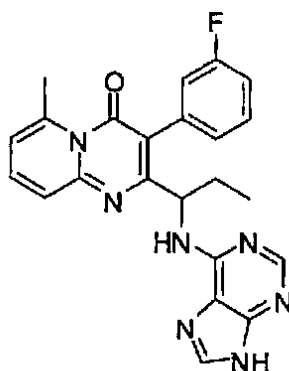
Step 2. 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

A mixture of 6-bromo-9H-purine (1.65 g, 0.008270 mol), 2-(1-aminopropyl)-3-iodo-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (2.58 g, 0.00752 mol), and *N,N*-diisopropylethylamine (1.571 mL, 0.009022 mol) in ethanol (60 mL) was refluxed under nitrogen overnight. The mixture was concentrated and the resulting residue was purified on silica gel, eluting with 0 to 10% methanol in methylene chloride, to provide the desired product (2.86 g, 82.5%). LCMS calculated for $C_{17}H_{17}N_7O(M+H)^+$: $m/z = 462.1$; Found: 462.2. ^1H NMR (DMSO- d_6 , 300 MHz) δ 8.31 (2H, m), 8.19 (1H, s), 8.15 (1H, s), 7.69 (1H, dd, $J = 8.7$ and 6.9 Hz), 7.44 (1H, d, $J = 8.7$ Hz), 6.99 (1H, d, $J = 6.9$ Hz), 5.69 (1H, m), 2.89 (3H, s), 1.91 (2H, m), 0.95 (3H, t, $J = 7.2$ Hz) ppm.

Step 3. 3-(5-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one

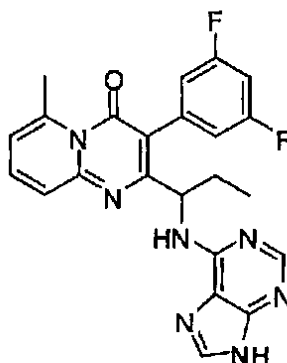
To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (0.030 g, 0.065 mmol) and (5-fluoropyridin-3-yl)boronic acid (Combi-Blocks, 11.0 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on RP-HPLC at pH 10 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH_4OH) to provide the desired product. LCMS calculated for $C_{22}H_{20}FN_8O(M+H)^+$: $m/z = 431.2$; Found: 431.3.

Example 4. 3-(3-fluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and (3-fluorophenyl)boronic acid (Aldrich, 10.9 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on RP-HPLC at pH 10 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH₄OH) to provide the desired product. LCMS calculated for C₂₃H₂₁FN₇O(M+H)⁺: m/z = 430.2; Found: 430.3. ¹H NMR (DMSO-d₆, 300 MHz) δ 8.11 (2H, m), 7.65 (1H, m), 7.45 (2H, m), 7.24 (4H, m), 7.08 (1H, m), 6.91 (1H, m), 5.17 (1H, m), 2.87 (3H, s), 1.79 (2H, m), 0.72 ((3H, t, J = 7.2 Hz) ppm. ¹⁹F NMR (DMSO-d₆, 282 MHz) δ -114 ppm.

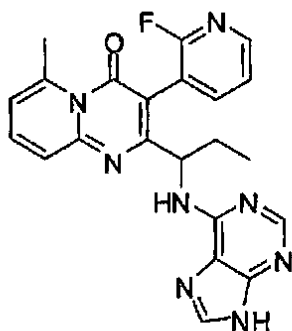
Example 5. 3-(3,5-difluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



(at)

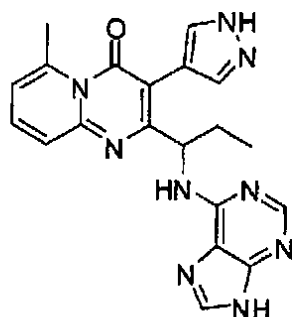
To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and (3,5-difluorophenyl)boronic acid (Aldrich, 12.3 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on RP-HPLC at pH 10 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.15% NH₄OH) to provide the desired product. LCMS calculated for C₂₃H₂₀F₂N₇O(M+H)⁺: m/z = 448.2; Found: 448.3. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.06 (2H, m), 7.61 (1H, m), 7.38 (1H, m), 7.14 (5H, m), 6.88 (1H, m), 5.08 (1H, m), 2.83 (3H, s), 1.75 (2H, m), 0.70 ((3H, t, *J* = 7.8 Hz) ppm. ¹⁹F NMR (DMSO-*d*₆, 282 MHz) δ -111 ppm.

Example 6. 3-(2-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one



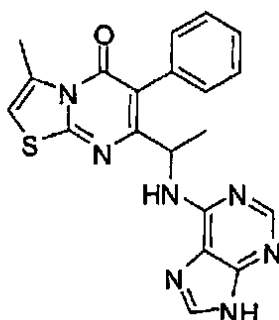
To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and (2-fluoropyridin-3-yl)boronic acid (Alfa Aesar, 11.0 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on RP-HPLC at pH 2 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to provide the desired product as a TFA salt. LCMS calculated for free base C₂₂H₂₀FN₈O(M+H)⁺: m/z = 431.2; Found: 431.3.

Example 7. 6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-3-(1H-pyrazol-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one



5 To a mixture of 3-iodo-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one (from example 3, step 2; 0.030 g, 0.065 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (Aldrich, 15.1 mg, 0.0780 mmol) in 1,4-dioxane (0.5 mL) was added a 1 M solution of sodium carbonate (8.27 mg, 0.0780 mmol) in water (0.077 mL) and tetrakis(triphenylphosphine)palladium (0) (3.76 mg, 0.00325 mmol). The reaction mixture was
10 heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on RP-HPLC at pH 2 conditions (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA) to provide the desired product as a TFA salt. LCMS calculated for free base C₂₀H₂₀N₉O(M+H)⁺: m/z = 402.2; Found: 402.1.

15 **Example 8. 3-methyl-6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one**



Step 1. methyl 4-bromo-3-oxopentanoate

20 Under a nitrogen atmosphere, a solution of bromine (8.61 mL, 167 mmol) in chloroform (20 mL, 200 mmol) was added dropwise over a period of 2 h to a solution of 3-oxopentanoic

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acid, methyl ester (Aldrich, 21.0 mL, 167 mmol) in chloroform (147 mL, 1840 mmol), at 0 °C (ice bath). The reaction mixture was stirred for 30 min at 0 °C and then allowed to stand at rt overnight. While stirring, a stream of air was bubbled through the solution for 1 h. After drying over sodium sulfate, the solvent was evaporated under reduced pressure leaving the desired compound.

Step 2. 7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a manually stirred polyphosphoric acid (80 g, 800 mmol) in a 1000 mL beaker was added 4-methyl-1,3-thiazol-2-amine (Aldrich, 16 g, 140 mmol), followed by methyl 4-bromo-3-oxopentanoate (34.9 g, 167 mmol). The mixture was heated with stirring at 110 °C for 5 h. After cooling, the dark slurry was transferred into 300 g of ice. The pH of the mixture was adjust to 6-7 with 10% sodium hydroxide. The aqueous layer was discarded and the dark oil layer was diluted with methylene chloride and washed with 1 N NaOH, brine, dried over magnesium sulfate, and evaporated to dryness to yield the desired product (16.2 g, 42.6%). LCMS calculated for $C_9H_{10}BrN_2OS(M+H)^+$: $m/z = 273.0$; Found: 273.1.

Step 2. 6-bromo-7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (16.2 g, 59.3 mmol) and *N*-bromosuccinimide (15.8 g, 89.0 mmol) in acetonitrile (500 mL) was stirred at 80 °C, under nitrogen, overnight. After removal of acetonitrile in vacuum, the resulting solid was dissolved in methylene chloride, washed with water, saturated $Na_2S_2O_3$, saturated sodium bicarbonate, and brine; and then the organic layers dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to provide the desired product (19.5 g, 93.4%). LCMS calculated for $C_9H_9Br_2N_2OS(M+H)^+$: $m/z = 350.9$; Found: 351.0.

Step 3. 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (11.1 g, 31.5 mmol) and sodium azide (6.15 g, 94.6 mmol) in dimethyl formamide (DMF) (100 mL) was stirred at rt for 2 h. After diluting with EtOAc, the mixture was washed with water, brine, dried over sodium sulfate, and evaporated under reduced pressure. The crude residue was purified on silica gel, eluting with 0 to 80% EtOAc in hexane, to provide the product

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(8.68 g, 87.6%). LCMS calculated for $C_9H_9BrN_5OS(M+H)^+$: $m/z = 314.0$; Found: 313.9. ^1H NMR (DMSO- d_6 , 300 MHz) δ 7.15 (1H, s), 4.83 (1H, q, $J = 6.6$ Hz), 2.69 (3H, s), 1.48 (3H, d, $J = 6.6$ Hz) ppm.

5 *Step 4. 7-(1-azidoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one*

To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.100 g, 0.318 mmol) and phenylboronic acid (46.6 mg, 0.382 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (40.5 mg, 0.382 mmol) in water (0.38 mL) and tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0159 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel, eluting with 0 to 50% EtOAc in hexane, to provide the desired product (44 mg, 44.4%). LCMS calculated for $C_{15}H_{14}N_5OS(M+H)^+$: $m/z = 312.1$; Found: 312.3.

15 *Step 5. 7-(1-aminoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one*

To a stirred solution of 7-(1-azidoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.044 g, 0.14 mmol) in tetrahydrofuran (0.4 mL) and water (0.102 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.17 mL) at rt and the mixture was stirred at rt for 1 h. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (36 mg, 89.3%). LCMS calculated for $C_{15}H_{16}N_3OS(M+H)^+$: $m/z = 286.1$; Found: 286.0.

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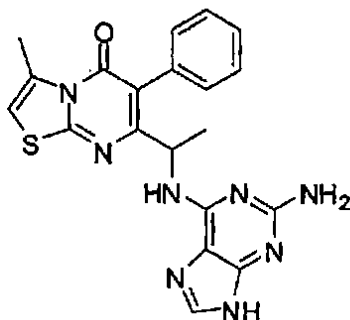
Step 6. 3-methyl-6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-9H-purine (0.01504 g, 0.0076 mmol), 7-(1-aminoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.018 g, 0.063 mmol), and N,N -diisopropylethylamine (0.013 mL, 0.0076 mol) in ethanol (0.5 mL) was refluxed under nitrogen overnight. The mixture was concentrated under reduced pressure and the residue was purified on

RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for free base $C_{20}H_{18}N_7OS(M+H)^+$: $m/z = 404.1$; Found: 404.3. ^1H NMR (DMSO- d_6 , 300 MHz) for a TFA salt: δ 8.54 (2H, m), 8.41 (2H, m), 7.44–7.36 (5H, m), 7.08 (1H, d, $J = 1.2$ Hz), 5.21 (1H, m), 2.64 (3H, s), 1.38 (3H, d, $J = 6.6$ Hz) ppm.

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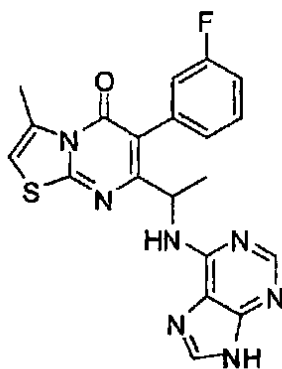
Example 9. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



A mixture of 2-amino-6-bromopurine (Aldrich, 0.01618 g, 0.007558 mmol), 7-(1-aminoethyl)-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 8, step 5; 0.018 g, 0.063 mmol), and *N,N*-diisopropylethylamine (0.01318 mL, 0.007569 mmol) in ethanol (0.5 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resulting residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{19}N_8OS(M+H)^+$: $m/z = 419.1$; Found: 419.3. ^1H NMR (DMSO- d_6 , 300 MHz) for TFA salt: δ 8.74 (1H, m), 8.16 (1H, s), 7.46–7.33 (6H, m), 7.14–7.11 (3H, m), 5.20 (1H, m), 2.66 (3H, d, $J = 1.5$ Hz), 1.32 (3H, d, $J = 6.6$ Hz) ppm.

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Example 10. 6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



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Step 1. 7-(1-azidoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 8, step 3; 0.100 g, 0.318 mmol) and (3-fluorophenyl)boronic acid (53.4 mg, 0.382 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (40.5 mg, 0.382 mmol) in water (0.38 mL) and tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0159 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on silica gel, eluting with 0 to 50% EtOAc in hexane, to provide the desired product (35 mg, 33.4%). LCMS calculated for C₁₅H₁₃FN₅OS(M+H)⁺: m/z = 330.1; Found:

330.2.

Step 2. 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

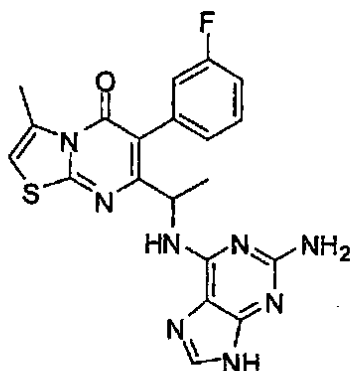
To a stirred solution of 7-(1-azidoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.037 g, 0.11 mmol) in tetrahydrofuran (0.3 mL) and water (0.0811 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.13 mmol) at rt and stirred for 1 h. To the mixture was added EtOAc and was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (31 mg, 90.9%). LCMS calculated for C₁₅H₁₅FN₃OS(M+H)⁺: m/z = 304.1; Found: 304.3.

Step 3. 6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-9H-purine (0.01258 g, 0.006320 mmol), 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.016 g, 0.053 mmol), and *N,N*-diisopropylethylamine (0.011 mL, 0.006329 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resulting residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for C₂₀H₁₇FN₇OS(M+H)⁺: m/z = 422.1; Found: 422.3. ¹H NMR (DMSO-*d*₆, 300 MHz) for TFA salt: δ 8.55 (2H, m), 8.40 (2H, m), 7.48 (1H, m), 7.25–7.22 (3H, m), 7.09 (1H, s), 5.19 (1H, m), 2.64 (3H, d, *J* = 0.9 Hz),

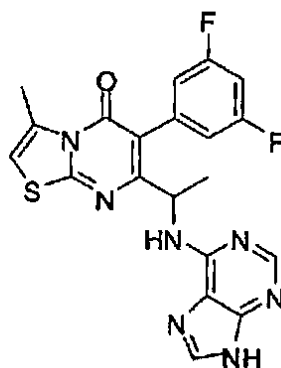
1.40 (3H, d, $J = 6.6$ Hz) ppm. ^{19}F NMR (DMSO- d_6 , 282 MHz) for TFA salt: δ -74.2, -114.0 ppm.

5 **Example 11. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one**



10 A mixture of 2-amino-6-bromopurine (0.01353 g, 0.006320 mmol), 7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 10, step 2; 0.016 g, 0.053 mmol), and *N,N*-diisopropylethylamine (0.01102 mL, 0.006329 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resultant residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $\text{C}_{20}\text{H}_{18}\text{FN}_8\text{OS}(\text{M}+\text{H})^+$: $m/z = 437.1$; Found: 437.3. ^1H NMR (DMSO- d_6 , 300 MHz) for TFA salt: δ 8.74 (1H, m), 8.16 (1H, s), 7.46 (1H, m), 7.20–7.13 (7H, m), 5.18 (1H, m), 2.66 (3H, s), 1.33 (3H, d, $J = 6.9$ Hz) ppm. ^{19}F NMR (DMSO- d_6 , 282 MHz) for TFA salt: δ -74.0, -114.0 ppm.

15 **Example 12. 6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one**



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Step 1. 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a mixture of 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.10 g, 0.318 mmol) and (3,5-difluorophenyl)boronic acid (60.3 mg, 0.382 mmol) in 1,4-dioxane (2 mL) was added a 1 M solution of sodium carbonate (40.5 mg, 0.382 mmol) in water (0.38 mL) and tetrakis(triphenylphosphine)palladium (0) (18.4 mg, 0.0159 mmol). The reaction mixture was heated at 100 °C overnight. After cooling to rt, the mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄, and concentrated. The residue was purified on silica gel, eluting with 0 to 40% EtOAc in hexane, to provide the desired product (42 mg, 38.0%). LCMS calculated for C₁₅H₁₂F₂N₅OS(M+H)⁺: m/z = 348.1; Found: 348.2.

Step 2. 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

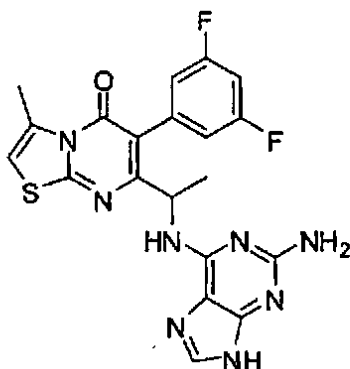
To a stirred solution of 7-(1-azidoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.042 g, 0.12 mmol) in tetrahydrofuran (0.3 mL) and water (0.0873 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.14 mmol) at rt and stirred for 1 h. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate, and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step (36 mg, 92.7%). LCMS calculated for C₁₅H₁₄F₂N₃OS(M+H)⁺: m/z = 322.1; Found: 322.3.

Step 3. 6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-9H-purine (0.01258 g, 0.006320 mmol), 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.017 g, 0.053 mmol), and *N,N*-diisopropylethylamine (0.011 mL, 0.006329 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was concentrated under reduced pressure and the resultant residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for C₂₀H₁₆F₂N₇OS(M+H)⁺: m/z = 440.1; Found: 440.3. ¹H NMR (DMSO-*d*₆, 300

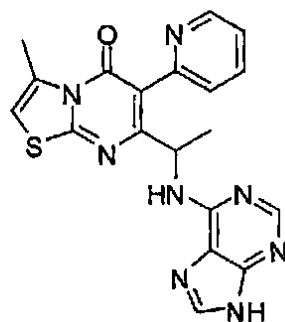
MHz) for TFA salt: δ 8.55 (1H, m), 8.39 (2H, m), 7.29 (1H, m), 7.15–7.11 (3H, m), 5.17 (1H, m), 2.64 (3H, d, $J = 1.2$ Hz), 1.42 (3H, d, $J = 6.9$ Hz) ppm.

Example 13. 7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



A mixture of 2-amino-6-bromopurine (0.01436 g, 0.006712 mmol), 7-(1-aminoethyl)-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 12, step 2; 0.018 g, 0.056 mmol), and *N,N*-diisopropylethylamine (0.01171 mL, 0.006722 mmol) in ethanol (0.4 mL) was refluxed under nitrogen overnight. The mixture was evaporated and the resultant residue was purified on RP-HPLC at pH 2 to provide the product as a TFA salt. LCMS calculated for $C_{20}H_{17}F_2N_8OS(M+H)^+$: $m/z = 455.1$; Found: 455.3. ^1H NMR (DMSO- d_6 , 300 MHz) for TFA salt: δ 8.74 (1H, m), 8.16 (1H, s), 7.26–7.06 (6H, m), 5.16 (1H, m), 2.66 (3H, d, $J = 1.2$ Hz), 1.36 (3H, d, $J = 6.9$ Hz) ppm.

Example 14. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



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Step 1. 7-(1-azidoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 2-(tributylstannyl)pyridine (Aldrich, 0.176 g, 0.382 mmol), 7-(1-azidoethyl)-6-bromo-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (from example 8, step 3; 0.10 g, 0.318 mmol), and tetrakis(triphenylphosphine)palladium (0) (0.0184 g, 0.0159 mmol) in 1,4-dioxane (0.5 mL) was heated at 65 °C overnight. After being cooled and quenched with saturated ammonium chloride, the resulting mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried and evaporated to dryness. The residue was purified on silica gel, eluting with 0 to 100% EtOAc in hexane, to provide the desired product (13 mg, 13%). LCMS calculated for $C_{14}H_{13}N_6OS(M+H)^+$: $m/z = 313.1$; Found: 313.0.

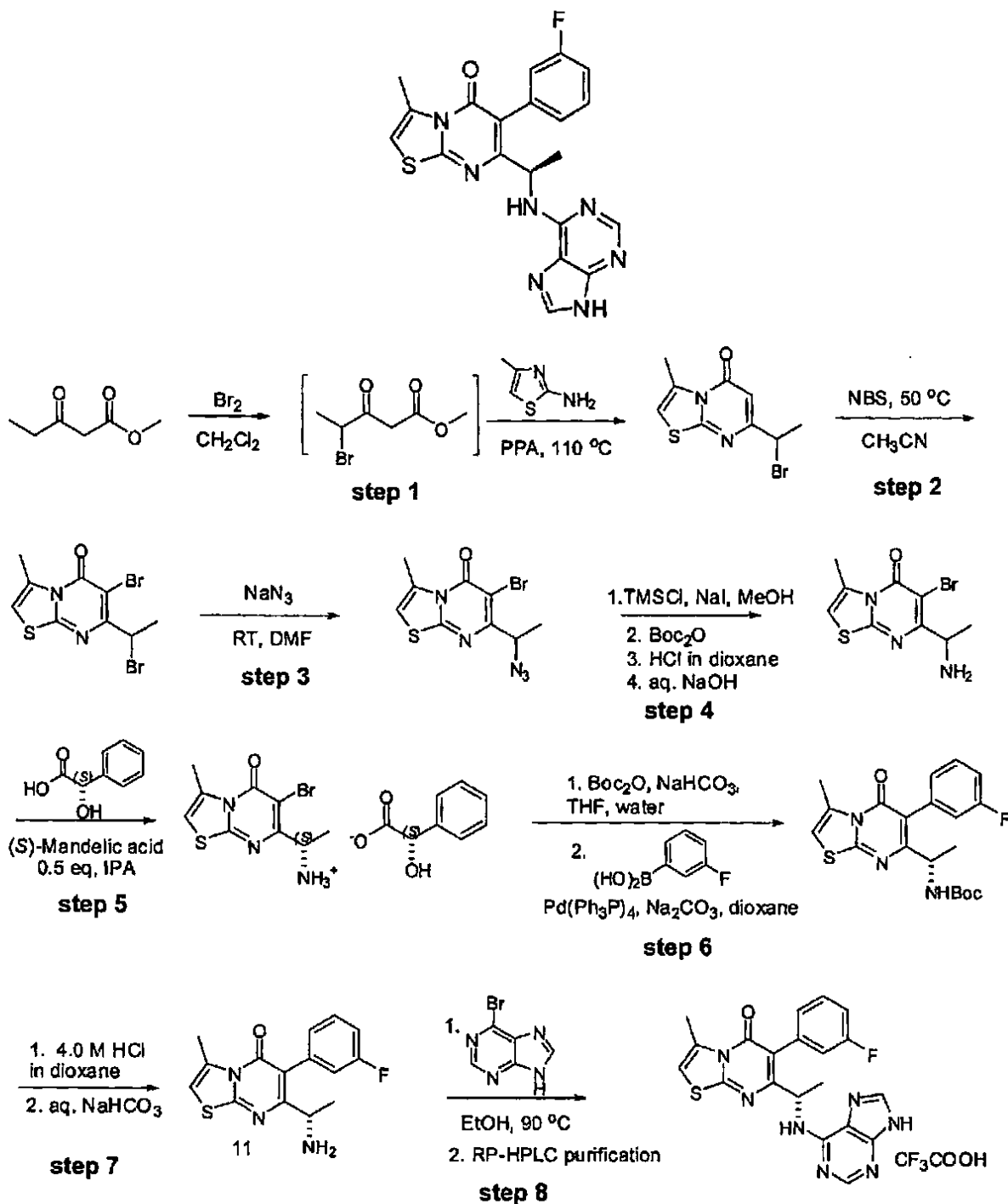
Step 2. 7-(1-aminoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

To a stirred solution of 7-(1-azidoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (0.012 g, 0.039 mmol) in tetrahydrofuran (0.1 mL) and water (0.0285 mL) was added 1.0 M of trimethylphosphine in tetrahydrofuran (0.047 mmol) at rt and stirred for 1 h. To the mixture was added EtOAc and the mixture was extracted twice with 1 N HCl. The combined extracts were neutralized with solid sodium bicarbonate and extracted with methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was used directly in next step. LCMS calculated for $C_{14}H_{15}N_4OS(M+H)^+$: $m/z = 287.1$; Found: 287.0.

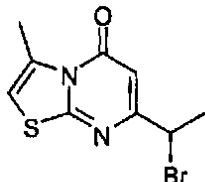
Step 3. 3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

A mixture of 6-bromo-9H-purine (9.300 mg, 0.004673 mmol), 7-(1-aminoethyl)-3-methyl-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (11 mg, 0.039 mmol), and *N,N*-diisopropylethylamine (8.152 μ L, 0.004680 mmol) in ethanol (0.3 mL) was refluxed under nitrogen overnight. The mixture was concentrated under reduced pressure and the residue was purified on RP-HPLC (eluting with a gradient of methanol/water containing 1% TFA) to provide the product as a TFA salt. LCMS calculated for $C_{19}H_{17}N_8OS(M+H)^+$: $m/z = 405.1$; Found: 405.3.

Example 15. (S)-7-(1-(9H-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one



Step 1. 7-(1-Bromoethyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one



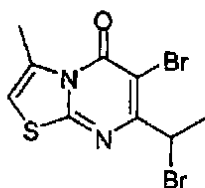
A solution of 3-oxopentanoic acid methyl ester (12.5 g, 96.0 mmol) in methylene chloride (50 mL) was cooled with an ice water bath. The outlet of the flask was attached to a NaOH trap. Bromine (5.19 mL, 101 mmol) in methylene chloride (10 mL, 200 mmol) was added dropwise over a 20-min period, and the reaction mixture was allowed to warm to room temperature and then stirred overnight. The reaction mixture was bubbled with nitrogen for 30 min and then concentrated to give an oil. This oil was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.89 (q, *J* = 6.9 Hz, 1H), 3.85 (s, 2H), 3.63 (s, 3H), 1.64 (d, *J* = 6.7 Hz, 3H).

Into a 3-neck flask fitted with a condenser, a thermometer, and a nitrogen inlet was added polyphosphoric acid (50.0 g, 458 mmol). The flask was heated to ~ 70 °C to give a liquid that was easy to stir. 4-Methyl-1,3-thiazol-2-amine (10.0 g, 87.6 mmol) was added in small portions with stirring. The internal temperature slowly increased to 78 °C upon mixing. The crude oil obtained above was then added to the flask *via* a pipette and the mixture was heated to 110 °C under nitrogen. After 6 h of heating, HPLC indicated that the reaction was complete.

The reaction mixture was cooled to ~ 35 °C. Water (70 mL) and EtOAc (200 mL) were added. The mixture was stirred until all solids dissolved. The organic layer was separated. The aqueous layer was extracted with EtOAc (200 mL x 2). The combined organic extracts were washed with 1 N aqueous HCl (40 mL x 2) with sat. NaHCO₃ (50 mL x 2) and brine (30 mL). The organic layer was dried and concentrated to give 7-(1-bromoethyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one as a yellow solid (11.8 g, 49.3%). LCMS calculated for C₉H₁₀BrN₂OS (M+H)⁺: *m/z* 274.96, 272.96; Found: 274.75, 272.75. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.05 (m, 1H), 6.27 (s, 1H), 5.17 (q, *J* = 6.9 Hz, 1H), 2.65 (s, 3H), 1.85 (d, *J* = 6.9 Hz, 3H).

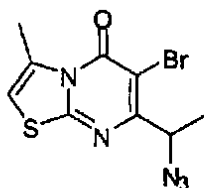
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Step 2. 6-Bromo-7-(1-bromoethyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one



Under nitrogen, a suspension of 7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (13.2 g, 48.3 mmol) in acetonitrile (100 mL, 2000 mmol) was stirred until a clear solution was obtained. *N*-Bromosuccinimide (9.891 g, 55.57 mmol) was then added and the reaction mixture was stirred at 50 °C. After 20 min, HPLC indicated that the reaction was complete. A solution of sodium sulfite (3.046 g, 24.16 mmol) in water (50 mL) was added and the mixture was stirred at room temperature for 20 min. Water (200 mL) was added slowly and the mixture stirred at room temperature for 30 min. and then filtered. The solid was washed with water (100 mL x 3) and dried to give 6-bromo-7-(1-bromoethyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one as an off-white solid (15.61 g, 91%). LCMS calculated for C₉H₉Br₂N₂OS (M+H)⁺: m/z 352.87, 354.87; Found: 352.65, 354.60. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.15 (q, *J* = 1.3 Hz, 1H), 5.51 (q, *J* = 6.7 Hz, 1H), 2.66 (d, *J* = 1.2 Hz, 3H), 1.90 (d, *J* = 6.7 Hz, 3H).

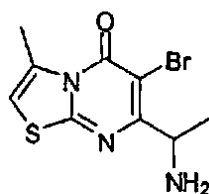
Step 3. 7-(1-Azidoethyl)-6-bromo-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one



To a suspension of 6-bromo-7-(1-bromoethyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one (6.85 g, 19.4 mmol) in *N,N*-dimethylformamide (30.1 mL) was added sodium azide (1.45 g, 22.4 mmol). The mixture slowly turned clear after 5-10 min. After 50 min, a solution of sodium bicarbonate (4.7 g, 56 mmol) in water (90 mL) was added dropwise with stirring. The mixture was stirred at room temperature for 1 h and the solid precipitates were filtered off. The solid was then washed with water (30 mL x 3), and dried to give 7-(1-azidoethyl)-6-bromo-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one as an off-white solid (5.94 g, 97.2%). LCMS calculated for C₉H₉BrN₅OS (M+H)⁺: m/z 313.96, 315.96; Found: 313.75, 315.75. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.15 (q, *J* = 1.3 Hz, 1H), 4.83 (q, *J* = 6.8 Hz, 1H), 2.67 (d, *J* = 1.4 Hz, 3H), 1.48 (d, *J* = 6.8 Hz, 3H).

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Step 4. 7-(1-Aminoethyl)-6-bromo-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one

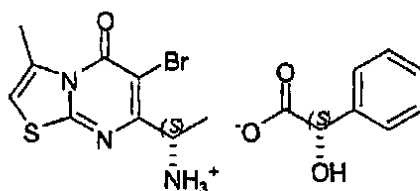


7-(1-Azidoethyl)-6-bromo-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (22.6 g, 71.9 mmol) was mixed with methanol (200 mL). Sodium iodide (64.7 g, 432 mmol) was added and stirred at room temperature for 10 min. Chlorotrimethylsilane (54.8 mL, 432 mmol) was dissolved in methanol (29.1 mL) and added dropwise over 10 min. at 5-25 °C. The reaction mixture was stirred at room temperature for 10 min. HPLC and TLC showed that the reaction was complete. The reaction was quenched by addition of a solution of sodium thiosulfate (69.4 g, 439 mmol) in water (259 ml) while maintaining the batch temperature at 5- 25 °C. A large amount of solid was formed, and the pH of the mixture was 3. The mixture was stirred at 0- 5 °C for 30 min. The pH was adjusted to 11 using 3 N aqueous sodium hydroxide (85 mL). In order to facilitate product purification and isolation, the *N*-Boc derivative of the product was prepared. To the mixture was added di-*t*-butyldicarbonate (28.3 g, 129 mmol) and the reaction mixture was stirred at room temperature for 2 h. HPLC indicated a small amount of amine remained unreacted. Additional di-*t*-butyldicarbonate (10.0 g, 45.8 mmol) was added followed by 3 N aqueous sodium hydroxide (15 mL) to adjust the pH to 11. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with ethyl acetate (150 mL x 3). The organic solution which contained the *N*-Boc derivative of the product was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was added to a 4 M solution of hydrogen chloride in 1,4-dioxane (206 mL, 824 mmol) and stirred at room temperature for 1.5 h. HPLC indicated the *N*-Boc-deprotection was complete. The hydrochloride salt of the product was isolated by filtration, the solid washed with MTBE, dried by suction filtration for 1 h to give 7-(1-aminoethyl)-6-bromo-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one hydrochloride salt (25.1 g) as a purple powder.

The hydrochloride salt was dissolved in water (50 mL) and a 50% solution of sodium hydroxide (about 5 mL) was added to adjust the pH to 11. The mixture was stirred at room temperature for 20 min. The product precipitated and was isolated by filtration. The wet solid

was washed with water (10 mL) and dried on the filter under vacuum for 18 h to give 7-(1-aminoethyl)-6-bromo-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (18.8 g, 65.2 mmol, 90.7 % yield) as a yellow powder. LCMS calculated for $C_9H_{11}BrN_3OS$ ($M+H$)⁺: m/z 287.97, 289.97; Found: 287.75, 289.75. ¹H NMR (400 MHz, DMSO-*d*₆) 7.08 (q, J = 1.3 Hz, 1H), 4.19 (q, J = 6.7 Hz, 1H), 2.65 (d, J = 1.3 Hz, 3H), 1.17 (d, J = 6.7 Hz, 3H).

Step 5. (*S*)-1-(6-bromo-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethanaminium (*S*)-2-hydroxy-2-phenylacetate



7-(1-Aminoethyl)-6-bromo-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (18.8 g, 65.2 mmol) was dissolved in isopropanol (375 mL) at reflux and then (*S*)-(+)-mandelic acid (4.84 g, 31.8 mmol) in isopropanol (375 mL) was added dropwise to the amine solution over 35 min. The reaction mixture was allowed to cool to about 72 °C and solid precipitation was observed. The slurry was cooled to room temperature and stirred for 1 h. The solid product was collected by filtration. The wet cake was washed with isopropanol (100 mL) and dried on the filter under suction for 1 h to give the product (*S*)-1-(6-bromo-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethanaminium (*S*)-2-hydroxy-2-phenylacetate (11.9 g) as a white solid. Chiral HPLC analysis was performed on a Lux Cellulose-2, 4.6 x 250 mm, 5 micron column using 60% ethanol/40% hexanes as the mobile phase at a flow rate of 1 mL/min. The major enantiomer eluted at retention time 11.21 min (99.0 area %). The minor enantiomer eluted at retention time 14.31 min (0.96 area %). The e.e. of the desired product was 98.08%.

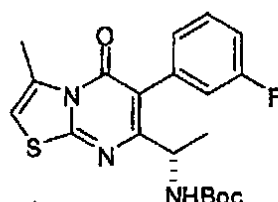
The product at 98.08% e.e. (11.9 g) was suspended in isopropanol (750 mL) and heated under reflux for 30 min. The slurry was cooled to room temperature with stirring. The solid was collected by filtration. The wet solid was washed with isopropanol (100 mL) and dried on the filter under suction for 18 h to give 10.9 g of white solid. Chiral HPLC by the method described above gave e.e. of 98.48%.

The product at 98.48% e.e. (10.9 g) was stirred in a solution of sodium carbonate (3.9 g, 37 mmol) in water (100 mL) at room temperature for 30 min. The solid free base was collected

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by filtration, washed with water (20 mL) and dried on the filter under suction for 2 h to give a slightly wet cake (13 g). The wet solid was dissolved in isopropanol (325 mL) at reflux and a solution of (*S*)-(+)-mandelic acid (3.613 g, 23.75 mmol) in isopropanol (325 mL) was added dropwise over 20 min to the free base solution. The solution was cooled to room temperature with stirring. The solid product was collected by filtration, washed with isopropanol (100 mL) and dried on the filter under suction for 48 h to give pure product (*S*)-1-(6-bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-7-yl)ethanaminium (*S*)-2-hydroxy-2-phenylacetate (8.4 g, 19.08 mmol, 29.3 % yield) as a white solid. The e.e. of this sample was determined to be 100 % as no minor enantiomer (retention time = 14.31 min) was detected. LCMS calculated for C₉H₁₁BrN₃OS (M+H)⁺ for the free base: *m/z* 289.97, 287.97; Found: 289.75, 287.75. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.33 (d, *J* = 7.5 Hz, 2H), 7.22 (dd, *J* = 7.1, 7.5 Hz, 2H), 7.16 (m, 2H), 4.61 (s, 1H), 4.47 (q, *J* = 6.9 Hz, 1H), 2.68 (d, *J* = 1.1 Hz, 3H), 1.31 (d, *J* = 6.8 Hz, 3H).

In order to determine the absolute stereochemistry of the product, a sample was sublimed at about 105 °C to provide colorless needles suitable for X-ray crystal structure analysis. The study determined the absolute configuration of the amine bearing carbon (C-8) is *S* (see Example 16 and Figure 1).

Step 6. (*S*)-*tert*-Butyl 1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-7-yl)ethylcarbamate

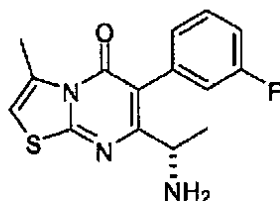


(*S*)-1-(6-Bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-7-yl)ethanaminium (*S*)-2-hydroxy-2-phenylacetate (4.93 g, 11.2 mmol) was dissolved in THF (100 mL) and water (33 mL). Di-*t*-butyldicarbonate (3.03 g, 13.9 mmol) was added, followed by sodium bicarbonate (1.88 g, 22.4 mmol). The reaction mixture was stirred at room temperature for 30 min. at which point the HPLC showed the reaction was near complete. Additional di-*t*-butyldicarbonate (0.49 g, 2.24 mmol) was then added and the reaction mixture was stirred at room temperature for 1 h. The reaction was shown to be complete by HPLC. The reaction mixture was diluted with water

(100 mL) and extracted with ethyl acetate (2 x 100 mL). The ethyl acetate solution was concentrated to give (*S*)-*tert*-butyl 1-(6-bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-7-yl)ethylcarbamate (5.46 g, 14.1 mmol, 126% yield) which was used in the subsequent Suzuki coupling reaction without further purification.

- 5 (*S*)-*tert*-Butyl 1-(6-bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-7-yl)ethylcarbamate (5.46 g, 14.1 mmol) and (3-fluorophenyl)boronic acid (2.95 g, 21.1 mmol) were suspended in 1,4-dioxane (110 mL). A solution of sodium carbonate (4.47g, 42.2 mmol) in water (27 mL) was added to the mixture followed by tetrakis(triphenylphosphine)palladium(0) catalyst (0.81 g, 0.70 mmol). The reaction mixture was degassed and heated under nitrogen at 100 °C for 16 h. HPLC indicated the starting material was consumed. The reaction mixture was cooled to room temperature and water (100 mL) was added. The resultant mixture was extracted with ethyl acetate (2 x 100 mL). The ethyl acetate solution was washed with saturated aqueous sodium bicarbonate (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel using 1- 50% ethyl acetate in hexane as eluent to give (*S*)-*tert*-butyl 1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-7-yl)ethylcarbamate (4.34 g, 10.8 mmol, 76%) as an off-white solid. LCMS calculated for C₂₆H₂₃FN₃O₃S (M+H)⁺: m/z 404.1; Found 404.1. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.48 (ddd, *J* = 8.1, 7.8, 6.2 Hz, 1H), 7.18 (m, 3H), 7.05 (q, *J* = 1.3 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 4.41 (m, 1H), 2.66 (d, *J* = 1.3 Hz, 3H), 1.33 (s, 9H), 1.13 (d, *J* = 6.8 Hz, 3H).

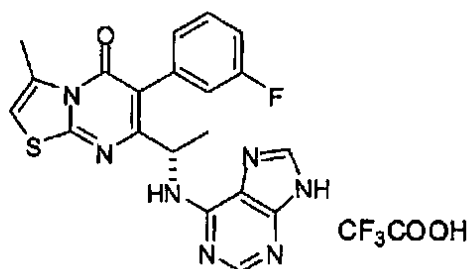
Step 7. (*S*)-7-(1-Aminoethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one



- 25 (*S*)-*tert*-Butyl 1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-7-yl)ethylcarbamate (4.15 g, 10.3 mmol) was dissolved in a 4.0 M solution of hydrogen chloride in 1,4-dioxane (25.7 mL, 102.8 mmol) and the solution was stirred at room temperature for 45 min. HPLC indicated that the reaction was complete. To the solution was added water (10 mL) followed by 3 N aqueous sodium hydroxide solution at 0- 5 °C to adjust the pH to 10. The

aqueous mixture was extracted with ethyl acetate (2 x 30 mL). The ethyl acetate solution was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (S)-7-(1-Aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (3.30 g, 10.88 mmol, 103% yield). LCMS calculated for C₁₅H₁₅FN₃OS (M+H)⁺: m/z 304.08; Found 303.9. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.45 (ddd, *J* = 8.1, 7.9, 5.9 Hz, 1H), 7.19 (m, 1H), 7.12 (m, 2H) 7.04 (q, *J* = 1.1 Hz, 1H), 3.57 (q, *J* = 6.6 Hz, 1H), 2.64 (d, *J* = 1.3 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H)

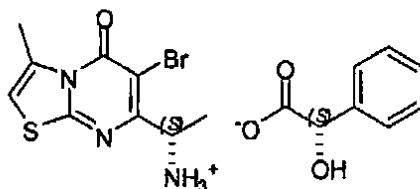
Step 8. (S)-7-(1-(9H-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt



(S)-7-(1-Aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (2.30 g, 7.58 mmol), 6-bromo-9H-purine (2.716 g, 13.65 mmol), *N,N*-diisopropylethylamine (6.60 mL, 37.9 mmol) were dissolved in ethanol (15 mL) and the resultant mixture was heated at reflux under a nitrogen atmosphere for 17 h. HPLC indicated the reaction was complete. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel using gradient elution starting at 100% DCM with increasing polarity to 25% of a mixture of DCM/MeOH/ aq.NH₄OH (100:5:0.5, v/v/v) in DCM. After the silica chromatography, 2.1 g of crude product was obtained. This crude product was further purified by preparative reversed phase HPLC using 0.1% TFA in water and acetonitrile as mobile phases at a flow rate of 60 mL/min. on a SunFire C18, 5 μM, 30 x 100 mm column. Pure (S)-7-(1-(9H-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one trifluoroacetic acid salt (INCB040093 trifluoroacetic acid salt) (1.86 g, 3.47 mmol, 45.8 % yield) was obtained as a white solid after lyophilization. LCMS calculated for C₂₀H₁₇FN₇OS (M+H)⁺ for the free base: m/z 422.1; Found: 422.0. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.03 (br s, 1H), 8.53 (s, 1H), 8.51 (s, 1H), 7.47 (m, 1H), 7.21 (m, 3H), 7.09 (s, 1H), 5.23 (m, 1H), 2.65 (d, *J* = 1.3 Hz, 3H), 1.43 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz,

DMSO-*d*₆) δ 164.0, 162.1 (J_{CF} = 244.9 Hz), 160.5, 160.3, 150.9, 147.6, 147.5, 144.4, 135.9, 135.9, 130.2 (J_{CF} = 8.3 Hz), 126.9, 117.4 (J_{CF} = 22.6 Hz), 116.1, 114.8 (J_{CF} = 21.5 Hz), 111.1, 107.8, 48.5, 19.6, 18.0. Reversed phase analytical HPLC showed purity at 99.8 area %. Chiral HPLC analysis was performed on Chiralcel OJ-H, 4.6 x 250 mm, 5 micron column using 60 % ethanol/40 % hexanes as eluent at a flow rate of 0.5 mL/min. The peak for the desired enantiomer (*S*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one was observed at a retention time of 21.171 min. (99.1 area %). The minor peak for the undesired enantiomer (*R*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one was observed at a retention time of 13.358 min (0.9 area %). The enantiomeric excess of the desired enantiomer was 98.2%.

Example 16. X-Ray Crystallography of (*S*)-1-(6-bromo-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-7-yl)ethanaminium (*S*)-2-hydroxy-2-phenylacetate (From Example 15, Step 5)



In order to determine the absolute stereochemistry of the product from Example 15, step 5, a sample was sublimed at about 105 °C to provide colorless needles suitable for X-ray crystal structure analysis. The study determined the absolute configuration of the amine bearing carbon (C-8) is *S*.

DATA COLLECTION: Bruker SMART APEX-II CCD system, MoK α radiation, standard focus tube, anode power = 50kV x 42 mA, crystal to plate distance = 5.0 cm, 512 x 512 pixels/frame, beam center = (256.13,253.14), total frames = 1081, oscillation/frame = 0.50°, exposure/frame = 300.1 sec/frame, SAINT integration, hkl min/max = (-4, 7, -14, 14, -31, 35), data input to shelx = 11285, unique data = 3870, two-theta range = 3.82 to 53.64°, completeness to two-theta 53.64 = 99.70%, $R(\text{int-xl})$ = 0.0908, SADABS correction applied.

SOLUTION AND REFINEMENT: Structure solved using XS(Shelxtl), refined using shelxtl software package, refinement by full-matrix least squares on F^2 , scattering factors from Int. Tab. Vol C Tables 4.2.6.8 and 6.1.1.4, number of data = 3870, number of restraints = 0, number of parameters = 309, data/parameter ratio = 12.52, goodness-of-fit on F^2 = 0.99, R

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indices[I>4sigma(I)] R1 = 0.0455, wR2 = 0.0674, R indices(all data) R1 = 0.1059, wR2 = 0.0825, max difference peak and hole = 0.420 and -0.863 e/Å³, refined flack parameter = 0.025(11). All of the hydrogen atoms have been found from a difference map and fully refined.

CRYSTAL DATA: C17 H18 Br N3 O4 S, from sublimation @ 105 °C, colorless, needle, ~0.160 x 0.020 x 0.020 mm, orthorhombic, P212121, a = 5.5572(18) Å, b = 11.547(4) Å, c = 28.207(10) Å, Vol = 1810.1(11) Å³, Z = 4, T = -100. °C, Formula weight = 440.31, Density = 1.616 g/cm³, μ(Mo) = 2.41 mm⁻¹.

RESULTS: This study determined the structure of C17,H18,N3,O4,S1,Br1 for the product of Example 15, step 5. The asymmetric unit contains one of each molecule as shown in Figure 1 with thermal ellipsoids drawn to the 50% probability level. The predicted structure was confirmed. The molecules form an infinite hydrogen bonded chain via the NH3's along the a-axis which is the needle axis, as shown in Figure 2. The absolute configuration was determined to be S at both C8 and C16 based upon the refinement of the flack parameter = 0.02(5). The configuration of C16 was known to be S.

Table A1. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å² x 10³). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

		x	y	z	U(eq)
20	Br(1)	5816(1)	1172(1)	1875(1)	34(1)
	S(1)	-2800(2)	-1679(1)	1030(1)	28(1)
	O(1)	2992(7)	-875(4)	2278(1)	48(1)
	O(2)	-1818(7)	-1946(3)	-193(1)	33(1)
	O(3)	-1693(5)	1147(3)	-24(1)	27(1)
25	O(4)	-4576(7)	-176(3)	77(1)	32(1)
	N(1)	285(6)	-1133(4)	1670(1)	22(1)
	N(2)	444(8)	26(3)	965(2)	25(1)
	N(3)	2679(10)	1576(4)	395(2)	23(1)
	C(1)	2242(9)	648(4)	1173(2)	20(1)
30	C(2)	3198(8)	351(4)	1606(2)	22(1)
	C(3)	2267(10)	-571(4)	1891(2)	29(1)
	C(4)	-474(9)	-820(4)	1219(2)	20(1)
	C(5)	-1135(9)	-2023(4)	1878(2)	25(1)
	C(6)	-2805(11)	-2394(5)	1565(2)	26(1)
35	C(7)	-807(18)	-2456(6)	2365(2)	41(2)
	C(8)	2920(10)	1736(4)	917(2)	23(1)
	C(9)	1254(13)	2703(5)	1078(3)	32(2)
	C(10)	-755(11)	-530(4)	-802(2)	21(1)
	C(11)	-2631(10)	-858(4)	-1102(2)	26(1)

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5	C(12)	-2597(11)	-528(5)	-1570(2)	28(1)
	C(13)	-732(12)	127(4)	-1755(2)	31(1)
	C(14)	1149(11)	434(5)	-1457(2)	31(1)
	C(15)	1156(10)	102(4)	-981(2)	26(1)
	C(16)	-926(12)	-817(4)	-274(2)	24(1)
	C(17)	-2506(10)	130(4)	-50(2)	23(1)

Table A2. Bond lengths [Å] and angles (deg)

10	Br(1)-C(2)	1.896(5)
	S(1)-C(4)	1.714(5)
	S(1)-C(6)	1.719(6)
	O(1)-C(3)	1.215(6)
	O(2)-C(16)	1.413(6)
15	O(3)-C(17)	1.260(6)
	O(4)-C(17)	1.256(6)
	N(1)-C(4)	1.387(6)
	N(1)-C(3)	1.422(6)
	N(1)-C(5)	1.423(6)
20	N(2)-C(4)	1.314(6)
	N(2)-C(1)	1.362(6)
	N(3)-C(8)	1.489(6)
	C(1)-C(2)	1.375(7)
	C(1)-C(8)	1.497(7)
25	C(2)-C(3)	1.431(7)
	C(5)-C(6)	1.350(8)
	C(5)-C(7)	1.474(8)
	C(8)-C(9)	1.521(8)
	C(10)-C(15)	1.385(8)
30	C(10)-C(11)	1.395(7)
	C(10)-C(16)	1.529(7)
	C(11)-C(12)	1.375(7)
	C(12)-C(13)	1.385(8)
	C(13)-C(14)	1.388(8)
35	C(14)-C(15)	1.394(8)
	C(16)-C(17)	1.538(7)
	C(4)-S(1)-C(6)	90.4(3)
	C(4)-N(1)-C(3)	121.2(4)
	C(4)-N(1)-C(5)	113.4(4)
40	C(3)-N(1)-C(5)	125.4(4)
	C(4)-N(2)-C(1)	116.3(5)
	N(2)-C(1)-C(2)	122.2(5)
	N(2)-C(1)-C(8)	114.8(5)
	C(2)-C(1)-C(8)	122.7(5)
45	C(1)-C(2)-C(3)	123.0(5)
	C(1)-C(2)-Br(1)	121.9(4)

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	C(3)-C(2)-Br(1)	115.1(4)
	O(1)-C(3)-N(1)	121.2(5)
	O(1)-C(3)-C(2)	126.8(5)
	N(1)-C(3)-C(2)	111.9(5)
5	N(2)-C(4)-N(1)	125.1(5)
	N(2)-C(4)-S(1)	123.6(4)
	N(1)-C(4)-S(1)	111.3(3)
	C(6)-C(5)-N(1)	110.0(5)
	C(6)-C(5)-C(7)	125.9(5)
10	N(1)-C(5)-C(7)	124.1(5)
	C(5)-C(6)-S(1)	114.8(5)
	N(3)-C(8)-C(1)	110.5(4)
	N(3)-C(8)-C(9)	109.4(5)
	C(1)-C(8)-C(9)	108.6(4)
15	C(15)-C(10)-C(11)	119.6(5)
	C(15)-C(10)-C(16)	121.2(5)
	C(11)-C(10)-C(16)	119.1(5)
	C(12)-C(11)-C(10)	119.8(5)
	C(11)-C(12)-C(13)	121.5(6)
20	C(12)-C(13)-C(14)	118.4(5)
	C(13)-C(14)-C(15)	121.0(5)
	C(10)-C(15)-C(14)	119.6(5)
	O(2)-C(16)-C(10)	112.3(4)
	O(2)-C(16)-C(17)	113.0(5)
25	C(10)-C(16)-C(17)	106.3(4)
	O(4)-C(17)-O(3)	125.1(5)
	O(4)-C(17)-C(16)	116.1(5)
	O(3)-C(17)-C(16)	118.8(5)
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Table A3. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) (symmetry transformations used to generate equivalent atoms. The anisotropic displacement factor exponent takes the form: $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

		U11	U22	U33	U23	U13	U12
	Br(1)	27(1)	40(1)	36(1)	-4(1)	-6(1)	-9(1)
	S(1)	27(1)	24(1)	33(1)	2(1)	-5(1)	-7(1)
	O(1)	54(3)	56(3)	33(3)	9(2)	-21(2)	-11(2)
	O(2)	41(3)	13(2)	46(3)	3(2)	6(2)	4(2)
40	O(3)	33(2)	14(2)	35(2)	5(2)	-7(1)	0(2)
	O(4)	31(3)	21(2)	44(3)	-1(2)	8(2)	0(2)
	N(1)	22(2)	22(2)	21(2)	1(2)	-3(2)	-3(2)
	N(2)	26(3)	21(2)	26(3)	5(2)	-2(2)	0(2)
	N(3)	27(3)	22(3)	19(3)	4(2)	3(2)	-8(2)
45	C(1)	16(3)	19(3)	26(3)	-4(2)	0(2)	-3(2)
	C(2)	13(3)	23(3)	29(3)	1(3)	1(2)	-2(2)

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5	C(3)	29(3)	31(3)	27(3)	-1(3)	-5(3)	2(3)
	C(4)	23(3)	17(3)	20(3)	4(2)	0(2)	1(2)
	C(5)	26(3)	22(3)	29(3)	11(3)	6(3)	-2(2)
	C(6)	22(3)	17(3)	40(4)	4(3)	0(3)	-4(3)
	C(7)	56(5)	36(4)	31(4)	11(3)	1(4)	-2(4)
10	C(8)	23(3)	21(3)	26(3)	-7(3)	-4(2)	-4(2)
	C(9)	34(5)	21(3)	41(5)	-3(3)	6(3)	-9(3)
	C(10)	23(3)	17(3)	23(3)	1(2)	6(3)	9(3)
	C(11)	26(3)	22(3)	31(4)	1(3)	3(3)	-6(3)
	C(12)	26(3)	19(3)	38(4)	-7(3)	-4(3)	11(3)
15	C(13)	37(3)	22(3)	32(4)	3(2)	5(3)	8(3)
	C(14)	22(4)	25(3)	45(4)	8(3)	10(3)	0(3)
	C(15)	27(3)	20(3)	33(3)	-1(3)	7(3)	6(3)
	C(16)	30(3)	10(3)	31(3)	-2(2)	1(3)	3(3)
	C(17)	29(3)	18(3)	22(3)	1(2)	-3(3)	6(3)

Table A4. Hydrogen coordinates (x 10⁴) and isotropic displacement parameters (A² x 10³)

20		x	y	z	U(eq)
	H(2)	-3600(200)	-1860(80)	-110(30)	160(40)
	H(3)	4250(110)	910(50)	254(19)	59(17)
	H(3A)	1260(150)	1240(60)	310(20)	80(20)
	H(3B)	2910(100)	2160(50)	266(19)	27(18)
25	H(6)	-3610(100)	-2890(40)	1579(18)	25(18)
	H(7)	-2240(160)	-3020(80)	2480(30)	120(30)
	H(7A)	-1360(90)	-1900(50)	2583(17)	30(17)
	H(7B)	640(120)	-2750(50)	2426(19)	41(19)
	H(8)	4800(80)	1970(40)	1003(17)	28(15)
30	H(9)	2070(100)	3440(50)	950(20)	56(19)
	H(9A)	1570(110)	2790(50)	1430(20)	60(20)
	H(9B)	-210(100)	2520(50)	1035(19)	34(19)
	H(11)	-3890(80)	-1350(40)	-963(14)	16(12)
	H(12)	-3720(100)	-740(50)	-1780(20)	60(20)
40	H(13)	-670(100)	380(40)	-2129(18)	40(15)
	H(14)	2390(110)	910(50)	-1573(18)	45(17)
	H(15)	2710(120)	320(50)	-760(20)	70(20)
	H(16)	780(100)	840(40)	-125(18)	50(16)

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Table A5. Torsion angles [deg].

	C(4)-N(2)-C(1)-C(2)	5.5(7)
	C(4)-N(2)-C(1)-C(8)	-168.8(4)
	N(2)-C(1)-C(2)-C(3)	-5.2(8)
5	C(8)-C(1)-C(2)-C(3)	168.7(5)
	N(2)-C(1)-C(2)-Br(1)	176.5(4)
	C(8)-C(1)-C(2)-Br(1)	-9.6(7)
	C(4)-N(1)-C(3)-O(1)	-177.1(5)
	C(5)-N(1)-C(3)-O(1)	4.4(8)
10	C(4)-N(1)-C(3)-C(2)	3.3(7)
	C(5)-N(1)-C(3)-C(2)	-175.2(4)
	C(1)-C(2)-C(3)-O(1)	-179.0(5)
	Br(1)-C(2)-C(3)-O(1)	-0.7(8)
	C(1)-C(2)-C(3)-N(1)	0.6(7)
15	Br(1)-C(2)-C(3)-N(1)	179.0(3)
	C(1)-N(2)-C(4)-N(1)	-1.5(7)
	C(1)-N(2)-C(4)-S(1)	178.2(4)
	C(3)-N(1)-C(4)-N(2)	-3.0(7)
	C(5)-N(1)-C(4)-N(2)	175.6(5)
20	C(3)-N(1)-C(4)-S(1)	177.2(4)
	C(5)-N(1)-C(4)-S(1)	-4.1(5)
	C(6)-S(1)-C(4)-N(2)	-177.2(5)
	C(6)-S(1)-C(4)-N(1)	2.5(4)
	C(4)-N(1)-C(5)-C(6)	3.8(6)
25	C(3)-N(1)-C(5)-C(6)	-177.6(5)
	C(4)-N(1)-C(5)-C(7)	-175.8(6)
	C(3)-N(1)-C(5)-C(7)	2.8(8)
	N(1)-C(5)-C(6)-S(1)	-1.8(6)
	C(7)-C(5)-C(6)-S(1)	177.7(5)
30	C(4)-S(1)-C(6)-C(5)	-0.4(5)
	N(2)-C(1)-C(8)-N(3)	-34.3(6)
	C(2)-C(1)-C(8)-N(3)	151.4(5)
	N(2)-C(1)-C(8)-C(9)	85.7(6)
	C(2)-C(1)-C(8)-C(9)	-88.6(6)
35	C(15)-C(10)-C(11)-C(12)	-1.5(8)
	C(16)-C(10)-C(11)-C(12)	174.9(5)
	C(10)-C(11)-C(12)-C(13)	0.0(8)
	C(11)-C(12)-C(13)-C(14)	1.0(8)
	C(12)-C(13)-C(14)-C(15)	-0.6(8)
40	C(11)-C(10)-C(15)-C(14)	1.9(8)
	C(16)-C(10)-C(15)-C(14)	-174.4(5)
	C(13)-C(14)-C(15)-C(10)	-0.9(8)
	C(15)-C(10)-C(16)-O(2)	-141.3(5)
	C(11)-C(10)-C(16)-O(2)	42.3(7)
45	C(15)-C(10)-C(16)-C(17)	94.7(6)
	C(11)-C(10)-C(16)-C(17)	-81.7(6)

O(2)-C(16)-C(17)-O(4)	-15.1(7)
C(10)-C(16)-C(17)-O(4)	108.4(5)
O(2)-C(16)-C(17)-O(3)	167.6(4)
C(10)-C(16)-C(17)-O(3)	-68.9(6)

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Example A1: PI3K Enzyme Assay

Materials: [γ - ^{33}P]ATP (10 mCi/mL) was purchased from Perkin-Elmer (Waltham, MA). Lipid kinase substrate, consisting of 1:19 molar ratio of phosphoinositol-4,5-bisphosphate (PIP2) with phosphoserine (PS), was purchased from Invitrogen (Carlsbad, CA). PI3K isoforms α , β , δ and γ were purchased from Millipore (Bedford, MA). ATP, NaCl, MgCl_2 , DTT, EDTA and CHAPS were purchased from Sigma-Aldrich (St. Louis, MO). HEPES 1 M, pH 7.0 stock buffer was purchased from Thermo Fisher Scientific (Pittsburgh, PA).

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The kinase reaction was conducted in clear-bottom 96-well plate from Thermo Fisher Scientific in a final volume of 40 μL . Inhibitors were first diluted serially in DMSO and added to the plate wells before the addition of other reaction components. The final concentration of DMSO in the assay was 2.5%. The PI3K assays were carried out at room temperature in 50 mM HEPES, pH 7.4, 5 mM MgCl_2 , NaCl 50 mM, 5 mM DTT and CHAPS 0.03%. The reaction mixture was prepared containing 20 μM PIP2:PS, kinase and varying concentration of inhibitors. Reactions were initiated by the addition of ATP containing 0.6 μCi [γ - ^{33}P]ATP to a final concentration of 200 μM . The final concentration of PI3K isoforms α , β , δ and γ in the assay were 0.34, 2.0, 0.76 and 13.7 nM respectively. Reactions were incubated for 60 min and terminated by the addition of 170 μL of 1 M potassium phosphate pH 8.0, 30 mM EDTA quench buffer. A 180 μL aliquot of the reaction solution was then transferred to 96-well Millipore MultiScreen IP 0.45 μm PVDF filter plate (The filter plate was prewetted with 200 μL 100% ethanol, distilled water, and 1 M potassium phosphate pH 8.0, respectively). The filter plate was aspirated on Millipore Manifold under vacuum and washed with $10 \times 200 \mu\text{L}$ wash buffer containing 1 M potassium phosphate pH 8.0 and 1 mM ATP. After drying by aspiration and blotting, the plate was air dried in an incubator at 37 $^\circ\text{C}$ overnight. Packard TopCount adapter (Millipore) was then attached to the plate followed with addition of 120 μL Microscint 20 scintillation cocktail (Perkin Elmer) in each well. After the plate sealing, the radioactivity of the product was determined by scintillation counting on Topcount (Perkin-Elmer). IC_{50} determination was performed by fitting the curve of percent control activity versus the log of the

inhibitor concentration using the GraphPad Prism 3.0 software. Compounds having an IC_{50} value of 10 μ M or less are considered active. See Table 1 for data related to compounds of the invention.

5 Example A2: PI3K Enzyme Assay

Materials: Lipid kinase substrate, phosphoinositol-4,5-bisphosphate (PIP2), was purchased from Echelon Biosciences (Salt Lake City, UT). PI3K isoforms α , β , δ and γ were purchased from Millipore (Bedford, MA). ATP, $MgCl_2$, DTT, EDTA, MOPS and CHAPS were purchased from Sigma-Aldrich (St. Louis, MO).

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The kinase reaction was conducted in clear-bottom 96-well plate from Thermo Fisher Scientific in a final volume of 24 μ L. Inhibitors were first diluted serially in DMSO and added to the plate wells before the addition of other reaction components. The final concentration of DMSO in the assay was 0.5%. The PI3K assays were carried out at room temperature in 20 mM MOPS, pH 6.7, 10 mM $MgCl_2$, 5 mM DTT and CHAPS 0.03%. The reaction mixture was prepared containing 50 μ M PIP2, kinase and varying concentration of inhibitors. Reactions were initiated by the addition of ATP containing 2.2 μ Ci [γ - ^{33}P]ATP to a final concentration of 1000 μ M. The final concentration of PI3K isoforms α , β , δ and γ in the assay were 1.3, 9.4, 2.9 and 10.8 nM respectively. Reactions were incubated for 180 min and terminated by the addition of 100 μ L of 1 M potassium phosphate pH 8.0, 30 mM EDTA quench buffer. A 100 μ L aliquot of the reaction solution was then transferred to 96-well Millipore MultiScreen IP 0.45 μ m PVDF filter plate (The filter plate was prewetted with 200 μ L 100% ethanol, distilled water, and 1 M potassium phosphate pH 8.0, respectively). The filter plate was aspirated on Millipore Manifold under vacuum and washed with 18 $\times$ 200 μ L wash buffer containing 1 M potassium phosphate pH 8.0 and 1 mM ATP. After drying by aspiration and blotting, the plate was air dried in an incubator at 37 $^{\circ}$ C overnight. Packard TopCount adapter (Millipore) was then attached to the plate followed with addition of 120 μ L Microscint 20 scintillation cocktail (Perkin Elmer) in each well. After the plate sealing, the radioactivity of the product was determined by scintillation counting on Topcount (Perkin-Elmer). IC_{50} determination was performed by fitting the curve of percent control activity versus the log of the inhibitor concentration using the

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GraphPad Prism 3.0 software. Compounds having and IC₅₀ value of 10 μM or less are considered active. See Table 1 for data related to compounds of the invention.

Table 1. IC₅₀ data for PI3Kδ enzyme assays A1 or A2*

Example ^a	PI3Kδ IC ₅₀ (nM)	PI3Kα IC ₅₀ (nM)	PI3Kβ IC ₅₀ (nM)	PI3Kγ IC ₅₀ (nM)
1	+++			
2	++			
3	+++			
4	+++			
5	+++			
6	+++			
7	+++			
8	++			
9	+	++++	++++	++
10	+	++++	++++	++++
11	+	++++	++++	+++
12	+			
13	+	++++	++++	+++
14	++			
15 ^b	+	++++	++++	++++

* “+” = <50 nM; “++” = 50-100 nM; “+++” = 100-500 nM; “++++” = >500 nM.
a. Assay A1 was used for Examples 1-14.
b. Assay A2 was used for Example 15.

Example B: B cell proliferation assay

To acquire B cells, human PBMC were isolated from the peripheral blood of normal, drug free donors by standard density gradient centrifugation on Ficoll-Hypaque (GE Healthcare, Piscataway, NJ) and incubated with anti-CD19 microbeads (Miltenyi Biotech, Auburn, CA). The B cells were then purified by positive immunosorting using an autoMacs (Miltenyi Biotech) according to the manufacture’s instruction.

The purified B cells (2×10⁵/well/200 μL) were cultured in 96-well ultra-low binding plates (Corning, Corning, NY) in RPMI1640, 10% FBS and goat F(ab’)₂ anti-human IgM (10 μg/ml) (Invitrogen, Carlsbad, CA), in the presence of different amount of test compounds, for three days. [³H]-thymidine (1 μCi/well) (PerkinElmer, Boston, MA) in PBS was then added to the B cell cultures for an additional 12 hrs before the incorporated radioactivity was separated by filtration with water through GF/B filters (Packard Bioscience, Meriden, CT) and measured by

liquid scintillation counting with a TopCount (Packard Bioscience). Compounds having an IC_{50} value of 10 μM or less are considered active. See Table 2 for data related to compounds of the invention.

5 **Table 2. IC_{50} data for B cell proliferation assay***

Example	B cell IC_{50} (nM)
1	+
2	+++
3	+
4	+
5	+
6	++
7	++++
8	+
9	+
10	+
11	+
12	+
13	+
14	
15	+

* "+" = <50 nM; "++" = 50-100 nM; "+++" = 100-500 nM; "++++" = >500 nM.

Example C: Akt phosphorylation assay

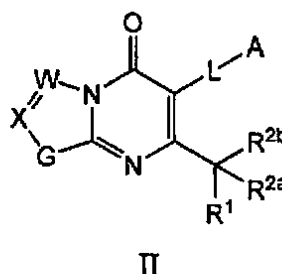
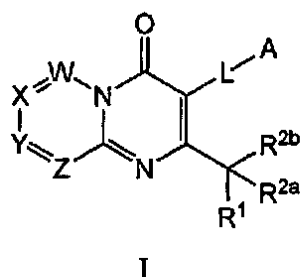
Ramos cells (B lymphocyte from Burkitts lymphoma) were obtained from ATCC (Manassas, VA) and maintained in RPMI1640 and 10% FBS. The cells (3×10^7 cells/tube/3 mL in RPMI) were incubated with different amounts of test compounds for 2 hrs at 37 °C and then stimulated with goat F(ab')₂ anti-human IgM (5 $\mu g/mL$) (Invitrogen) for 17 min. in a 37 °C water bath. The stimulated cells were spun down at 4 °C with centrifugation and whole cell extracts prepared using 300 μL lysis buffer (Cell Signaling Technology, Danvers, MA). The resulting lysates were sonicated and supernatants were collected. The phosphorylation level of Akt in the supernatants were analyzed by using PathScan phospho-Akt1 (Ser473) sandwich ELISA kits (Cell Signaling Technology) according to the manufacture's instruction.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also

intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A compound of Formula I or II:



or a pharmaceutically acceptable salt thereof, wherein:

A is C₁₋₁₀ alkyl, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

L is absent, (CR^{7a}R^{7b})_m, (CR^{7a}R^{7b})_pO(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pS(O)₂(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)NR^{7c}(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(O)O(CR^{7a}R^{7b})_q, (CR^{7a}R^{7b})_pNR^{7c}C(=NR^{7d})NR^{7c}(CR^{7a}R^{7b})_q, or (CR^{7a}R^{7b})_pNR^{7c}S(O)₂(CR^{7a}R^{7b})_q;

W is N or CR³;

X is N or CR⁴;

Y is N or CR⁵;

Z is N or CR⁶;

G is O, S, or NR^N;

R^1 is OR^A , SR^A , $S(O)R^A$, $S(O)_2R^A$, $NR^A R^B$, $NR^C C(O)NR^A R^B$, $NR^C C(O)OR^A$, $NR^C C(=NR^E)NR^A R^B$, $NR^C S(O)_2R^A$, $NR^C S(O)_2NR^C R^A$, heterocycloalkyl, or heteroaryl, wherein said heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from $-(C_{1-4} \text{ alkyl})-Cy^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}C(=NR^e)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^{2a} and R^{2b} are independently selected from H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl ring or a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl ring, each optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^e)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$;

R^3 , R^4 , R^5 , and R^6 are independently selected from H, halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)_2NR^{c3}R^{d3}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4,

or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

R^{7a} and R^{7b} are independently selected from H, halo, or C₁₋₄ alkyl;

R^{7c} is H or C₁₋₄ alkyl;

R^{7d} is H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, or C(O)NR^{c5}R^{d5};

R^A is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)_r, Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^B and R^C are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^E is H, CN, NO₂, OR^{a5}, SR^{b5}, S(O)₂R^{b5}, C(O)R^{b5}, S(O)₂NR^{c5}R^{d5}, or C(O)NR^{c5}R^{d5};

R^N is H or C₁₋₄ alkyl;

Cy¹ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^a , R^b , R^c , and R^d are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^c and R^d together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

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R^{a2} , R^{b2} , R^{c2} , and R^{d2} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^{a3} , R^{b3} , R^{c3} , and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

R^e and R^f are independently selected from H, CN, NO_2 , OR^{a5} , SR^{b5} , $S(O)_2R^{b5}$, $C(O)R^{b5}$, $S(O)_2NR^{c5}R^{d5}$, and $C(O)NR^{c5}R^{d5}$;

R^{a5} , R^{b5} , R^{c5} , and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $di(C_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $di(C_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

m is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

p is 0, 1, 2, 3, or 4;

q is 0, 1, 2, 3, or 4; and

r is 0 or 1.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having Formula I.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having Formula II.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein A is C_{1-10} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfonyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2 , OR^a , SR^a , $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d , $NR^cC(O)R^b$, $NR^cC(O)OR^a$, $NR^cC(O)NR^cR^d$, $C(=NR^e)R^b$, $C(=NR^e)NR^cR^d$, $NR^cC(=NR^e)NR^cR^d$, $NR^cS(O)R^b$, $NR^cS(O)_2R^b$, $NR^cS(O)_2NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, and $S(O)_2NR^cR^d$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl,

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cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

6. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a,

OC(O)R^b , $\text{OC(O)NR}^c\text{R}^d$, $\text{C(=NR}^e\text{)NR}^c\text{R}^d$, $\text{NR}^c\text{C(=NR}^e\text{)NR}^c\text{R}^d$, NR^eR^d , $\text{NR}^c\text{C(O)R}^b$,
 $\text{NR}^c\text{C(O)OR}^a$, $\text{NR}^c\text{C(O)NR}^c\text{R}^d$, $\text{NR}^c\text{S(O)R}^b$, $\text{NR}^c\text{S(O)}_2\text{R}^b$, $\text{NR}^c\text{S(O)}_2\text{NR}^c\text{R}^d$, S(O)R^b , $\text{S(O)NR}^c\text{R}^d$,
 $\text{S(O)}_2\text{R}^b$, and $\text{S(O)}_2\text{NR}^c\text{R}^d$.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein L is absent.

8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein L is $(\text{CR}^{7a}\text{R}^{7b})_m$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{O}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{S}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{S(O)}$
 $(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{S(O)}_2(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}(\text{CR}^{7a}\text{R}^{7b})_q$,
 $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{C(O)NR}^{7c}(\text{CR}^{7a}\text{R}^{7b})_q$, $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{C(O)O}(\text{CR}^{7a}\text{R}^{7b})_q$,
 $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{C(=NR}^{7d}\text{)NR}^{7c}(\text{CR}^{7a}\text{R}^{7b})_q$, or $(\text{CR}^{7a}\text{R}^{7b})_p\text{NR}^{7c}\text{S(O)}_2(\text{CR}^{7a}\text{R}^{7b})_q$.

9. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein L is $(\text{CR}^{7a}\text{R}^{7b})_m$.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein W is N.

11. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein W is CR^3 .

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein X is N.

13. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein X is CR^4 .

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein Y is N.

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15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein Y is CR⁵.
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein Z is N.
17. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein Z is CR⁶.
18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein G is O.
19. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein G is S.
20. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein G is NR^N.
21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R¹ is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from from -(C₁₋₄ alkyl)-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{al}, SR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, OC(O)R^{bl}, OC(O)NR^{cl}R^{dl}, C(=NR^e)NR^{cl}R^{dl}, NR^{cl}C(=NR^e)NR^{cl}R^{dl}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}C(O)NR^{cl}R^{dl}, NR^{cl}S(O)R^{bl}, NR^{cl}S(O)₂R^{bl}, NR^{cl}S(O)₂NR^{cl}R^{dl}, S(O)R^{bl}, S(O)NR^{cl}R^{dl}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{dl}.
22. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R¹ is NR^AR^B.
23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are independently selected from H and C₁₋₆ alkyl optionally substituted with

1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}.

24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R³, R⁴, R⁵, and R⁶ are independently selected from H or C₁₋₆ alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}.

25. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R³ is C₁₋₆ alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}.

26. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R⁴, R⁵, and R⁶ are each H.

27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein R^{7a}, R^{7b}, R^{7c}, and R^{7d} are each H.

28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein R^A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1},

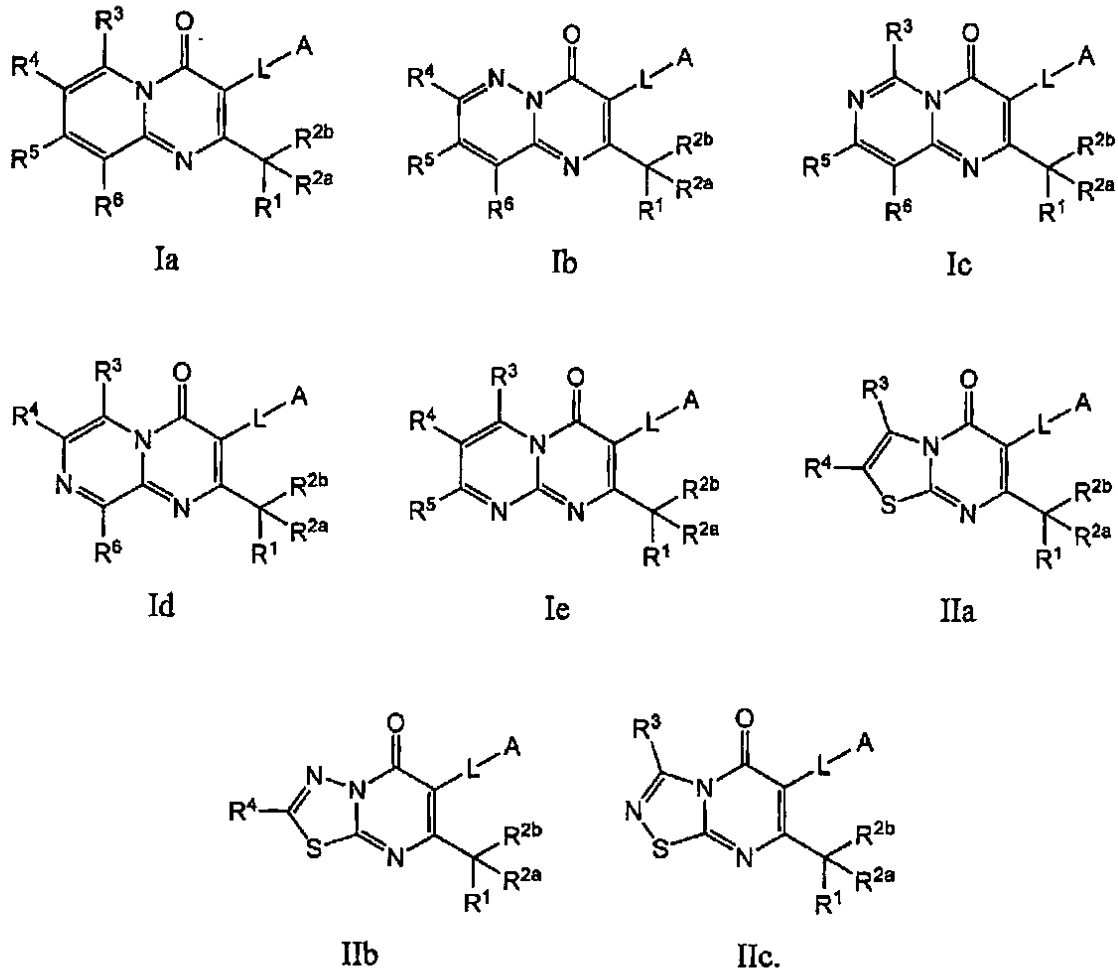
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$\text{NR}^{\text{cl}}\text{C}(\text{O})\text{OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{C}(\text{O})\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{S}(\text{O})\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S}(\text{O})_2\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S}(\text{O})_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S}(\text{O})\text{R}^{\text{bl}}$, $\text{S}(\text{O})\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S}(\text{O})_2\text{R}^{\text{bl}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$.

29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^{B} and R^{C} are independently selected from H and C_{1-5} alkyl.

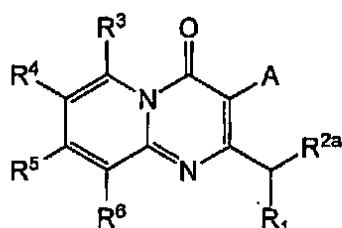
30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein A is other than phenyl substituted at the 4-position by halogen.

31. The compound of any one of claims 1-30, or a pharmaceutically acceptable salt thereof, having Formula Ia, Ib, Ic, Id, Ie, IIa, IIb, or IIc:

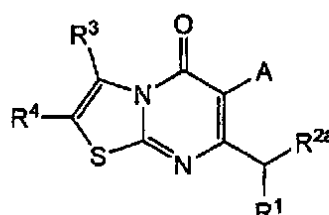


32. The compound of claim 1 having Formula If or IId:

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If



IId

or a pharmaceutically acceptable salt thereof.

33. The compound of claim 32, or pharmaceutically acceptable salt thereof, wherein:

A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

R¹ is OR^a, SR^a, S(O)R^a, S(O)₂R^a, NR^aR^b, NR^cC(O)NR^aR^b, NR^cC(O)OR^a, NR^cC(=NR^e)NR^aR^b, NR^cS(O)₂R^a, NR^cS(O)₂NR^cR^a, heterocycloalkyl, or heteroaryl, wherein said heterocycloalkyl or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^{2a} is H, halo, OH, CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl,

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cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^e)NR^{c2}R^{d2}, NR^{c2}C(=NR^e)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2},

R³, R⁴, R⁵, and R⁶ are independently selected from H, halo, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)₂NR^{c3}R^{d3}, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^e)NR^{c3}R^{d3}, NR^{c3}C(=NR^e)NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

R^A is heteroaryl, heterocycloalkyl, heteroarylalkyl, or heterocycloalkylalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)_r, Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^e)NR^{c1}R^{d1}, NR^{c1}C(=NR^e)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

R^B and R^C are independently selected from H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5},

$\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{E} is H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, or $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

Cy^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a1} , SR^{a1} , $\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{OC}(\text{O})\text{R}^{\text{b1}}$, $\text{OC}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(=\text{NR}^{\text{e}})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{OR}^{\text{a1}}$, $\text{NR}^{\text{c1}}\text{C}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{R}^{\text{b1}}$, $\text{NR}^{\text{c1}}\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})\text{R}^{\text{b1}}$, $\text{S}(\text{O})\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$, $\text{S}(\text{O})_2\text{R}^{\text{b1}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$;

R^{a} , R^{b} , R^{c} , and R^{d} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

or R^{c} and R^{d} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$,

NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a2} , R^{b2} , R^{c2} , and R^{d2} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$;

or R^{c2} and R^{d2} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}C(O)OR^{a5}, C(=NR^f)NR^{c5}R^{d5}, NR^{c5}C(=NR^f)NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, and S(O)₂NR^{c5}R^{d5};

R^{a3} , R^{b3} , R^{c3} , and R^{d3} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$,

$\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

or R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or a heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} haloalkyl, CN, OR^{a5} , SR^{a5} , $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{OC}(\text{O})\text{R}^{\text{b5}}$, $\text{OC}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{C}(=\text{NR}^{\text{f}})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{e} and R^{f} are independently selected from H, CN, NO_2 , OR^{a5} , SR^{b5} , $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{C}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, and $\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

R^{a5} , R^{b5} , R^{c5} , and R^{d5} are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $\text{di}(\text{C}_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy;

or R^{c5} and R^{d5} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group or heteroaryl group, each optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino, $\text{di}(\text{C}_{1-6} \text{ alkyl})\text{amino}$, C_{1-6} haloalkyl, and C_{1-6} haloalkoxy; and

r is 0 or 1;

provided that:

a) in Formula If, when A is 3-fluorophenyl; $\text{R}^{2\text{a}}$ is H; R^3 is methyl; and R^4 , R^5 , and R^6 are H; then, R^1 is other than 4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl; and

b) in Formula If, when A is 1,3-dioxolan-2-yl; $\text{R}^{2\text{a}}$, R^3 , R^4 , and R^6 are H; then, R^1 is other than 1-(tert-butoxycarbonyl)piperidin-4-yl.

34. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein the compound has Formula If.

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35. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein the compound has Formula IId.

36. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

37. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

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38. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

39. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

40. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is phenyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

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41. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is phenyl.

42. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

43. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is 6-membered heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

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44. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is pyridyl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

45. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is 5-membered heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^c)R^b, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^c)NR^cR^d, NR^cC(=NR^c)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d.

46. The compound of any one of claims 33-35, or a pharmaceutically acceptable salt thereof, wherein A is pyrazolyl optionally substituted with 1 or 2 substituents independently selected from halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

47. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R¹ is heteroaryl optionally substituted with 1, 2, or 3 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^c)NR^{c1}R^{d1}, NR^{c1}C(=NR^c)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}.

48. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R¹ is bicyclic heteroaryl optionally substituted with 1, 2, or 3 substituents independently

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selected from $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{al} , SR^{al} , C(O)R^{bl} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)OR}^{\text{al}}$, $\text{OC(O)R}^{\text{bl}}$, $\text{OC(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{S(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, S(O)R^{bl} , $\text{S(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, and $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$.

49. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R^1 is purinyl optionally substituted with $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{al} , SR^{al} , C(O)R^{bl} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)OR}^{\text{al}}$, $\text{OC(O)R}^{\text{bl}}$, $\text{OC(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{S(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, S(O)R^{bl} , $\text{S(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, or $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$.

50. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R^1 is OR^{A} , SR^{A} , S(O)R^{A} , $\text{S(O)}_2\text{R}^{\text{A}}$, $\text{NR}^{\text{A}}\text{R}^{\text{B}}$, $\text{NR}^{\text{C}}\text{C(O)NR}^{\text{A}}\text{R}^{\text{B}}$, $\text{NR}^{\text{C}}\text{C(O)OR}^{\text{A}}$, $\text{NR}^{\text{C}}\text{C(=NR}^{\text{E}}\text{)NR}^{\text{A}}\text{R}^{\text{B}}$, $\text{NR}^{\text{C}}\text{S(O)}_2\text{R}^{\text{A}}$, or $\text{NR}^{\text{C}}\text{S(O)}_2\text{NR}^{\text{C}}\text{R}^{\text{A}}$.

51. The compound of any one of claims 33-46, or a pharmaceutically acceptable salt thereof, wherein R^1 is $\text{NR}^{\text{A}}\text{R}^{\text{B}}$.

52. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^{A} is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{al} , SR^{al} , C(O)R^{bl} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)OR}^{\text{al}}$, $\text{OC(O)R}^{\text{bl}}$, $\text{OC(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(=NR}^{\text{e}}\text{)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{C(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{C(O)OR}^{\text{al}}$, $\text{NR}^{\text{cl}}\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{NR}^{\text{cl}}\text{S(O)R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{NR}^{\text{cl}}\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, S(O)R^{bl} , $\text{S(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, and $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$.

53. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^{A} is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from $-(C_{1-4} \text{ alkyl})_r\text{-Cy}^1$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{al} , SR^{al} , C(O)R^{bl} , $\text{C(O)NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)OR}^{\text{al}}$, $\text{OC(O)R}^{\text{bl}}$,

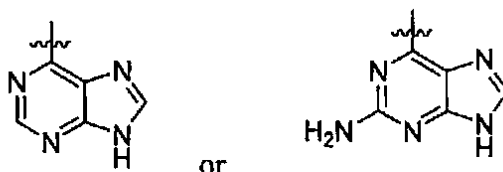
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OC(O)NR^{cl}R^{dl}, C(=NR^e)NR^{cl}R^{dl}, NR^{cl}C(=NR^e)NR^{cl}R^{dl}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}C(O)NR^{cl}R^{dl}, NR^{cl}S(O)R^{bl}, NR^{cl}S(O)₂R^{bl}, NR^{cl}S(O)₂NR^{cl}R^{dl}, S(O)R^{bl}, S(O)NR^{cl}R^{dl}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{dl}.

54. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy^l, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{al}, SR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, OC(O)R^{bl}, OC(O)NR^{cl}R^{dl}, C(=NR^e)NR^{cl}R^{dl}, NR^{cl}C(=NR^e)NR^{cl}R^{dl}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}C(O)NR^{cl}R^{dl}, NR^{cl}S(O)R^{bl}, NR^{cl}S(O)₂R^{bl}, NR^{cl}S(O)₂NR^{cl}R^{dl}, S(O)R^{bl}, S(O)NR^{cl}R^{dl}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{dl}.

55. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^A is purinyl optionally substituted with 1 or 2 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, NR^{cs}R^{ds}, NR^{cs}C(O)R^{bs}, NR^{cs}C(O)NR^{cs}R^{ds}, NR^{cs}C(O)OR^{as}, NR^{cs}C(=NR^f)NR^{cs}R^{ds}, NR^{cs}S(O)₂R^{bs}, NR^{cs}S(O)₂NR^{cs}R^{ds}, and S(O)₂NR^{cs}R^{ds}.

56. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^A is:



57. The compound of any one of claims 33-51, or a pharmaceutically acceptable salt thereof, wherein R^A is bicyclic heteroaryl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from -(C₁₋₄ alkyl)_r-Cy^l, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, halosulfanyl, CN, NO₂, OR^{al}, SR^{al}, C(O)R^{bl}, C(O)NR^{cl}R^{dl}, C(O)OR^{al}, OC(O)R^{bl}, OC(O)NR^{cl}R^{dl}, C(=NR^e)NR^{cl}R^{dl}, NR^{cl}C(=NR^e)NR^{cl}R^{dl}, NR^{cl}R^{dl}, NR^{cl}C(O)R^{bl}, NR^{cl}C(O)OR^{al}, NR^{cl}C(O)NR^{cl}R^{dl}, NR^{cl}S(O)R^{bl}, NR^{cl}S(O)₂R^{bl}, NR^{cl}S(O)₂NR^{cl}R^{dl}, S(O)R^{bl}, S(O)NR^{cl}R^{dl}, S(O)₂R^{bl}, and S(O)₂NR^{cl}R^{dl}.

58. The compound of any one of claims 33-57, or a pharmaceutically acceptable salt thereof, wherein R^B and R^C are independently selected from H and C_{1-6} alkyl.
59. The compound of any one of claims 33-57, or a pharmaceutically acceptable salt thereof, wherein R^B and R^C are each H.
60. The compound of any one of claims 33-59, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^c)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^c)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.
61. The compound of any one of claims 33-59, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, halosulfanyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^c)NR^{c2}R^{d2}$, $NR^{c2}C(=NR^c)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.
62. The compound of any one of claims 33-59, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.
63. The compound of any one of claims 33-59, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is methyl or ethyl.
64. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is halo, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}R^{d3}$,

$\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkylalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{OC}(\text{O})\text{R}^{\text{b3}}$, $\text{OC}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})\text{R}^{\text{b3}}$, $\text{S}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$.

65. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is H, halo, CN, NO_2 , OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, or C_{1-6} alkyl, wherein said C_{1-6} alkyl, is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{OC}(\text{O})\text{R}^{\text{b3}}$, $\text{OC}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{=NR}^{\text{e}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})\text{R}^{\text{b3}}$, $\text{S}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$.

66. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is H or C_{1-6} alkyl.

67. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-6} alkyl.

68. The compound of any one of claims 33-63, or a pharmaceutically acceptable salt thereof, wherein R^3 is methyl.

69. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R^4 , R^5 , and R^6 are independently selected from H, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl.

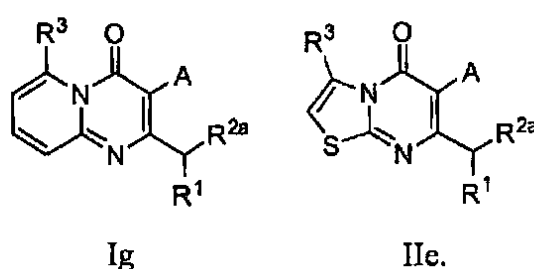
70. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R^4 , R^5 , and R^6 are each H.

71. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R⁴ is H.

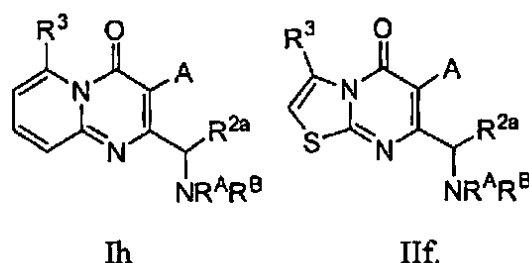
72. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R⁵ is H.

73. The compound of any one of claims 33-68, or a pharmaceutically acceptable salt thereof, wherein R⁶ is H.

74. The compound of any one of claims 33-73, or a pharmaceutically acceptable salt thereof, having Formula Ig or IIe:

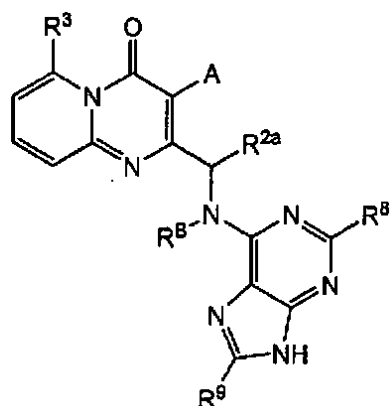


75. The compound of any one of claims 33-74, or a pharmaceutically acceptable salt thereof, having Formula Ih or IIf:

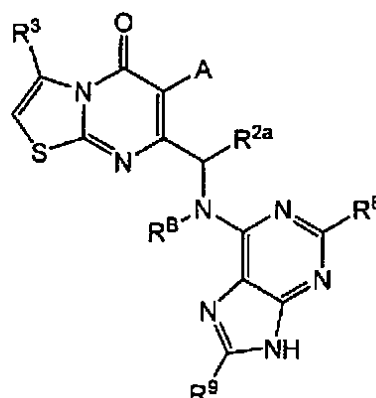


76. The compound of any one of claims 33-75, or a pharmaceutically acceptable salt thereof, having Formula Ii or IIg:

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II



IIg.

wherein R^8 and R^9 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}C(O)OR^{a5}$, $C(=NR^f)NR^{c5}R^{d5}$, $NR^{c5}C(=NR^f)NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, and $S(O)_2NR^{c5}R^{d5}$.

77. The compound of claim 1, selected from:

2-[1-(6-amino-9H-purin-9-yl)ethyl]-6-methyl-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one;

6-methyl-3-phenyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

3-(5-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

3-(3-fluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

3-(3,5-difluorophenyl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

3-(2-fluoropyridin-3-yl)-6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-4H-pyrido[1,2-a]pyrimidin-4-one;

6-methyl-2-[1-(9H-purin-6-ylamino)propyl]-3-(1H-pyrazol-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one;

3-methyl-6-phenyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-3-methyl-6-phenyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

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6-(3-fluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3-fluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

6-(3,5-difluorophenyl)-3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one;

7-{1-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(3,5-difluorophenyl)-3-methyl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one; and

3-methyl-7-[1-(9H-purin-6-ylamino)ethyl]-6-pyridin-2-yl-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one, or a pharmaceutically acceptable salt thereof.

78. The compound of claim 1, which is (*S*)-7-(1-(9*H*-purin-6-ylamino)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one, or a pharmaceutically acceptable salt thereof.

79. A composition comprising a compound according to any one of claims 1-78, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

80. A method of modulating an activity of a PI3K kinase comprising contacting the kinase with a compound of any one of claims 1-78, or a pharmaceutically acceptable salt thereof.

81. The method of claim 80 wherein the PI3K is selected from the group consisting of PI3K α , PI3K β , PI3K γ , and PI3K δ .

82. The method of claim 80 wherein said PI3K comprises a mutation.

83. The method of any one of claims 80-82 wherein said modulating is inhibiting.

84. The method of any one of claims 80-82 wherein said compound is a selective inhibitor for PI3K δ over one or more of PI3K α , PI3K β , and PI3K γ .

85. A method of treating a disease in a patient, wherein said disease is associated with abnormal expression or activity of a PI3K kinase, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1-78, or a pharmaceutically acceptable salt thereof.
86. The method of claim 85 wherein said disease is osteoarthritis, restenosis, atherosclerosis, bone disorders, arthritis, diabetic retinopathy, psoriasis, benign prostatic hypertrophy, atherosclerosis, inflammation, angiogenesis, pancreatitis, kidney disease, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, or Sjogren's syndrome.
87. The method of claim 85 wherein the PI3K is selected from the group consisting of PI3K α , PI3K β , PI3K γ , and PI3K δ .
88. The method of claim 85 wherein the PI3K is PI3K δ .
89. The method of any one of claims 85-88 wherein more than one of said compounds is administered.
90. The method of claim 89 wherein the compound is administered in combination with a kinase inhibitor that inhibits a kinase other than a PI3K kinase.
91. A method of treating an immune-based disease in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1-78, or a pharmaceutically acceptable salt thereof.
92. The method of claim 91 wherein said immune-based disease is rheumatoid arthritis, allergy, asthma, glomerulonephritis, lupus, or inflammation related to any of the aforementioned.
93. A method of treating a cancer in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1-78, or a pharmaceutically acceptable salt thereof.

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94. The method of claim 93 wherein said cancer is breast, prostate, colon, endometrial, brain, bladder, skin, uterus, ovary, lung, pancreatic, renal, gastric, or a hematological cancer.

95. The method of claim 94 wherein said hematological cancer is acute myeloblastic leukemia, chronic myeloid leukemia, or B cell lymphoma.

96. A method of treating a lung disease in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1-78, or a pharmaceutically acceptable salt thereof.

97. The method of claim 96 wherein said lung disease is acute lung injury (ALI) or adult respiratory distress syndrome (ARDS).

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ABSTRACT

The present invention provides pyrimidinones that modulate the activity of phosphoinositide 3-kinases (PI3Ks) and are useful in the treatment of diseases related to the activity of PI3Ks including, for example, inflammatory disorders, immune-based disorders, cancer, and other diseases.

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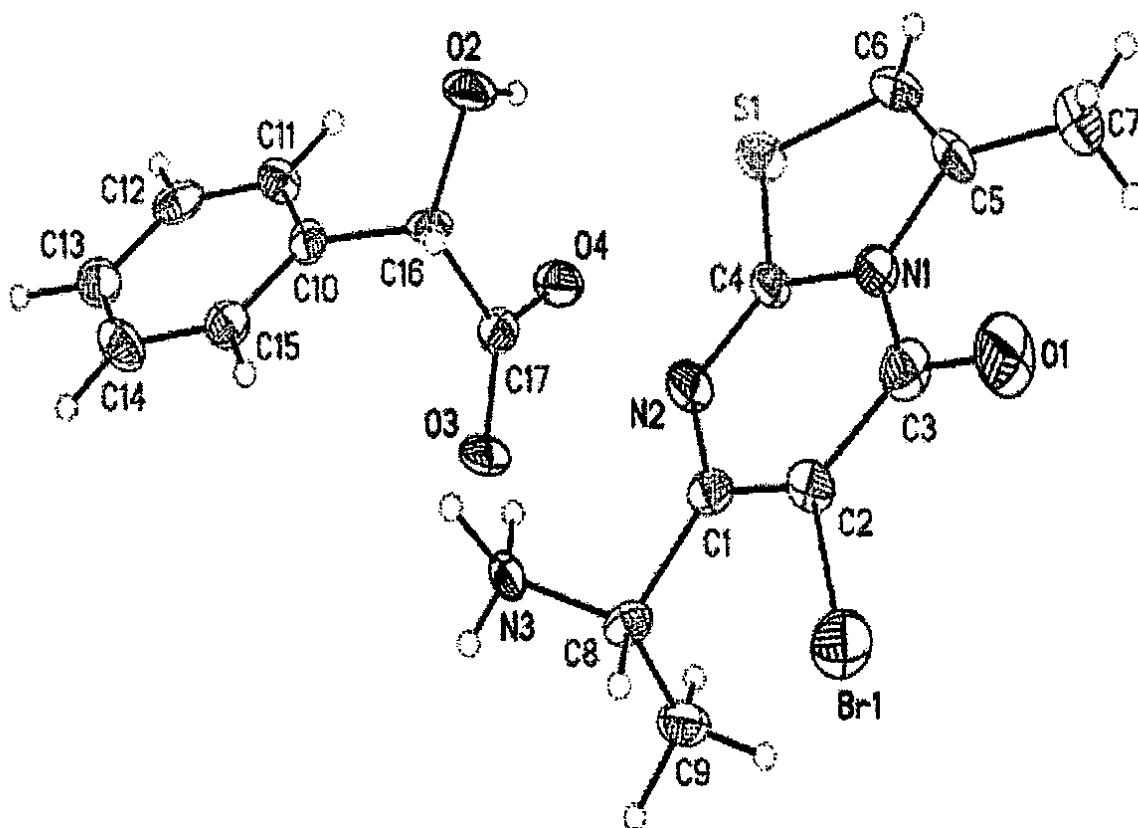


Fig. 1

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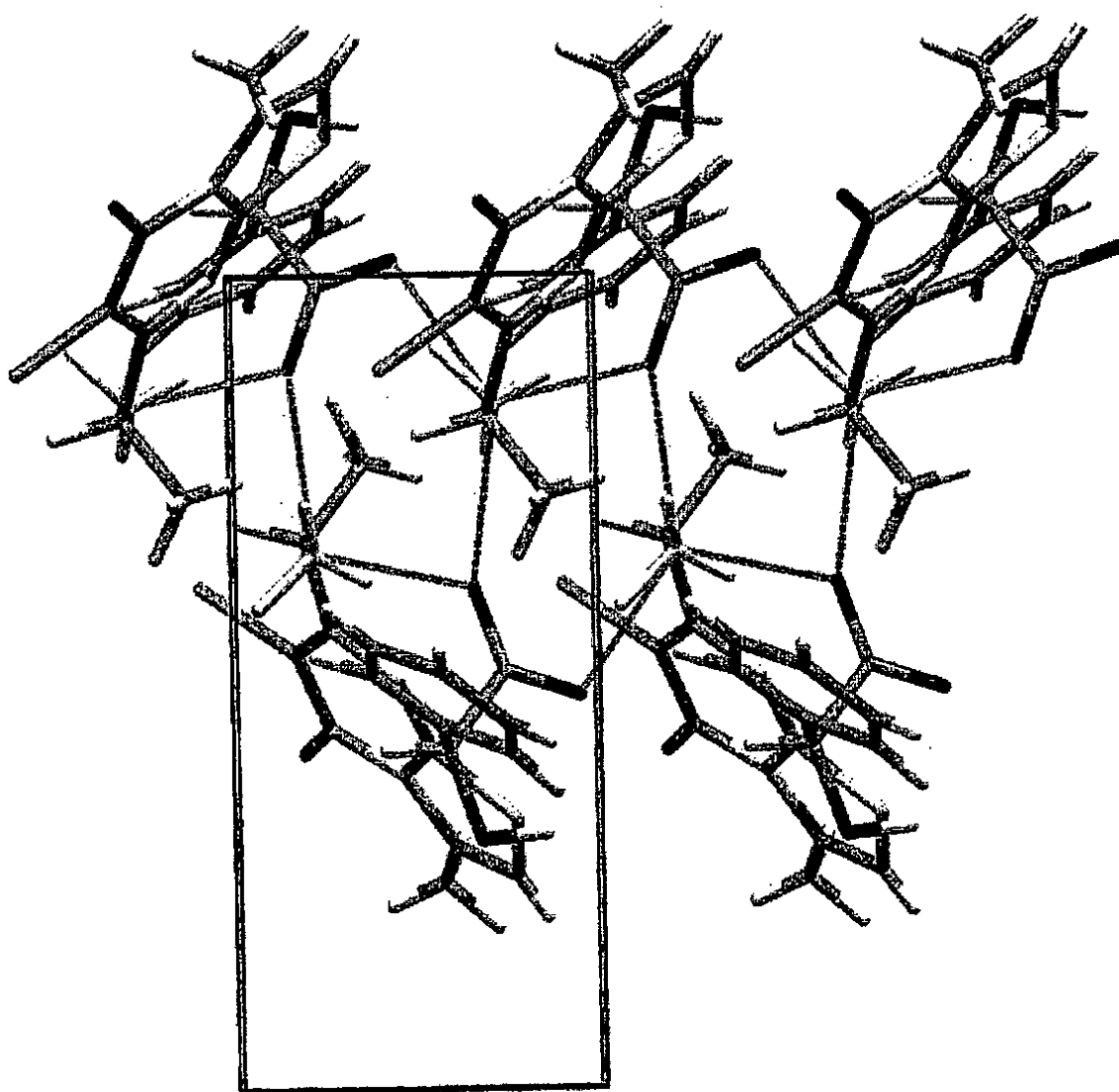


Fig. 2