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SUPERINDUSTRIA Y COMERCIO  
Radicación : 00096650 00000001 Folios: 188  
Fecha (ATD): 2001-02-09 16:16:30  
Tránsito : 002 PATENTES Y 1 REGISTRO/ 229 COTPLESE  
Dependencia: 2080 DIVISION DE NUEVAS CREACIONES

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO  
DIVISION DE NUEVAS CREACIONES

E. \_\_\_\_\_ S. \_\_\_\_\_ D. \_\_\_\_\_

Re: P1.-MERCK FROSST CANADA & CO.- Solicitud de Patente de  
Invención para "INHIBIDORES DE LA FOSFODIESTERASA-4  
8-ARILQUINOLINAS SUSTITUIDAS".- Clase A61 .-Expediente  
número 00-096.650.-

1. Me refiero a mi solicitud arriba nombrada de fecha 20 de Diciembre de 2000.

2. Anexos me permito presentar a usted:

- (1) Copia autentica, 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 60/171.522 de 22 de Diciembre de 1999, junto con su traducción correspondiente a las legalizaciones y reivindicaciones de dicho documento; y
- (2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial del señor Gabriel Rueda Chadid quien elaboró la traducción de la legalizaciones de la solicitud estadinense número 60/171.522 de 22 de Diciembre de 1999.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA

T.P. 10.784

Código 231

EL SUSCRITO JEFE DEL AREA DE  
LEGALIZACIONES DE MINISTERIO DE  
RELACIONES EXTERIORES.

HACE CONSTAR

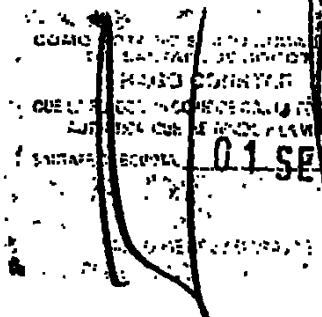
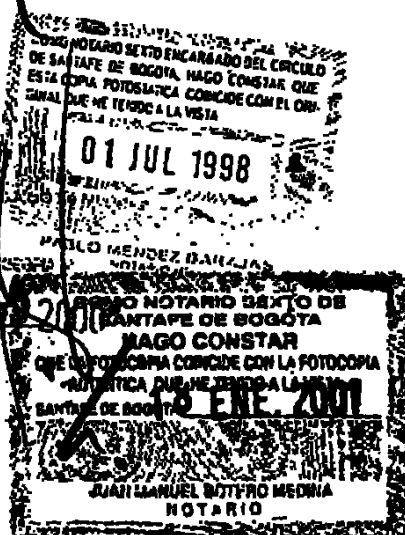
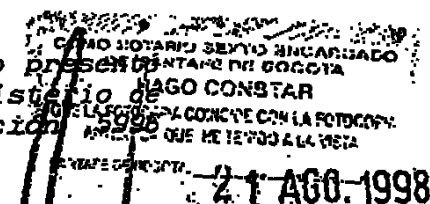
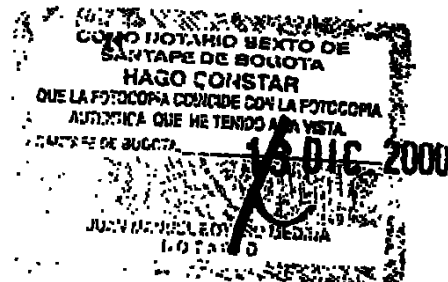
Que el señor Gabriel Rueda, se encuentra debidamente  
registrado ante este Ministerio, como traductor e  
intérprete oficial para los idiomas INGLES -ESPAÑOL,  
ESPAÑOL - INGLES.

Para efectos de esta certificación el interesado presenta  
copia autenticada de la certificación del Ministerio de  
Justicia acerca de la vigencia de la resolución 5988  
1982.

Dada en Santafé de Bogotá, D.C., a los diez y nueve días  
(19) del mes de diciembre de 1994.

Neilson Sánchez Torres  
Jefe Area de Legalizaciones

NST/gcm.





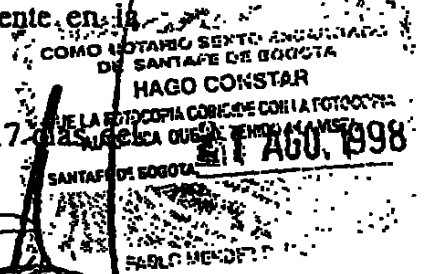
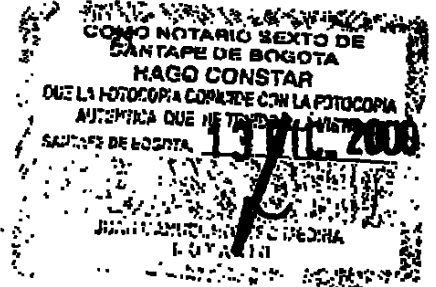
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EL SECRETARIO GENERAL DEL MINISTERIO DE  
JUSTICIA Y DEL DERECHO

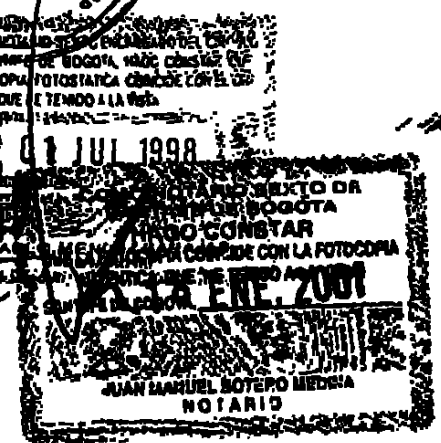
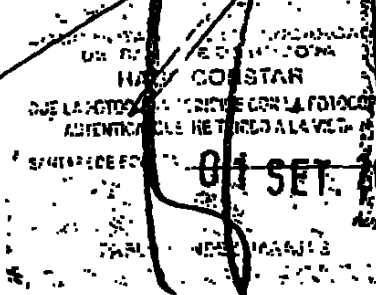
CERTIFICA:

Que por Resolución 5996 del 29 de noviembre de 1982, le fue expedida licencia para ejercer funciones de Traductor e Intérprete Oficial en los idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES a GABRIEL RUEDA CHADID, identificado con la cédula de ciudadanía No. 17.124.145 expedida en Bogotá. Que dicha resolución se encuentra vigente en la fecha.

A solicitud del interesado, en Santafé de Bogotá D.C., a los 17 días del mes de noviembre de 1994.



*[Handwritten signature]*  
JORGE LOIS SARDAGAL SARDAGAL  
SECRETARIO GENERAL



*[Handwritten initials]*

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TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFE DE BOGOTA  
SECRETARIA GENERAL

LA SUSCRITA SECRETARIA DEL H. TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL  
DE SANTAFE DE BOGOTA,

COMO NOTARIO SEXTO DE  
SANTAFE DE BOGOTA  
HAGO CONSTAR  
QUE LA FOTOCOPIA CONCIDE CON LA FOTOCOPIA  
AUTENTICA QUE HE TENIDO A LA VISTA  
SANTAFE DE BOGOTA 13 DIC 2000  
JUAN MANUEL BOTERO MEDINA  
NOTARIO

CERTIFICA :

Que el Acuerdo No. 183 de diciembre 3 de 1982 emanado de esta Corporación, por medio del cual dió posesión al señor GABRIEL RUEDA CHADID, identificado con Cédula de Ciudadanía número 17.124.145 de Bogotá, como TRADUCTOR E INTERPRETE OFICIAL de los idiomas INGLES-ESPAÑOL-ESPAÑOL-INGLES, en virtud de la Resolución No. 5996, se encuentra VIGENTE.

COMO NOTARIO SEXTO ENCARGADO  
DE SANTAFE DE BOGOTA  
HAGO CONSTAR  
QUE LA FOTOCOPIA CONCIDE CON LA FOTOCOPIA  
AUTENTICA QUE HE TENIDO A LA VISTA  
SANTAFE DE BOGOTA 01 SET 2000  
JUAN MANUEL BOTERO MEDINA  
NOTARIO  
21 AGO 1998

Se expide en Santafé de Bogotá D.C., a dieciseis (16) de noviembre  
mil novecientos noventa y cuatro (1994).

  
MARIA INES RODRIGUEZ TORRES  
SECRETARIA

COMO NOTARIO SEXTO ENCARGADO  
DE SANTAFE DE BOGOTA  
HAGO CONSTAR  
QUE LA FOTOCOPIA CONCIDE CON LA FOTOCOPIA  
AUTENTICA QUE HE TENIDO A LA VISTA  
SANTAFE DE BOGOTA 01 JUL 1998  
JUAN MANUEL BOTERO MEDINA  
NOTARIO  
01 JUL 1998  
JUAN MANUEL BOTERO MEDINA  
NOTARIO  
NOV 1998  
JUAN MANUEL BOTERO MEDINA  
NOTARIO

CRM./

REF: LLC-138-2000.. La presente es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial).

**ESTADOS UNIDOS DE AMERICA**

**A TODOS AQUELLOS QUE LLEGAREN A LEER EL CONTENIDO DEL  
PRESENTE DOCUMENTO LES CERTIFICAMOS:**

**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS**

**Oficina de Marcas y Patentes de los Estados Unidos**

**Octubre 19 del 2000**

Se certifica que anexo se encuentra fiel copia de los Registros de la Oficina de Marcas y Patentes de los Estados Unidos correspondientes a los documentos de la patente solicitada y cuya identificación aparece más adelante, la cual cumplió con los requerimientos exigidos para que se otorgue una fecha de presentación de acuerdo con los dispuesto en la Sección 35 USC 111.

**Número de Solicitud: 60/171.522**

**Fecha de presentación: Diciembre 22, 1989**

**Por autorización del**

**COMISIONADO DE MARCAS REGISTRADAS Y PATENTES**

**N. WOODSON**

**Funcionario Encargado de Certificaciones (Hay firma y sello)**

*GABRIEL RUEDA CHADID*  
**GABRIEL RUEDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 5996 DE NOV. 29-03**  
**MINISTERIO DE JUSTICIA**

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272

Indicar con un signo (+) dentro de esta casilla --> +

Oficina de Marcas y Patentes:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

**PORTADA PARA LA SOLICITUD PROVISIONAL DE PATENTES**

La presente solicitud de presentación de solicitud provisional de acuerdo con 37 CFR 1.53 (c)

Expediente No.: MC015PV

**INVENTOR(ES)**

| Apellido | Primer Nombre | Lugar de Residencia<br>(Ciudad y Estado o País) |
|----------|---------------|-------------------------------------------------|
| Denis    | Deschenes     | Dorval, Quebec, Canada H9S 1M7                  |
| Daniel   | Dube          | St-Lazare, Quebec, Canada J7T 2J9               |
| Michel   | Gallant       | Montreal-Ouest, Quebec, Canada H4X 2B1          |
| Yves     | Girard        | Ile-Bizard, Quebec, Canada H9C 2E1              |
| Patrick  | Lacombe       | Montreal, Quebec, Canada H3T 1H9                |
| Dwight   | MacDonald     | L'ile Bizard, Quebec, Canada H9C 1E2            |
| Anthony  | Mastracchio   | Montreal, Quebec, Canada H3T 1H9                |

**TITULO DEL INVENTO (280 caracteres máximo)**

**INHIBIDORES SUSTITUIDOS 8-ARILQUINOLINA FOSFODIESTERASA-4**

**DIRECCION DE CORRESPONDENCIA**

Enviar correspondencia a:

Merck & Co., Inc.

Patent Department - RY60-30 [X] No. de Cliente 000210

P.O. Box 2000

Rahway

Estado: New Jersey Código: 07065 País: USA

GABRIEL RUEDA CHADID  
TRADUCTOR OFICIAL  
RESOLUCION 1194 DE NOV. 29-83  
MINISTERIO DE JUSTICIA

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PARTES ADJUNTAS DE LA SOLICITUD (indicar lo que se aplica)

X Especificaciones Número de Páginas: 13

**FORMA DE PAGO (Indicar)**

X El Comisionado queda autorizado para cobrar los derechos  
de presentación y acreditar la cuenta No. 13-2755

DERECHOS PROVISIONALES DE PRESENTACION: \$ 150.00

Fue elaborado por una entidad del Gobierno de los Estados Unidos, o bajo contrato con entidades del Gobierno de dicho país

[X] No.

Firmado. Fecha: 12/22/89

NOMBRE: Shu Muk Lee No. de Registro: 41.147

Tel. (732) 584-4858

**CERTIFICADO DE ENVIO POR CORREO EXPRESO**

FECHA DE DEPOSITO: Diciembre 22. 1989

No. de Etiqueta de Correo Expreso: EM358365538US

Certifico que los siguientes documentos en relación con la solicitud mencionada fueron depositados en el servicio postal de los Estados Unidos, correo Expreso "Oficina Postal al Destinatario" en Washington, D.C. 2023.

(Hay firma) Fecha: Diciembre 22. 1989.

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**PORTADA PARA LA SOLICITUD PROVISIONAL DE PATENTES**

**Página Adicional**

La presente solicitud de presentación de solicitud provisional de acuerdo con 37 CFR 1.53 (c)

Expediente No.: MC015PV

Indicar con un signo (+) dentro de esta casilla --> +

**INVENTOR(ES)**

Apellido Primer Nombre Lugar de Residencia

(Ciudad y Estado o País)

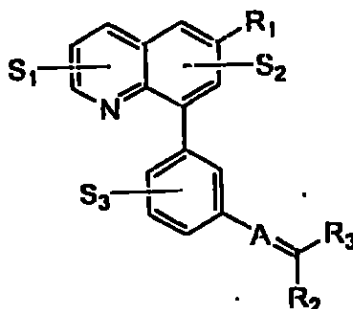
Helene Perrier Montreal, Quebec, Canada H3T 1H9

Número 2 de 2 portadas totales, incluida la portada primaria.

**Firmado**

**BARBARA RUEDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 1996 DE NOV. 29-83**  
**MINISTERIO DE JUSTICIA**

1. Un compuesto representando por la formula (I):



o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

R<sub>1</sub> es un halógeno, carbonilo, -alquiloC<sub>1</sub>-C<sub>8</sub>, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, -alqueniloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, arilo, heteroarilo, -CN, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -amino, -alquilaminoC<sub>1</sub>-C<sub>8</sub>, -(alquiloC<sub>1</sub>-C<sub>8</sub>)(alquiloC<sub>1</sub>-C<sub>8</sub>)amino, -alquiloC<sub>1</sub>-C<sub>8</sub>(oxi)alquiloC<sub>1</sub>-C<sub>8</sub>, -C(O)NH(arilo), -C(O)NH(heteroarilo), -SO<sub>n</sub>NH(arilo), -SO<sub>n</sub>NH(heteroarilo), -SO<sub>n</sub>NH(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloC<sub>6</sub>-C<sub>8</sub>)(alquiloC<sub>6</sub>-C<sub>8</sub>), -NH-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -carbamoil, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-O-C(CN)-dialquilamino, o -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>) en grupos, donde uno de estos grupos se sustituye opcionalmente con sustitutos 1-5; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloC<sub>6</sub>-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo,

heteroarilo, carbonilo, carbamoil, o  $-SO_n-(alquiloC_1-C_6)$ ;

A es CH, C-ester, o C- $R_4$ ;

$R_2$  y  $R_3$  son independientemente un arilo, heteroarilo, H, halógeno, -CN,  $-alquiloC_1-C_6$ ,  $-alcoxiC_1-C_6$ , carbonilo, carbamoil,  $-COOH$ ,  $-(alquiloC_1-C_6)-SO_n-(alquiloC_1-C_6)$ ,  $-C(O)N(alquiloCo-C_6)(alquiloCo-C_6)$ , o grupo  $-alquilacilaminoC_1-C_6$ , donde uno de los grupos se sustituye opcionalmente por 1-5 sustitutos, donde cada uno de estos sustitutos es independientemente un halógeno,  $-NO_2$ ,  $-COOH$ , carbonilo, -CN,  $-alquiloC_1-C_6$ ,  $-SO_n-(alquiloC_1-C_6)$ , -O-arilo, -O-heteroarilo,  $-C(O)-heterocicloalquiloC_3-C_6$ ,  $-NH-cicloalquiloC_3-C_6$ , amino, -OH, o  $-alquiloC_1-C_6(amino)$  en grupos sustituidos, donde cada grupo sustituido independientemente se sustituye de manera opcional por -OH,  $-O(alquiloC_1-C_6)$ ,  $-O(arilo)$ ,  $-COOH$ ,  $-COO(alquiloC_1-C_6)$ , halógeno,  $-NO_2$ , -CN, o  $-C(O)-N(alquiloCo-C_6)(alquiloCo-C_6)$ ;

uno de los  $R_2$  y  $R_3$  debe ser un arilo o heteroarilo, sustituido opcionalmente;

cuando  $R_2$  y  $R_3$  son ambos un arilo, entonces  $R_2$  y  $R_3$  se conectan opcionalmente por un puente tio, oxi, o  $(alquiloC_1-C_4)$  para formar un sistema fusionado de tres anillos;

$R_4$  es un arilo, heteroarilo, -CN, -carbonilo, carbamoil,  $-(alquiloC_1-C_6)-SO_n-(alquiloC_1-C_6)$ ,  $-C(O)N(alquiloCo-C_6)(alquiloCo-C_6)$ , o grupo  $-alquilacilaminoC_1-C_6$ , donde uno de los grupos es sustituido opcionalmente por 1-5 sustitutos,

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donde cada sustituto es independientemente un carbonilo, -CN, halógeno, -C(O)(alquiloCo-Ce), -alquiloC<sub>1</sub>-Ce, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-Ce), amino, -OH, o grupo alquiloC<sub>1</sub>-Ce(amino); y

n es independientemente 0, 1, o 2.

2. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptable, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-Ce, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-Ce;

R<sub>1</sub> es halógeno, carbonilo, -alquiloC<sub>1</sub>-Ce, -cicloalquiloC<sub>3</sub>-Ce, -alqueniloC<sub>1</sub>-Ce, -alcoxiC<sub>1</sub>-Ce, arilo, heteroarilo, -CN, heterocicloalquiloC<sub>3</sub>-Ce, -amino, -alquilaminoC<sub>1</sub>-Ce, -(alquiloC<sub>1</sub>-Ce)(alquiloC<sub>1</sub>-Ce)amino, -alquiloC<sub>1</sub>-Ce(oxi)alquiloC<sub>1</sub>-Ce, -C(O)NH(arilo), -C(O)NH(heteroarilo), -SO<sub>n</sub>NH(arilo), -SO<sub>n</sub>NH(heteroarilo), -SO<sub>n</sub>NH(alquiloC<sub>1</sub>-Ce), -C(O)N(alquiloCo-Ce)(alquiloCo-Ce), -NH-SO<sub>n</sub>-(alquiloC<sub>1</sub>-Ce), -SO<sub>n</sub>-(alquiloC<sub>1</sub>-Ce), -carbamoil, -(alquiloC<sub>1</sub>-Ce)-O-C(CN)-dialquilamino, o -(alquiloC<sub>1</sub>-Ce)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-Ce) en grupos, donde uno de los grupos es sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-Ce), -C(O)-O-(alquiloCo-Ce), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-Ce, heterocicloalquiloC<sub>3</sub>-Ce, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-Ce);

A es CH;

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R<sub>2</sub> y R<sub>3</sub> es independientemente un arilo, heteroarilo, H, halógeno, -CN, -alquiloC<sub>1</sub>-C<sub>6</sub>, -alcoxiC<sub>1</sub>-C<sub>6</sub>, carbonilo, carbamoyl, -COOH, -(alquiloC<sub>1</sub>-C<sub>6</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>6</sub>), -C(O)N(alquiloC<sub>6</sub>-C<sub>6</sub>)(alquiloC<sub>6</sub>-C<sub>6</sub>), o -alquilacilaminoC<sub>1</sub>-C<sub>6</sub> en grupos, donde uno de los grupos es sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>6</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>6</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>6</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>6</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-C<sub>6</sub>(amino) donde cada grupo sustituto es independientemente y de manera opcional sustituido por -OH, -O(alquiloC<sub>1</sub>-C<sub>6</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>6</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloC<sub>6</sub>-C<sub>6</sub>)(alquiloC<sub>6</sub>-C<sub>6</sub>); uno de los R<sub>2</sub> y R<sub>3</sub> debe ser un arilo o heteroarilo, opcionalmente sustituidos; y cuando R<sub>2</sub> y R<sub>3</sub> son ambos un arilo entonces R<sub>2</sub> y R<sub>3</sub> se conectan opcionalmente por un puente tio, oxi, o (alquiloC<sub>1</sub>-C<sub>4</sub>) para formar un sistema fusionado de tres anillos; y

n es independientemente 0, 1, o 2.

3. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>6</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>6</sub>;

R<sub>1</sub> es un -alquiloC<sub>1</sub>-C<sub>6</sub>, sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>6</sub>), -C(O)-O-

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(alquiloCo-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

R<sub>2</sub> y R<sub>3</sub> independientemente es un arilo, heteroarilo, H, halógeno, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, carbonilo, carbamoil, -COOH, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>), o grupo -alquilacilaminoC<sub>1</sub>-C<sub>8</sub>, donde uno de los grupos es sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>); uno de los R<sub>2</sub> y R<sub>3</sub> debe ser un arilo o heteroarilo, sustituido opcionalmente; y cuando R<sub>2</sub> y R<sub>3</sub> son ambos arilo, entonces R<sub>2</sub> y R<sub>3</sub> se conectan opcionalmente mediante un puente tio, oxi, o (alquiloC<sub>1</sub>-C<sub>4</sub>) para formar un sistema fusionado de tres anillos; y

n es independientemente 0, 1, o 2.

4. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

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S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

R<sub>1</sub> es un -cicloalquiloC<sub>3</sub>-C<sub>8</sub> sustituido opcionalmente por 1-5 sustitutos; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloC<sub>6</sub>-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

R<sub>2</sub> y R<sub>3</sub> independientemente es un arilo, heteroarilo, H, halógeno, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, carbonilo, carbamoil, -COOH, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloC<sub>6</sub>-C<sub>8</sub>)(alquiloC<sub>6</sub>-C<sub>8</sub>), o grupo -alquilacilaminoC<sub>1</sub>-C<sub>8</sub>, donde uno de los grupos es sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloC<sub>6</sub>-C<sub>8</sub>)(alquiloC<sub>6</sub>-C<sub>8</sub>); uno de los R<sub>2</sub> y R<sub>3</sub> debe ser un arilo o heteroarilo, sustituido opcionalmente; y cuando R<sub>2</sub> y R<sub>3</sub> son ambos arilo, entonces R<sub>2</sub> y R<sub>3</sub> se conectan opcionalmente mediante un puente tio, oxi, o (alquiloC<sub>1</sub>-C<sub>4</sub>) para formar un sistema fusionado de tres anillos; y

n es independientemente 0, 1, o 2.

5. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

R<sub>1</sub> es un -alqueniloC<sub>1</sub>-C<sub>8</sub> sustituido opcionalmente por 1-5 sustitutos; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloC<sub>6</sub>-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

R<sub>2</sub> y R<sub>3</sub> independientemente es un arilo, heteroarilo, H, halógeno, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, carbonilo, carbamoil, -COOH, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloC<sub>6</sub>-C<sub>8</sub>)(alquiloC<sub>6</sub>-C<sub>8</sub>), o grupo -alquilacilaminoC<sub>1</sub>-C<sub>8</sub>, donde uno de los grupos es sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-

$N(\text{alquiloCo-C}_8)(\text{alquiloCo-C}_8)$ ; uno de los  $R_2$  y  $R_3$  debe ser un arilo o heteroarilo, sustituido opcionalmente; y cuando  $R_2$  y  $R_3$  son ambos arilo, entonces  $R_2$  y  $R_3$  se conectan opcionalmente mediante un puente tio, oxi, o  $(\text{alquiloC}_1-\text{C}_4)$  para formar un sistema fusionado de tres anillos; y

$n$  es independientemente 0, 1, o 2.

6. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

$S_1$ ,  $S_2$  y  $S_3$  son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

$R_1$  es un heteroarilo, sustituido opcionalmente por 1-5 sustitutos; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloCo-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

$R_2$  y  $R_3$  independientemente es un arilo, heteroarilo, H, halógeno, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, carbonilo, carbamoil, -COOH, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>), o grupo -alquilacilaminoC<sub>1</sub>-C<sub>8</sub>, donde uno de los grupos es sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -

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CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloC<sub>2</sub>-C<sub>8</sub>)(alquiloC<sub>2</sub>-C<sub>8</sub>); uno de los R<sub>2</sub> y R<sub>3</sub> debe ser un arilo o heteroarilo, sustituido opcionalmente; y cuando R<sub>2</sub> y R<sub>3</sub> son ambos arilo, entonces R<sub>2</sub> y R<sub>3</sub> se conectan opcionalmente mediante un puente tio, oxi, o (alquiloC<sub>1</sub>-C<sub>4</sub>) para formar un sistema fusionado de tres anillos; y

n es independientemente 0, 1, o 2.

7. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

R<sub>1</sub> es un -amino, -alquilaminoC<sub>1</sub>-C<sub>8</sub>, o grupo -(alquiloC<sub>1</sub>-C<sub>8</sub>)(alquiloC<sub>1</sub>-C<sub>8</sub>)amino, donde uno de los grupos es sustituido opcionalmente por 1-5 sustitutos; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloC<sub>2</sub>-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoyl, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

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R<sub>2</sub> y R<sub>3</sub> independientemente es un arilo, heteroarilo, H, halógeno, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, carbonilo, carbamoyl, -COOH, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>), o grupo -alquilacilaminoC<sub>1</sub>-C<sub>8</sub>, donde uno de los grupos es sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>); uno de los R<sub>2</sub> y R<sub>3</sub> debe ser un arilo o heteroarilo, sustituido opcionalmente; y cuando R<sub>2</sub> y R<sub>3</sub> son ambos arilo, entonces R<sub>2</sub> y R<sub>3</sub> se conectan opcionalmente mediante un puente tio, oxi, o (alquiloC<sub>1</sub>-C<sub>4</sub>) para formar un sistema fusionado de tres anillos; y

n es independientemente 0, 1, o 2.

8. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

R<sub>1</sub> es un halógeno, carbonilo, -alquiloC<sub>1</sub>-C<sub>8</sub>, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, -alqueniloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, arilo, heteroarilo, -CN, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -amino, -

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alquilaminoC<sub>1</sub>-C<sub>8</sub>, -(alquiloC<sub>1</sub>-C<sub>8</sub>)(alquiloC<sub>1</sub>-C<sub>8</sub>)amino, -  
alquiloC<sub>1</sub>-C<sub>8</sub>(oxi)alquiloC<sub>1</sub>-C<sub>8</sub>, -C(O)NH(arilo), -  
C(O)NH(heteroarilo), -SO<sub>n</sub>NH(arilo), -SO<sub>n</sub>NH(heteroarilo), -  
SO<sub>n</sub>NH(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>), -NH-  
SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -carbamoil, -  
(alquiloC<sub>1</sub>-C<sub>8</sub>)-O-C(CN)-dialquilamino, o -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-  
(alquiloC<sub>1</sub>-C<sub>8</sub>) en grupos, donde uno de estos grupos se  
sustituye opcionalmente con sustitutos 1-5; donde cada  
sustituto es independientemente un halógeno, -OH, -CN, -  
C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloCo-C<sub>8</sub>), -C(O)-  
O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -  
cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo,  
heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

R<sub>2</sub> es un arilo, sustituido opcionalmente por 1-5  
sustitutos, donde cada sustituto es independientemente un  
halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-  
(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-  
heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o  
grupo sustituto -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo  
sustituto independientemente se sustituye opcionalmente por -  
OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>),  
halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>);

R<sub>3</sub> es un heteroarilo, sustituido opcionalmente por 1-5  
sustitutos, donde cada sustituto es independientemente un  
halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-  
(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-

heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>); y

n es independientemente 0, 1, o 2.

9. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

R<sub>1</sub> es un halógeno, carbonilo, -alquiloC<sub>1</sub>-C<sub>8</sub>, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, -alquenoC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, arilo, heteroarilo, -CN, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -amino, -alquilaminoC<sub>1</sub>-C<sub>8</sub>, -(alquiloC<sub>1</sub>-C<sub>8</sub>)(alquiloC<sub>1</sub>-C<sub>8</sub>)amino, -alquiloC<sub>1</sub>-C<sub>8</sub>(oxi)alquiloC<sub>1</sub>-C<sub>8</sub>, -C(O)NH(arilo), -C(O)NH(heteroarilo), -SO<sub>n</sub>NH(arilo), -SO<sub>n</sub>NH(heteroarilo), -SO<sub>n</sub>NH(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>), -NH-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -carbamoil, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-O-C(CN)-dialquilamino, o -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>) en grupos, donde uno de estos grupos se sustituye opcionalmente con sustitutos 1-5; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloCo-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

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A es CH;

R<sub>2</sub> es un arilo, sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>);

R<sub>3</sub> es un arilo, sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>); y

n es independientemente 0, 1, o 2.

10. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

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R<sub>1</sub> es un halógeno, carbonilo, -alquiloC<sub>1</sub>-C<sub>8</sub>, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, -alqueniloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, arilo, heteroarilo, -CN, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -amino, -alquilaminoC<sub>1</sub>-C<sub>8</sub>, -(alquiloC<sub>1</sub>-C<sub>8</sub>)(alquiloC<sub>1</sub>-C<sub>8</sub>)amino, -alquiloC<sub>1</sub>-C<sub>8</sub>(oxi)alquiloC<sub>1</sub>-C<sub>8</sub>, -C(O)NH(arilo), -C(O)NH(heteroarilo), -SO<sub>n</sub>NH(arilo), -SO<sub>n</sub>NH(heteroarilo), -SO<sub>n</sub>NH(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>), -NH-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -carbamoil, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-O-C(CN)-dialquilamino, o -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>) en grupos, donde uno de estos grupos se sustituye opcionalmente con sustitutos 1-5; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloCo-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

R<sub>2</sub> es un carbonilo, sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>);

R<sub>3</sub> es un arilo, sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un

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halógeno,  $-\text{NO}_2$ ,  $-\text{COOH}$ , carbonilo,  $-\text{CN}$ ,  $-\text{alquiloC}_1\text{-C}_8$ ,  $-\text{SO}_n$ -  
( $\text{alquiloC}_1\text{-C}_8$ ),  $-\text{O-arilo}$ ,  $-\text{O-heteroarilo}$ ,  $-\text{C(O)-}$   
heterocicloalquilo $\text{C}_3\text{-C}_8$ ,  $-\text{NH-cicloalquiloC}_3\text{-C}_8$ , amino,  $-\text{OH}$ , o  
 $-\text{alquiloC}_1\text{-C}_8(\text{amino})$ , donde cada grupo sustituto  
independientemente se sustituye opcionalmente por  $-\text{OH}$ ,  $-\text{O}(\text{alquiloC}_1\text{-C}_8)$ ,  
 $-\text{O(arilo)}$ ,  $-\text{COOH}$ ,  $-\text{COO}(\text{alquiloC}_1\text{-C}_8)$ ,  
halógeno,  $-\text{NO}_2$ ,  $-\text{CN}$ , o  $-\text{C(O)-N}(\text{alquiloCo-C}_8)(\text{alquiloCo-C}_8)$ ; y

n es independientemente 0, 1, o 2.

11. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H,  $-\text{OH}$ , halógeno,  $-\text{alquiloC}_1\text{-C}_8$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ , o  $-\text{alcoxiC}_1\text{-C}_8$ ;

R<sub>1</sub> es un halógeno, carbonilo,  $-\text{alquiloC}_1\text{-C}_8$ ,  $-\text{cicloalquiloC}_3\text{-C}_8$ ,  $-\text{alquieniloC}_1\text{-C}_8$ ,  $-\text{alcoxiC}_1\text{-C}_8$ , arilo, heteroarilo,  $-\text{CN}$ , heterocicloalquilo $\text{C}_3\text{-C}_8$ ,  $-\text{amino}$ ,  $-\text{alquilaminoC}_1\text{-C}_8$ ,  $-(\text{alquiloC}_1\text{-C}_8)(\text{alquiloC}_1\text{-C}_8)\text{amino}$ ,  $-\text{alquiloC}_1\text{-C}_8(\text{oxi})\text{alquiloC}_1\text{-C}_8$ ,  $-\text{C(O)NH(arilo)}$ ,  $-\text{C(O)NH(heteroarilo)}$ ,  $-\text{SO}_n\text{NH(arilo)}$ ,  $-\text{SO}_n\text{NH(heteroarilo)}$ ,  $-\text{SO}_n\text{NH(alquiloC}_1\text{-C}_8)$ ,  $-\text{C(O)N(alquiloCo-C}_8)(\text{alquiloCo-C}_8)$ ,  $-\text{NH-SO}_n$ ,  $-\text{SO}_n$ ,  $-\text{SO}_n(\text{alquiloC}_1\text{-C}_8)$ ,  $-\text{SO}_n$ ,  $-\text{SO}_n(\text{alquiloC}_1\text{-C}_8)$ ,  $-\text{carbamoil}$ ,  $-(\text{alquiloC}_1\text{-C}_8)-\text{O-C(CN)-dialquilamino}$ , o  $-(\text{alquiloC}_1\text{-C}_8)-\text{SO}_n$ ,  $-(\text{alquiloC}_1\text{-C}_8)$  en grupos, donde uno de estos grupos se sustituye opcionalmente con sustitutos 1-5; donde cada sustituto es independientemente un halógeno,  $-\text{OH}$ ,  $-\text{CN}$ ,  $-\text{C(O)(heterocicloalquiloC}_3\text{-C}_8)$ ,  $-\text{C(O)-O-(alquiloCo-C}_8)$ ,  $-\text{C(O)-O-arilo}$ ,  $-\text{alcoxi}$ ,  $-\text{cicloalquiloxi}$ ,  $-\text{acilo}$ ,  $-\text{aciloxi}$ ,  $-\text{cicloalquiloC}_3\text{-C}_8$ ,  $-\text{heterocicloalquiloC}_3\text{-C}_8$ ,  $-\text{arilo}$ ,

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heteroarilo, carbonilo, carbamoil, o  $-SO_n-(alquiloC_1-C_8)$ ;

A es CH;

R<sub>2</sub> es un carbamoilo, sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno,  $-NO_2$ ,  $-COOH$ , carbonilo,  $-CN$ ,  $-alquiloC_1-C_8$ ,  $-SO_n-(alquiloC_1-C_8)$ ,  $-O-arilo$ ,  $-O-heteroarilo$ ,  $-C(O)-heterocicloalquiloC_3-C_8$ ,  $-NH-cicloalquiloC_3-C_8$ , amino,  $-OH$ , o grupo sustituto  $-alquiloC_1-C_8(amino)$ , donde cada grupo sustituto independientemente se sustituye opcionalmente por  $-OH$ ,  $-O(alquiloC_1-C_8)$ ,  $-O(arilo)$ ,  $-COOH$ ,  $-COO(alquiloC_1-C_8)$ , halógeno,  $-NO_2$ ,  $-CN$ , o  $-C(O)-N(alquiloCo-C_8)(alquiloCo-C_8)$ ;

R<sub>3</sub> es un arilo, sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno,  $-NO_2$ ,  $-COOH$ , carbonilo,  $-CN$ ,  $-alquiloC_1-C_8$ ,  $-SO_n-(alquiloC_1-C_8)$ ,  $-O-arilo$ ,  $-O-heteroarilo$ ,  $-C(O)-heterocicloalquiloC_3-C_8$ ,  $-NH-cicloalquiloC_3-C_8$ , amino,  $-OH$ , o  $-alquiloC_1-C_8(amino)$ , donde cada grupo sustituto independientemente se sustituye opcionalmente por  $-OH$ ,  $-O(alquiloC_1-C_8)$ ,  $-O(arilo)$ ,  $-COOH$ ,  $-COO(alquiloC_1-C_8)$ , halógeno,  $-NO_2$ ,  $-CN$ , o  $-C(O)-N(alquiloCo-C_8)(alquiloCo-C_8)$ ; y

n es independientemente 0, 1, o 2.

12. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H,  $-OH$ , halógeno,  $-alquiloC_1-C_8$ ,  $-NO_2$ ,  $-CN$ , o  $-alcoxiC_1-C_8$ ;

R<sub>1</sub> es un halógeno, carbonilo, -alquiloC<sub>1</sub>-C<sub>8</sub>, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, -alqueniloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, arilo, heteroarilo, -CN, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -amino, -alquilaminoC<sub>1</sub>-C<sub>8</sub>, -(alquiloC<sub>1</sub>-C<sub>8</sub>)(alquiloC<sub>1</sub>-C<sub>8</sub>)amino, -alquiloC<sub>1</sub>-C<sub>8</sub>(oxi)alquiloC<sub>1</sub>-C<sub>8</sub>, -C(O)NH(arilo), -C(O)NH(heteroarilo), -SO<sub>n</sub>NH(arilo), -SO<sub>n</sub>NH(heteroarilo), -SO<sub>n</sub>NH(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloC<sub>3</sub>-C<sub>8</sub>)(alquiloC<sub>3</sub>-C<sub>8</sub>), -NH-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -carbamoil, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-O-C(CN)-dialquilamino, o -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>) en grupos, donde uno de estos grupos se sustituye opcionalmente con sustitutos 1-5; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

R<sub>2</sub> y R<sub>3</sub> son cada uno y de manera independientemente un arilo, sustituido opcionalmente, conectado entre sí por un puente tio, oxi, o (alquiloC<sub>1</sub>-C<sub>4</sub>) para formar un sistema fusionado de tres anillos; y

n es independientemente 0, 1, o 2.

13. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

R<sub>1</sub> es un halógeno, carbonilo, -alquiloC<sub>1</sub>-C<sub>8</sub>, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, -alqueniloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, arilo, heteroarilo, -CN, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -amino, -alquilaminoC<sub>1</sub>-C<sub>8</sub>, -(alquiloC<sub>1</sub>-C<sub>8</sub>)(alquiloC<sub>1</sub>-C<sub>8</sub>)amino, -alquiloC<sub>1</sub>-C<sub>8</sub>(oxi)alquiloC<sub>1</sub>-C<sub>8</sub>, -C(O)NH(arilo), -C(O)NH(heteroarilo), -SO<sub>n</sub>NH(arilo), -SO<sub>n</sub>NH(heteroarilo), -SO<sub>n</sub>NH(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>), -NH-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -carbamoil, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-O-C(CN)-dialquilamino, o -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>) en grupos, donde uno de estos grupos se sustituye opcionalmente con sustitutos 1-5; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloCo-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

R<sub>2</sub> es un -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>);

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R<sub>3</sub> es un arilo, sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>- (alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>); y

n es independientemente 0, 1, o 2.

14. El compuesto de acuerdo con la reivindicación 1, o una de sus sales farmacéuticamente aceptables, donde:

S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

R<sub>1</sub> es un halógeno, carbonilo, -alquiloC<sub>1</sub>-C<sub>8</sub>, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, -alquenoC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, arilo, heteroarilo, -CN, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -amino, -alquilaminoC<sub>1</sub>-C<sub>8</sub>, -(alquiloC<sub>1</sub>-C<sub>8</sub>)(alquiloC<sub>1</sub>-C<sub>8</sub>)amino, -alquiloC<sub>1</sub>-C<sub>8</sub>(oxi)alquiloC<sub>1</sub>-C<sub>8</sub>, -C(O)NH(arilo), -C(O)NH(heteroarilo), -SO<sub>n</sub>NH(arilo), -SO<sub>n</sub>NH(heteroarilo), -SO<sub>n</sub>NH(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloCo-C<sub>8</sub>)(alquiloCo-C<sub>8</sub>), -NH-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -carbamoil, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-O-C(CN)-dialquilamino, o -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>) en grupos, donde uno de estos grupos se sustituye opcionalmente con sustitutos 1-5; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloCo-C<sub>8</sub>), -C(O)-

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O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -  
cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo,  
heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

R<sub>2</sub> es un -C(O)-N(alquiloC<sub>3</sub>-C<sub>8</sub>)(alquiloC<sub>3</sub>-C<sub>8</sub>), sustituido  
opcionalmente por 1-5 sustitutos, donde cada sustituto es  
independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -  
CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-  
heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-  
cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o grupo sustituto -alquiloC<sub>1</sub>-  
C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se  
sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo),  
-COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-  
N(alquiloC<sub>3</sub>-C<sub>8</sub>)(alquiloC<sub>3</sub>-C<sub>8</sub>);

R<sub>3</sub> es un arilo, sustituido opcionalmente por 1-5  
sustitutos, donde cada sustituto es independientemente un  
halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-  
(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-  
heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o  
-alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto  
independientemente se sustituye opcionalmente por -OH, -  
O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>),  
halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloC<sub>3</sub>-C<sub>8</sub>)(alquiloC<sub>3</sub>-C<sub>8</sub>); y

n es independientemente 0, 1, o 2.

15. El compuesto de acuerdo con la reivindicación 1, o  
una de sus sales farmacéuticamente aceptables, donde:

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S<sub>1</sub>, S<sub>2</sub> y S<sub>3</sub> son independientemente H, -OH, halógeno, -alquiloC<sub>1</sub>-C<sub>8</sub>, -NO<sub>2</sub>, -CN, o -alcoxiC<sub>1</sub>-C<sub>8</sub>;

R<sub>1</sub> es un halógeno, carbonilo, -alquiloC<sub>1</sub>-C<sub>8</sub>, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, -alqueniloC<sub>1</sub>-C<sub>8</sub>, -alcoxiC<sub>1</sub>-C<sub>8</sub>, arilo, heteroarilo, -CN, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -amino, -alquilaminoC<sub>1</sub>-C<sub>8</sub>, -(alquiloC<sub>1</sub>-C<sub>8</sub>)(alquiloC<sub>1</sub>-C<sub>8</sub>)amino, -alquiloC<sub>1</sub>-C<sub>8</sub>(óxi)alquiloC<sub>1</sub>-C<sub>8</sub>, -C(O)NH(arilo), -C(O)NH(heteroarilo), -SO<sub>n</sub>NH(arilo), -SO<sub>n</sub>NH(heteroarilo), -SO<sub>n</sub>NH(alquiloC<sub>1</sub>-C<sub>8</sub>), -C(O)N(alquiloC<sub>6</sub>-C<sub>8</sub>)(alquiloC<sub>6</sub>-C<sub>8</sub>), -NH-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -carbamoil, -(alquiloC<sub>1</sub>-C<sub>8</sub>)-O-C(CN)-dialquilamino, o -(alquiloC<sub>1</sub>-C<sub>8</sub>)-SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>) en grupos, donde uno de estos grupos se sustituye opcionalmente con sustitutos 1-5; donde cada sustituto es independientemente un halógeno, -OH, -CN, -C(O)(heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>), -C(O)-O-(alquiloC<sub>6</sub>-C<sub>8</sub>), -C(O)-O-arilo, alcoxi, cicloalquiloxi, acilo, aciloxi, -cicloalquiloC<sub>3</sub>-C<sub>8</sub>, heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, arilo, heteroarilo, carbonilo, carbamoil, o -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>);

A es CH;

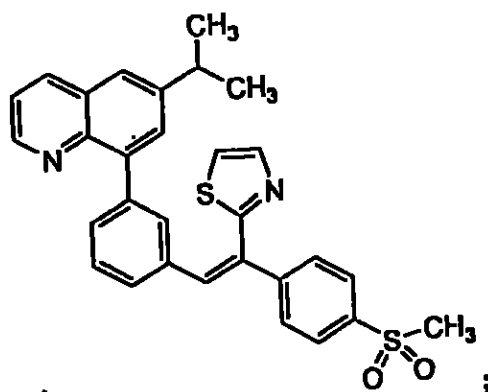
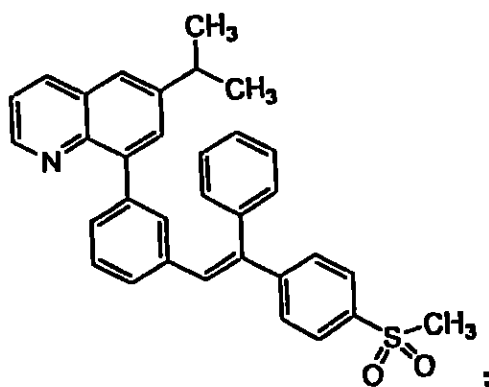
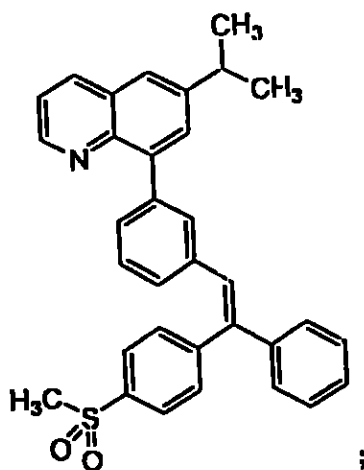
R<sub>2</sub> es -CN;

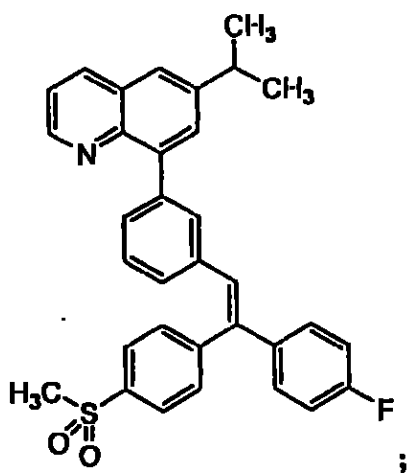
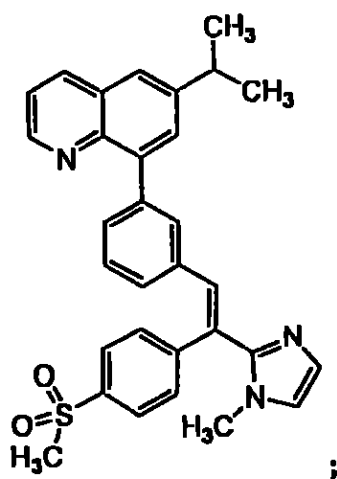
R<sub>3</sub> es un arilo, sustituido opcionalmente por 1-5 sustitutos, donde cada sustituto es independientemente un halógeno, -NO<sub>2</sub>, -COOH, carbonilo, -CN, -alquiloC<sub>1</sub>-C<sub>8</sub>, -SO<sub>n</sub>-(alquiloC<sub>1</sub>-C<sub>8</sub>), -O-arilo, -O-heteroarilo, -C(O)-heterocicloalquiloC<sub>3</sub>-C<sub>8</sub>, -NH-cicloalquiloC<sub>3</sub>-C<sub>8</sub>, amino, -OH, o -alquiloC<sub>1</sub>-C<sub>8</sub>(amino), donde cada grupo sustituto independientemente se sustituye opcionalmente por -OH, -O(alquiloC<sub>1</sub>-C<sub>8</sub>), -O(arilo), -COOH, -COO(alquiloC<sub>1</sub>-C<sub>8</sub>), halógeno, -NO<sub>2</sub>, -CN, o -C(O)-N(alquiloC<sub>6</sub>-C<sub>8</sub>)(alquiloC<sub>6</sub>-C<sub>8</sub>); y

n es independientemente 0, 1, o 2.

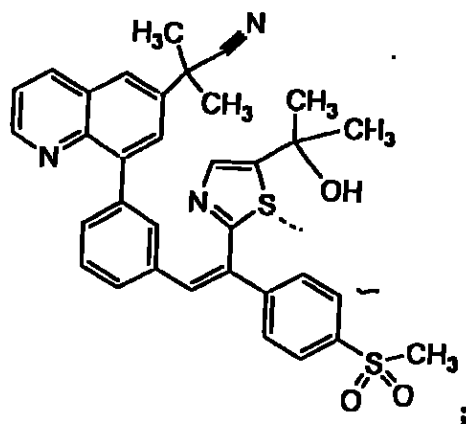
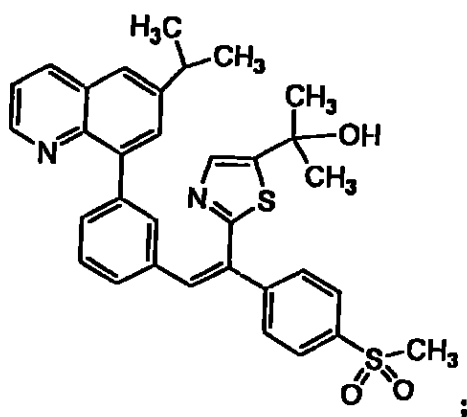
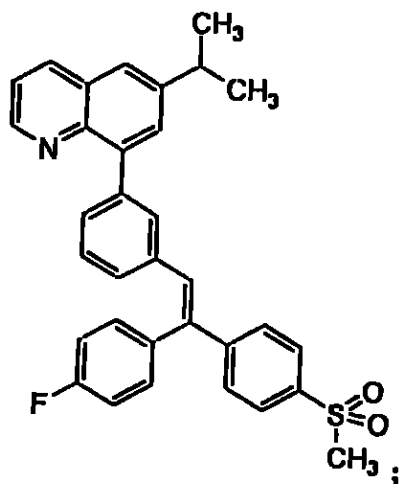
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16. El compuesto de acuerdo con la reivindicación 1,  
que comprende:

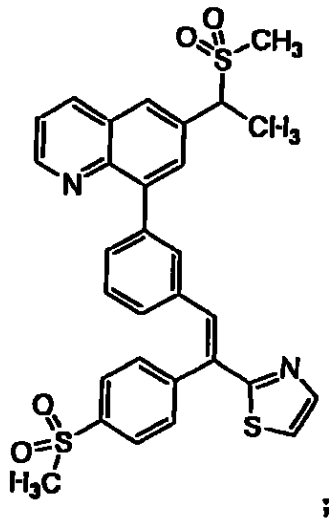
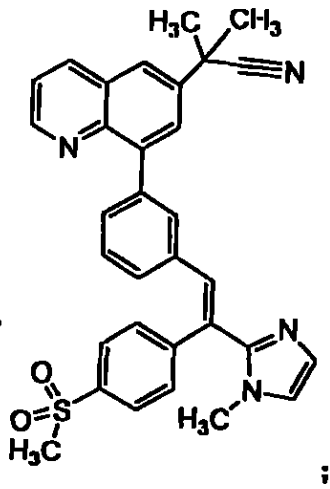




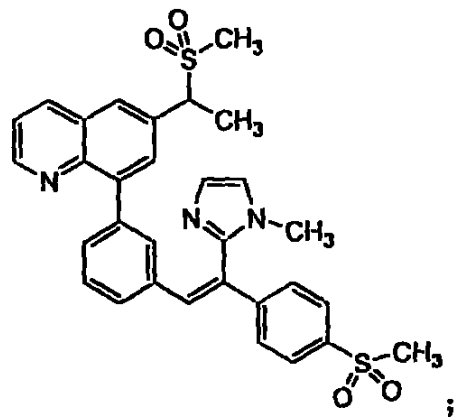
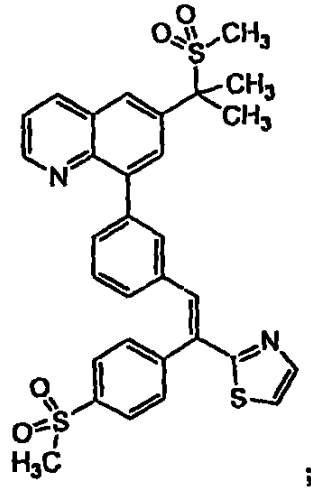
*fg*  
GABRIEL RUEDA CHADID  
TRADUCTOR OFICIAL  
RESOLUCION 5996 DE NOV. 29-82  
MINISTERIO DE JUSTICIA



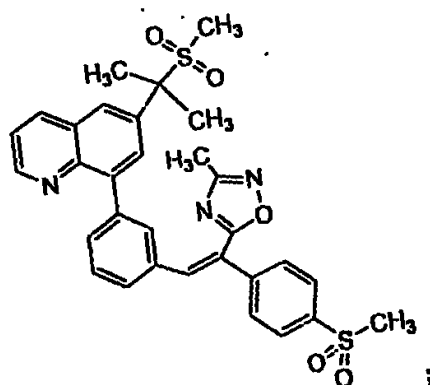
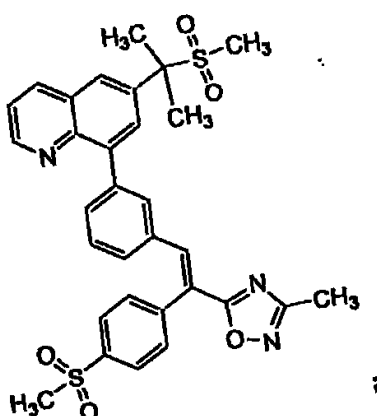
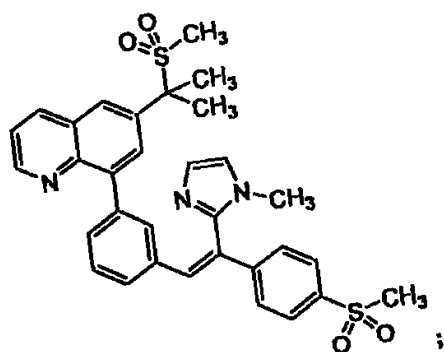
GABRIEL RUEBA CHADID  
TRANSCRIPTOR OFICIAL  
RESOLUCION 5996 DE NOV. 29-82  
MINISTERIO DE JUSTICIA



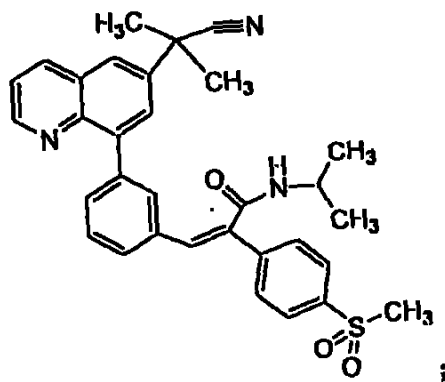
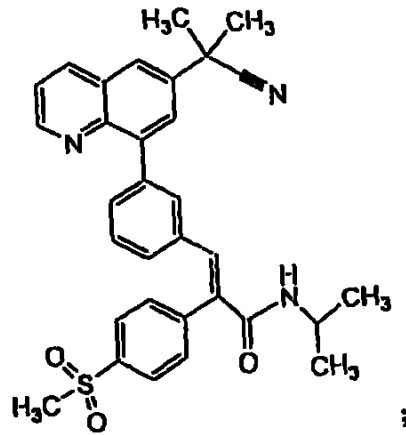
**GABRIEL RUEDA CHADID**  
**INTERDUCTOR OFICIAL**  
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**MINISTERIO DE JUSTICIA**



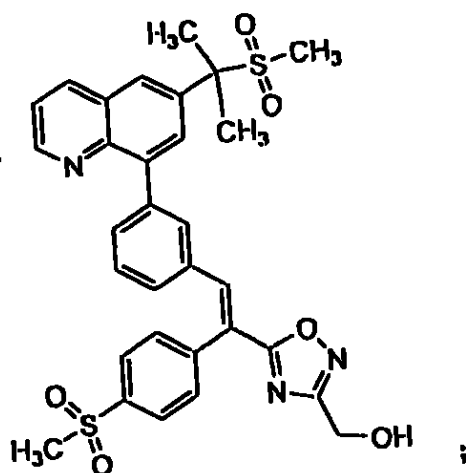
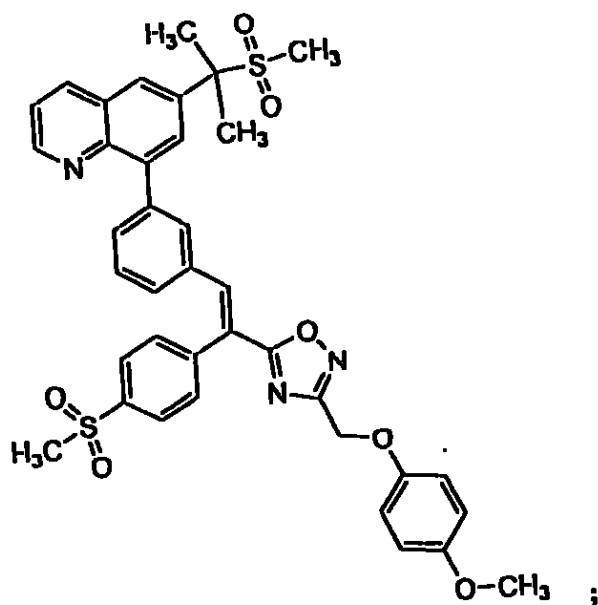
**GABRIEL RUEDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 5996 DE NOV. 29-82**  
**MINISTERIO DE JUSTICIA**



*fu* **GABRIEL PUEBA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 5994 DE NOV. 20-82**  
**MINISTERIO DE JUSTICIA**



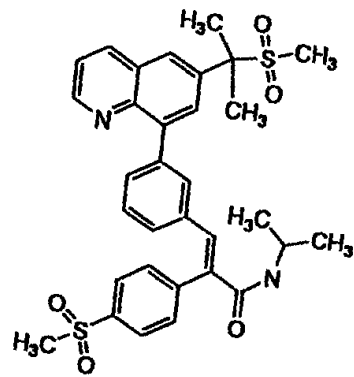
**GABRIEL RUEDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 5996 DE NOV. 29-81**  
**MINISTERIO DE JUSTICIA**



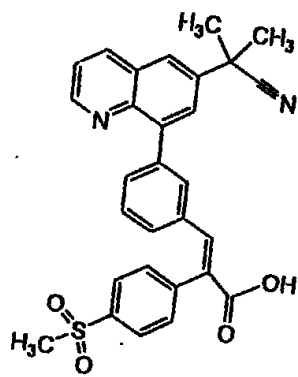
*f. GABRIEL RUEDA CHADID*  
**TRADUCTOR OFICIAL**  
**RESOLUCION 1696 DE NOV. 29-83**  
**MINISTERIO DE JUSTICIA**

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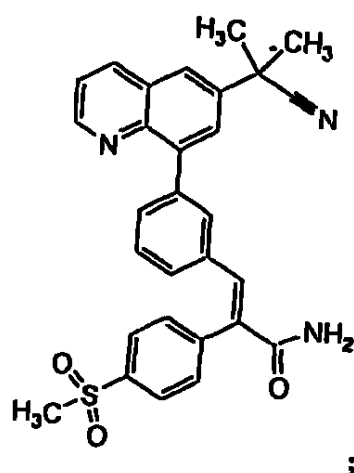
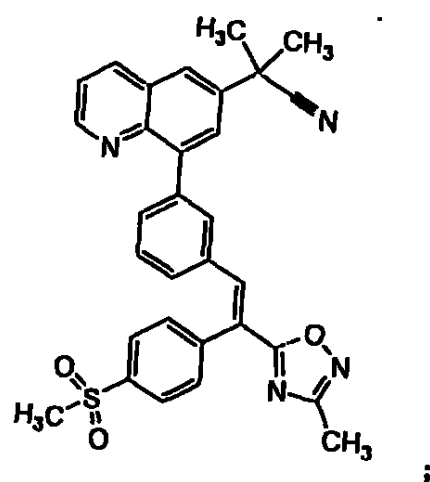
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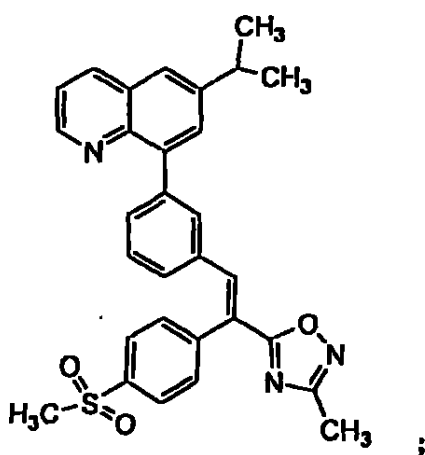
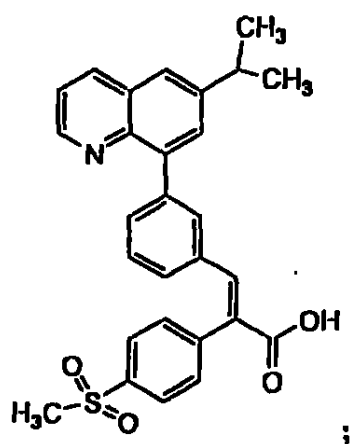
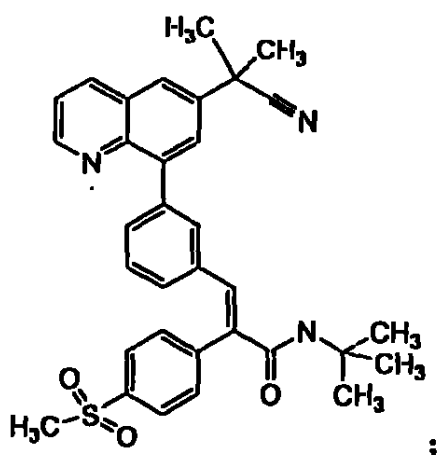
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 **GABRIEL RUEDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 5994 DE NOV. 20-01**  
**MINISTERIO DE JUSTICIA**

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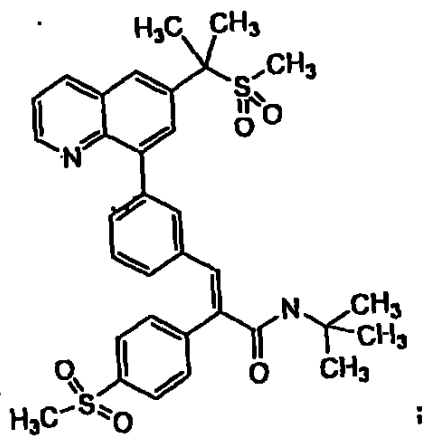
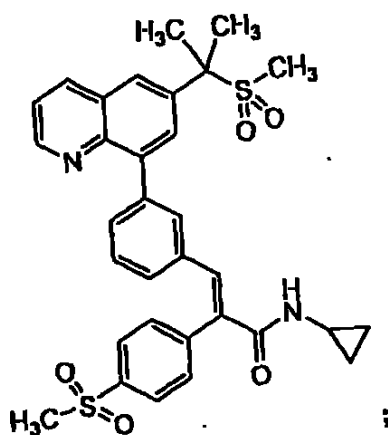
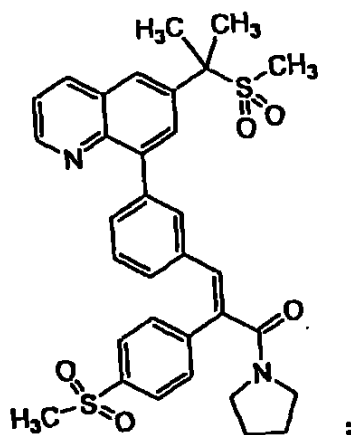
*Lo 4*  
**DANIEL RUEDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 3196 DE NOV. 29-03**  
**MINISTERIO DE JUSTICIA**



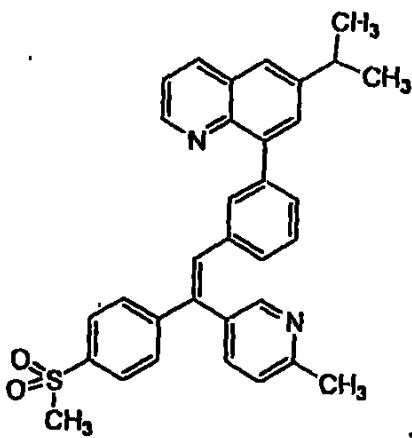
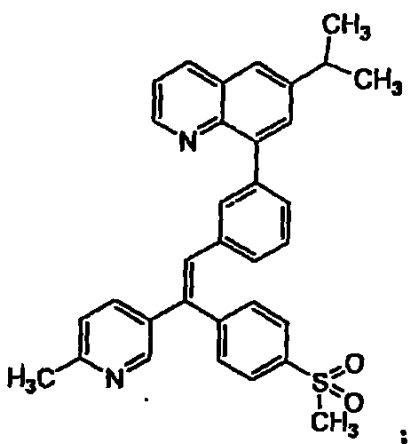
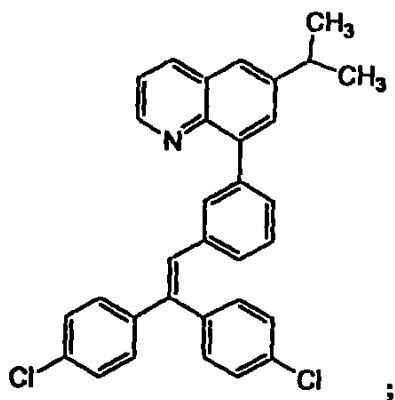
**GABRIEL RUEDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 3996 DE NOV. 29-83**  
**MINISTERIO DE JUSTICIA**

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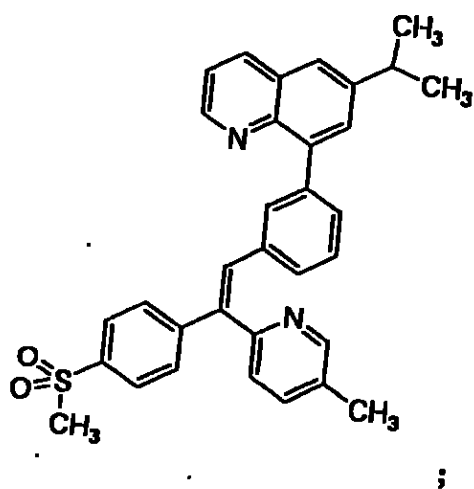
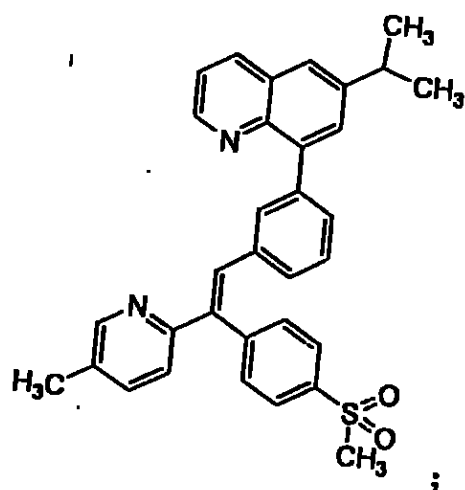


*ha* GABRIEL FUEDA CHADID  
 TRADUCTOR OFICIAL  
 RESOLUCION 5996 DE NOV. 29-83  
 MINISTERIO DE JUSTICIA

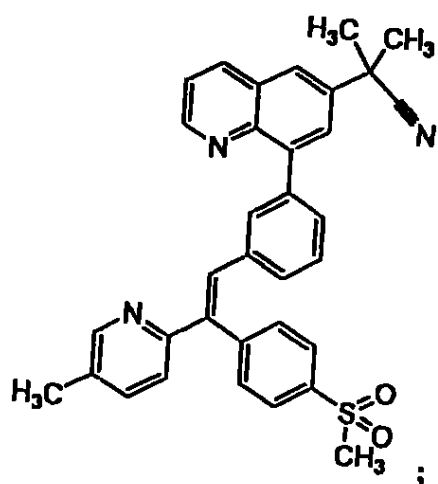
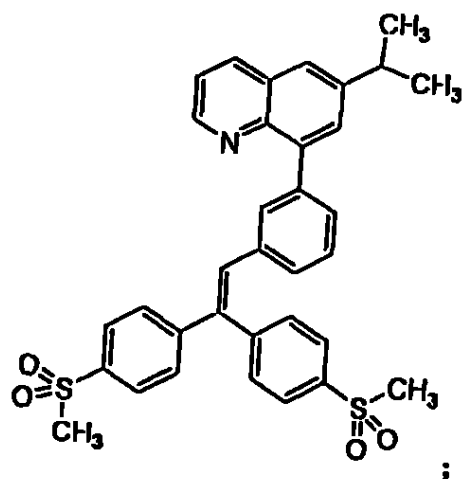


*Fic* **FABRIEL RUEDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 5996 DE NOV. 20-82**  
**MINISTERIO DE JUSTICIA**

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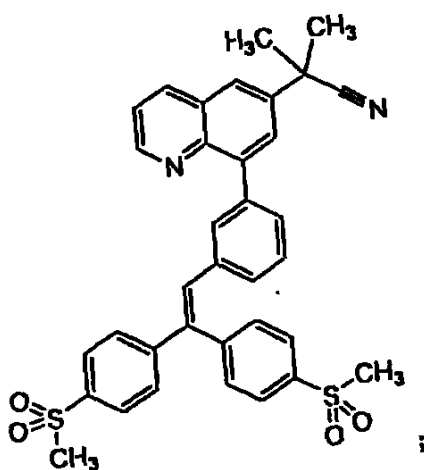
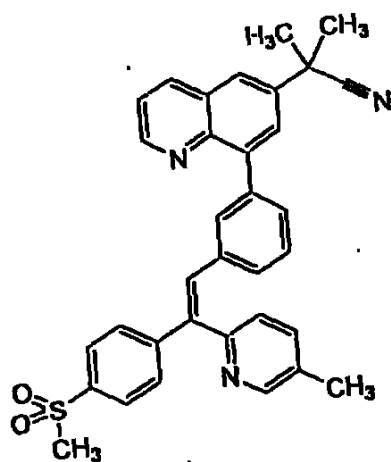


GABRIEL FUEDA CHADID  
 DIRECTOR OFICIAL  
 RESOLUCION 5194 DE NOV. 29-82  
 MINISTERIO DE JUSTICIA



*for* **GABRIEL RUEDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 5996 DE NOV. 29-43**  
**MINISTERIO DE JUSTICIA**

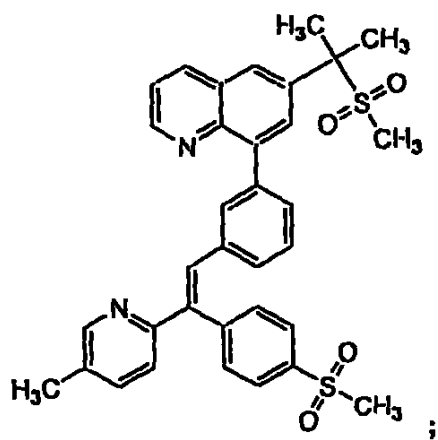
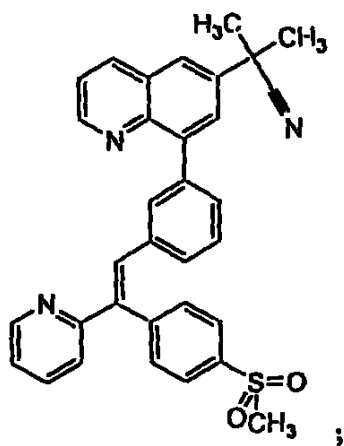
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*GAETIL FLEDA CH...*  
 A **TRADUCTOR OFICIAL**  
**RESOLUCION 5196 DE NOV. 19-61**  
**MINISTERIO DE JUSTICIA**

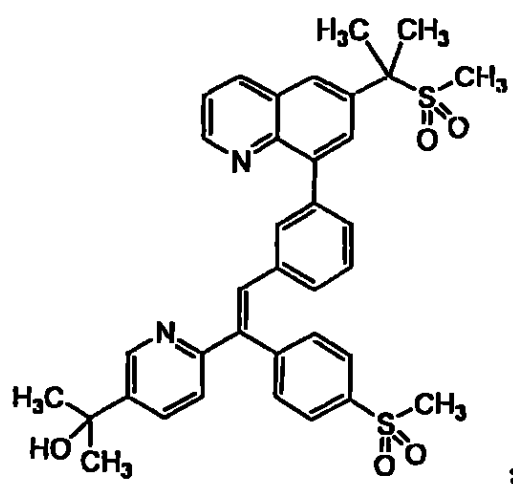
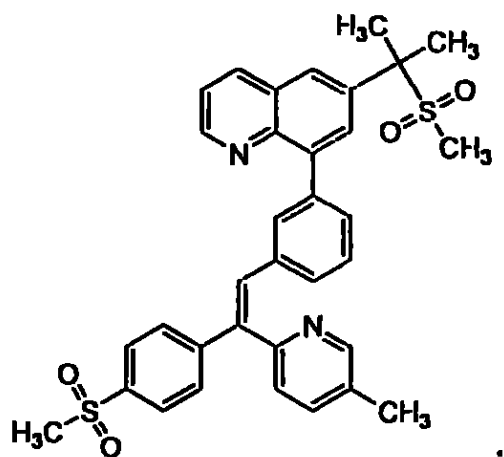
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**GABRIEL RUKDA CHADID**  
**TRADUCTOR OFICIAL**  
**RESOLUCION 5996 DE NOV. 29-82**  
**MINISTERIO DE JUSTICIA**

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o una de sus sales farmacéuticamente aceptables.

17. El compuesto de acuerdo con la reivindicación 1, que comprende:

6-isopropil-8-(3-((Z/E)-2-[4-(metilsulfonil)fenil]-2-feniletetil)fenil)quinolina;

6-isopropil-8-(3-[(E/Z)-2-[4-(metilsulfonil)fenil]-2-(1,3-tiazol-2-il)etenil]fenil)quinolina;

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6-isopropil-8-(3-((E)-2-(1-metil-1H-imidazol-2-il)-2-[4-(metilsulfonil)fenil]etenil}fenil)quinolina;  
6-isopropil-8-(3-((Z/E)-2-(4-fluorofenil)-2-[4-(metilsulfonil)fenil]etenil}fenil)quinolina;  
2-(2-((E/Z)-2-[3-(6-isopropil-8-quinolinil)fenil]-1-[4-(metilsulfonil)fenil]etenil}-1,3-tiazol-5-il)-2-propanol;  
2-[8-(3-((E/Z)-2-[5-(1-hidroxi-1-metiletil)-1,3-tiazol-2-il]-2-[4-(metilsulfonil)fenil]etenil}fenil)-6-quinolinil]-2-metilpropanonitrilo;  
2-metil-2-[8-(3-((E)-2-(1-metil-1H-imidazol-2-il)-2-[4-(metilsulfonil)fenil]etenil}fenil)-6-quinolinil]-propanonitrilo;  
6-[1-(metilsulfonil)etil]-8-(3-((E)-2-[4-(metilsulfonil)fenil]-2-(1,3-tiazol-2-il)etenil}fenil)quinolina;  
6-[1-metil-1-(metilsulfonil)etil]-8-(3-((E)-2-[4-(metilsulfonil)fenil]-2-(1,3-tiazol-2-il)etenil}fenil)quinolina;  
8-(3-((Z)-2-(1-metil-1H-imidazol-2-il)-2-[4-(metilsulfonil)fenil]etenil}fenil)-6-[1-(metilsulfonil)etil]quinolina;  
8-(3-((Z)-2-(1-metil-1H-imidazol-2-il)-2-[4-(metilsulfonil)fenil]etenil}fenil)-6-[1-metil-1-(metilsulfonil)etil]-quinolina;  
6-[1-metil-1-(metilsulfonil)etil]-8-(3-((E/Z)-2-(3-metil-1,2,4-oxadiazol-5-il)-2-[4-(metilsulfonil)fenil]etenil}fenil)quinolina;  
(E/Z)-3-{3-[6-(1-ciano-1-metiletil)-8-quinolinil]fenil}-N-isopropil-2-[4-(metilsulfonil)fenil]-2-propanamida;  
8-(3-((E)-2-[3-[(4-metoxifenoxi)metil]-1,2,4-oxadiazol-5-il]-2-[4-(metilsulfonil)fenil]etenil}fenil)-6-[1-metil-1-(metilsulfonil)etil]quinolina;

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(5-{(E)-2-(3-{6-[1-metil-1-(metilsulfonil)etil]-8-quinolinil}fenil)-1-[4-(metilsulfonil)fenil]etenil}-1,2,4-oxadiazol-3-il)metanol;

(E)-N-isopropil-3-(3-{6-[1-metil-1-(metilsulfonil)etil]-8-quinolinil}fenil)-2-[4-(metilsulfonil)fenil]-2-propanamida;

(E)-3-{3-[6-(1-ciano-metiletil)-8-quinolinil]fenil}-2-[4-(metilsulfonil)fenil]-2-ácido propanoico;

2-metil-2-[8-(3-{(E)-2-(3-metil-1,2,4-oxadiazol-5-il)-2-[4-(metilsulfonil)fenil]etenil}fenil)-6-quinolinil]-propanonitrilo;

(E)-3-{3-[6-(1-ciano-metiletil)-8-quinolinil]fenil}-2-[4-(metilsulfonil)fenil]-2-propanamida;

(E)-N-(tert-butil)-3-{3-[6-(1-ciano-metiletil)-8-quinolinil]fenil}-2-[4-(metilsulfonil)fenil]-2-propanamida;

(E)-3-[3-(6-isopropil-8-quinolinil]fenil]-2-[4-(metilsulfonil)fenil]-2-ácido propanoico;

6-isopropil-8-(3-{(E)-2-(3-metil-1,2,4-oxadiazol-5-il)-2-[4-(metilsulfonil)fenil]etenil}fenil)quinolina;

(E)-3-(3-{6-[1-metil-1-(metilsulfonil)etil]-8-quinolinil}-fenil)-2-[4-(metilsulfonil)fenil]-1-(1-pirrolidinil)-2-propen-1-ona;

(E)-N-ciclopropil-3-(3-{6-[1-metil-1-(metilsulfonil)etil]-8-quinolinil}fenil)-2-[4-(metilsulfonil)fenil]-2-propanamida;

(E)-N-(tert-butil)-3-(3-{6-[1-metil-1-(metilsulfonil)etil]-8-quinolinil}fenil)-2-[4-(metilsulfonil)fenil]-2-propanamida;

8-{3-[2,2-bis(4-clorofenil)vinil]fenil}-6-isopropilquinolina;

6-isopropil-8-(3-{(E/Z)-2-(6-metil-3-piridinil)-2-[4-(metilsulfonil)fenil]etenil}fenil)quinolina;

6-isopropil-8-(3-{(E/Z)-2-(5-metil-2-piridinil)-2-[4-(metilsulfonil)fenil]etenil}fenil)quinolina;

8-(3-(2,2-bis[4-(metilsulfonil)fenil]vinil}fenil)-6-isopropilquinolina;  
 2-metil-2-[8-(3-((E/Z)-2-(5-metil-2-piridinil)-2-[4-(metilsulfonil)fenil]etenil}fenil)-6-quinolinil]-propanonitrilo;  
 2-[8-(3-(2,2-bis[4-(metilsulfonil)fenil]vinil}fenil)-6-quinolinil]-2-metilpropanonitrilo;  
 2-metil-2-(8-(3-((E)-2-(4-(metilsulfonil)fenil)-2-(2-piridinil)etenil}fenil)-6-quinolinil]propanonitrilo;  
 6-[1-metil-1-(metilsulfonil)etil]-8-(3-((E/Z)-2-(5-metil-2-piridinil)-2-[4-(metilsulfonil)fenil]etenil}fenil)quinolina;  
 2-(6-((E)-2-(3-(6-[1-metil-1-(metilsulfonil)etil]-8-quinolinil}fenil)-1-[4-(metilsulfonil)fenil]etenil)-3-piridinil)-2-propanol;  
 o una de sus sales farmacéuticamente aceptables.

18. Una composición farmacéutica que comprende una cantidad eficaz del compuesto de acuerdo con la reivindicación 1 o una de sus sales farmacéuticamente aceptables; y

un portador farmacéuticamente aceptable.

19. La composición farmacéutica de acuerdo con la reivindicación 18, que comprende además un antagonista receptor Leukotriene, un inhibidor de biosíntesis Leukotriene, o antagonista M2/M3.

20. Un método para el tratamiento o prevención de asma, bronquitis crónica, enfermedad pulmonar obstructiva crónica, granuloma eosinofílico, psoriasis y otras enfermedades de la

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piel proliferativas benignas o malignas, choque endotóxico, laminitis en caballos, cólico en caballos, choque séptico, colitis ulcerativa, enfermedad de Crohn, reperfusión del miocardio y cerebro, artritis inflamatoria, glomerulonefritis crónica, dermatitis atópica, urticaria, síndrome de incomodidad respiratoria en el adulto, enfermedad pulmonar obstructiva crónica en animales, diabetes insipidus, rinitis alérgica, conjuntivitis alérgica, conjuntivitis vernal, restenosis arterial, arterosclerosis, aterosclerosis, inflamación neurogénica, dolor, tos, artritis reumatoide, espondilitis anquilosante, rechazo a trasplantes, enfermedad injerto vs huésped, hipersecreción de ácidos gástricos, sepsis inducida por bacterias u hongos, sepsis inducida por virus, choque séptico inducido por hongos, choque séptico inducido por virus, degeneración tisular crónica mediada por inflamación, degeneración tisular crónica mediada por citoquina, osteoartritis, cáncer, cachexia, desgaste muscular, depresión, alteración de la memoria, crecimiento tumoral, o invasión cancerosa de tejidos normales que comprende el paso de administrar una cantidad terapéuticamente eficaz, o una cantidad profilácticamente eficaz del compuesto de acuerdo con la reivindicación 1 o una de sus sales farmacéuticamente aceptables.

21. Un compuesto predroga que forma *in vivo* el compuesto de acuerdo con la reivindicación 1.

22. Un método de tratamiento o prevención de asma, bronquitis crónica, enfermedad pulmonar obstructiva crónica, granuloma eosinofílico, psoriasis y otras enfermedades de la

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piel proliferativas benignas o malignas, choque endotóxico, laminitis en caballos, cólico en caballos, choque séptico, colitis ulcerativa, enfermedad de Crohn, perfusión del miocardio y cerebro, artritis inflamatoria, glomerulonefritis crónica, dermatitis atópica, urticaria, síndrome de incomodidad respiratoria en el adulto, enfermedad pulmonar obstructiva crónica en animales, diabetes insipidus, rinitis alérgica, conjuntivitis alérgica, conjuntivitis vernal, restenosis arterial, arterosclerosis, aterosclerosis, inflamación neurogénica, dolor, tos, artritis reumatoide, espondilitis anquilosante, rechazo a trasplantes, enfermedad injerto vs huésped, hipersecreción de ácidos gástricos, sepsis inducida por bacterias u hongos, sepsis inducida por virus, choque séptico inducido por hongos, choque séptico inducido por virus, degeneración tisular crónica mediada por inflamación, degeneración tisular crónica mediada por citoquina, osteoartritis, cáncer, cachexia, desgaste muscular, depresión, alteración de la memoria, crecimiento tumoral, o invasión cancerosa de tejidos normales que comprende el paso de formar *in vivo* una cantidad terapéuticamente eficaz, o una cantidad profilácticamente eficaz, del compuesto de acuerdo con la reivindicación 1.

La anterior es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción fue realizada por GABRIEL RUEDA CHADID (Traductor Oficial). Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firmo.

Santafé de Bogotá D.C., Diciembre 20 del 2000.

 GABRIEL RUEDA CHADID  
TRADUCTOR OFICIAL  
RESOLUCION 5996 DE NOV. 29-83  
MINISTERIO DE JUSTICIA

PA 315935



# THE UNITED STATES OF AMERICA

**TO ALL TO WHOM THESE PRESENTS SHALL COME:**

**UNITED STATES DEPARTMENT OF COMMERCE**

**United States Patent and Trademark Office**

**October 19, 2000**

**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.**

**APPLICATION NUMBER: 60/171,522**

**FILING DATE:** *December 22, 1999*



**By Authority of the  
COMMISSIONER OF PATENTS AND TRADEMARKS**

  
N. WOODSON  
Certifying Officer

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# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

A/prov

DOCKET NUMBER

MC015PV

## INVENTOR(S)

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☒ Additional inventors are being named on the 1 separately numbered sheets attached hereto

## TITLE OF THE INVENTION (210 characters max)

SUBSTITUTED 8-ARYLQUINOLINE PHOSPHODIESTERASE-4 INHIBITORS

## CORRESPONDENCE ADDRESS

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ZIP CODE

07065

COUNTRY

U.S.A.

## ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification

Number of Pages

13

☐ Drawing(s)

Number of Sheets

☐ Other (specify)

## METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

☐ A check or money order is enclosed to cover the filing fees

☒ The Commissioner is hereby authorized to charge filing fees or credit to Deposit Account Number:

13-2755

FILING FEE  
AMOUNT (\$)

\$150.00

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

*Shu Muk Lee*

Date 12/22/1999

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## EXPRESS MAIL CERTIFICATE

DATE OF DEPOSIT December 22, 1999

EXPRESS MAIL NO. EM35836538U5

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20531.

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PROVISIONAL APPLICATION COVER SHEET

Additional Page

|                                        |                        |                                                    |                                        |   |
|----------------------------------------|------------------------|----------------------------------------------------|----------------------------------------|---|
| DOCKET NUMBER                          |                        | MC015PV                                            | Type a plus sign (+) inside this box → | + |
| INVENTOR(S)/APPLICANT(S)               |                        |                                                    |                                        |   |
| Given Name (first and middle (if any)) | Family Name or Surname | Residence City and either State or Foreign Country |                                        |   |
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NUMBER 2 or 2 total sheets  
including Primary cover sheet  
*Elia M. Lee*



## TITLE OF THE INVENTION

## SUBSTITUTED 8-ARYLQUINOLINE PHOSPHODIESTERASE-4 INHIBITORS

## 5 BACKGROUND OF THE INVENTION

## FIELD OF THE INVENTION

The present invention is directed to compounds that are substituted 8-arylquinolines. In particular, this invention is directed to substituted 8-arylquinolines  
10 which are phosphodiesterase-4 inhibitors wherein the aryl group at the 8-position contains a substituent substituted-alkenyl group.

## RELATED BACKGROUND

Hormones are compounds that variously affect cellular activity. In  
15 many respects, hormones act as messengers to trigger specific cellular responses and activities. Many effects produced by hormones, however, are not caused by the singular effect of just the hormone. Instead, the hormone first binds to a receptor, thereby triggering the release of a second compound that goes on to affect the cellular activity. In this scenario, the hormone is known as the first messenger while the  
20 second compound is called the second messenger. Cyclic adenosine monophosphate (adenosine 3', 5'-cyclic monophosphate, "cAMP" or "cyclic AMP") is known as a second messenger for hormones including epinephrine, glucagon, calcitonin, corticotrophin, lipotropin, luteinizing hormone, norepinephrine, parathyroid hormone, thyroid-stimulating hormone, and vasopressin. Thus, cAMP mediates cellular  
25 responses to hormones. Cyclic AMP also mediates cellular responses to various neurotransmitters.

Phosphodiesterases ("PDE") are a family of enzymes that metabolize 3', 5' cyclic nucleotides to 5' nucleoside monophosphates, thereby terminating cAMP second messenger activity. A particular phosphodiesterase, phosphodiesterase-4  
30 ("PDE4", also known as "PDE-IV"), which is a high affinity, cAMP specific, type IV PDE, has generated interest as potential targets for the development of novel anti-asthmatic and anti-inflammatory compounds. PDE4 is known to exist as at least four isoenzymes, each of which is encoded by a distinct gene. Each of the four known PDE4 gene products is believed to play varying roles in allergic and/or inflammatory  
35 responses. Thus, it is believed that inhibition of PDE4, particularly the specific PDE4

isoforms that produce detrimental responses, can beneficially affect allergy and inflammation symptoms. It would be desirable to provide novel compounds and compositions that inhibit PDE4 activity.

5 A major concern with the use of PDE4 inhibitors is the side effect of emesis which has been observed for several candidate compounds as described in C.Burnouf et al., ("Burnouf"), *Ann. Rep. In Med. Chem.*, 33:91-109(1998). B.Hughes et al., *Br. J.Pharmacol.*, 118:1183-1191(1996); M.J.Perry et al., *Cell Biochem. Biophys.*, 29:113-132(1998); S.B.Christensen et al., *J.Med. Chem.*, 41:821-835(1998); and Burnouf describe the wide variation of the severity of the undesirable side effects  
10 exhibited by various compounds. As described in M.D.Houslay et al., *Adv. In Pharmacol.*, 44:225-342(1998) and D.Spina et al., *Adv. In Pharmacol.*, 44:33-89(1998), there is great interest and research of therapeutic PDE4 inhibitors.

International Patent Publication WO9422852 describes quinolines as PDE4 inhibitors.

15 A.H.Cook, et al., *J.Chem. Soc.*, 413-417(1943) describes gamma-pyridylquinolines. Other quinoline compounds are described in Kei Manabe et al., *J.Org. Chem.*, 58(24):6692-6700(1993); Kei Manabe et al., *J.Am. Chem. Soc.*, 115(12):5324-5325(1993); and Kei Manabe et al., *J.Am. Chem. Soc.*, 114(17):6940-6941(1992).

20 Compounds that include ringed systems are described by various investigators as effective for a variety of therapies and utilities. For example, International Patent Publication No. WO 98/25883 describes ketobenzamides as calpain inhibitors, European Patent Publication No. EP 811610 and U.S. Patent Nos. 5,679,712, 5,693,672 and 5,747,541 describe substituted benzoylguanidine sodium  
25 channel blockers, U.S. Patent No. 5,736,297 describes ring systems useful as a photosensitive composition.

U.S. Patent Nos. 5,491,147, 5,608,070, 5,622,977, 5,739,144, 5,776,958, 5,780,477, 5,786,354, 5,798,373, 5,849,770, 5,859,034, 5,866,593, 5,891,896, and International Patent Publication WO 95/35283 describe PDE4  
30 inhibitors that are tri-substituted aryl or heteroaryl phenyl derivatives. U.S. Patent No. 5,580,888 describes PDE4 inhibitors that are styryl derivatives. U.S. Patent No. 5,550,137 describes PDE4 inhibitors that are phenylaminocarbonyl derivatives. U.S. Patent No. 5,340,827 describes PDE4 inhibitors that are phenylcarboxamide compounds. U.S. Patent No. 5,780,478 describes PDE4 inhibitors that are tetra-  
35 substituted phenyl derivatives. International Patent Publication WO 96/00215

describes substituted oxime derivatives useful as PDE4 inhibitors. U.S. Patent No. 5,633,257 describes PDE4 inhibitors that are cyclo(alkyl and alkenyl)phenyl-alkenyl (aryl and heteroaryl) compounds.

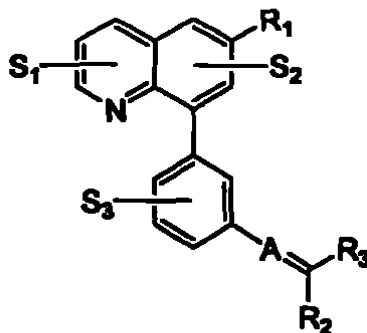
However, there remains a need for novel compounds and compositions that therapeutically inhibit PDE4 with minimal side effects.

#### SUMMARY OF THE INVENTION

The present invention is directed to novel substituted 8-arylquinolines that are PDE4 inhibitors, wherein the aryl group at the 8-position is substituted by a substituted-alkenyl-group. This invention also provides a pharmaceutical composition which includes an effective amount of the novel substituted 8-arylquinoline and a pharmaceutically acceptable carrier. This invention further provides a method of treatment in mammals of, for example, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthrosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth and cancerous invasion of normal tissues by the administration of an effective amount of the novel substituted 8-arylquinoline or a precursor compound which forms *in vivo* the novel substituted 8-arylquinoline.

#### DETAILED DESCRIPTION OF THE INVENTION

A compound of this invention is represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

- S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;
- R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>2</sub>NH(aryl), -SO<sub>2</sub>NH(heteroaryl), -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, aryloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);
- A is CH, C-ester, or C-R<sub>4</sub>;
- R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted;  
when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally  
connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system;

R<sub>4</sub> is an aryl, heteroaryl, -CN, carbonyl, carbamoyl,

5 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or  
-C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with  
1-5 substituents, wherein each substituent is independently a carbonyl, -CN, halogen,  
-C(O)(C<sub>0</sub>-C<sub>6</sub>alkyl), -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), amino, -OH, or  
-C<sub>1</sub>-C<sub>6</sub>alkyl(amino) group; and

10 n is independently 0, 1, or 2.

In one aspect, a compound of this invention is represented by Formula  
(I) or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl,

15 -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl,

-C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino,  
-C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl,  
-C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl),

20 -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl),  
-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or

-(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally  
substituted with 1-5 substituents; wherein each substituent is independently a halogen,  
-OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl,

25 alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl,  
heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN,

-C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH,

30 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or

-C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with  
1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH,  
carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl,  
-C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or

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- 5 -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and  
n is independently 0, 1, or 2.

- 10 In one embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

- 15 R<sub>1</sub> is a -C<sub>1</sub>-C<sub>6</sub>alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

- 20 R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, 25 -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and 30 R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and  
n is independently 0, 1, or 2.

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In another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

5 R<sub>1</sub> is a -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

10 A is CH<sub>3</sub>;

R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -C<sub>1</sub>-C<sub>6</sub>alkyl-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 15 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, 20 -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and n is independently 0, 1, or 2.

25

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

30 R<sub>1</sub> is a -C<sub>1</sub>-C<sub>6</sub>alkenyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

35 A is CH<sub>3</sub>;

R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN,  
 -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH,  
 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or  
 -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with  
 5 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH,  
 carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl,  
 -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or  
 -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently  
 is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH,  
 10 -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one  
 of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and  
 R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or  
 (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and  
 n is independently 0, 1, or 2.

15 In another embodiment of this aspect, a compound of this invention is  
 represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein  
 S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl,  
 -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;  
 20 R<sub>1</sub> is a heteroaryl, optionally substituted with 1-5 substituents; wherein  
 each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-  
 C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy,  
 -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl; aryl, heteroaryl, carbonyl, carbamoyl, or  
 -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

25 A is CH;  
 R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN,  
 -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH,  
 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or  
 -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with  
 30 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH,  
 carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl,  
 -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or  
 -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently  
 is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH,

- 5 -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and  
n is independently 0, 1, or 2.

- In still another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein
- 10 S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;
- R<sub>1</sub> is a an -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, or  
-C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen,
- 15 -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);
- A is CH;
- R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN,
- 20 -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl,
- 25 -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and
- 30 R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and  
n is independently 0, 1, or 2.

In an embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

5 R<sub>1</sub> is a -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl), -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl),  
10 -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

15 A is CH<sub>3</sub>;

R<sub>2</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group,  
20 wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

R<sub>3</sub> is a heteroaryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and  
25  
30 n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl),  
 5 -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl,  
 10 alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

R<sub>2</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl,  
 15 -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group,  
 20 wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and

n is independently 0, 1, or 2.

In still another embodiment of this aspect, a compound of this  
 30 invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl),  
 5 -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl,  
 10 alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

R<sub>2</sub> is a carbonyl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);  
 15  
 20 R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and  
 25

n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein  
 30

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino,

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- C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl), -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or
- 5 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl);
- 10 A is CH;
- R<sub>2</sub> is a carbamoyl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or
- 15 -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);
- R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and
- 20
- 25 n is independently 0, 1, or 2.

- In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein
- S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;
- 30
- R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl),

-SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl),  
 -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or  
 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally  
 substituted with 1-5 substituents; wherein each substituent is independently a halogen,  
 5 -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl,  
 alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl,  
 heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

R<sub>2</sub> and R<sub>3</sub> are each independently an aryl, optionally substituted,  
 10 connected to each other by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three  
 ring system; and  
 n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention  
 15 is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein  
 S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl,  
 -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl,  
 -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino,  
 20 -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl,  
 -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl),  
 -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl),  
 -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or  
 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally  
 25 substituted with 1-5 substituents; wherein each substituent is independently a halogen,  
 -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl,  
 alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl,  
 heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

30 R<sub>2</sub> is a -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), optionally substituted with  
 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH,  
 carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl,  
 -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or  
 -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently

is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

- 5 R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and
- 10 n is independently 0, 1, or 2.

In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

- 15 S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;
- R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl),
- 20 -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl,
- 25 alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

- R<sub>2</sub> is a -C(O)N-(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl,
- 30 -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group,

- 5 wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and

n is independently 0, 1, or 2.

- 10 In yet another embodiment of this aspect, a compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl,

- 15 -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl), -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or

- 20 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

- 25 A is CH;

R<sub>2</sub> is -CN;

R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl,

- 30 -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and

n is independently 0, 1, or 2.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "cycloalkyloxy" unless specifically stated otherwise includes a cycloalkyl group connected by a short C<sub>1</sub>-C<sub>2</sub>alkyl length to the oxy connecting atom.

The term "C<sub>0</sub>-C<sub>6</sub>alkyl" includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent.

The term "hetero" unless specifically stated otherwise includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a heterocycloC<sub>5</sub>alkyl is a five member ring containing from 5 to no carbon atoms.

The term "amine" unless specifically stated otherwise includes primary, secondary and tertiary amines.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring.

Compounds described herein contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers.

5                   Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a  
10                   definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the  
15                   products of such procedures can be a mixture of stereoisomers.

                  The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and  
20                   organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of  
25                   primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-  
30                   dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Such additional therapeutic ingredients include, for example, i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, and iii) M2/M3 antagonists. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

Creams, ointments, jellies, solutions, or suspensions containing the compound of Formula I can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of conditions such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, arteriosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced

sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth and cancerous invasion of normal tissues which are responsive to PDE4 inhibition, or alternatively about 0.5mg to about 7g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01mg to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Further, it is understood that the PDE4 inhibiting compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 500mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled

release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and

each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or

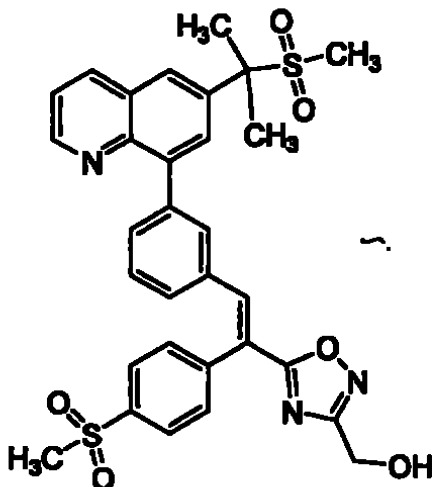
more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as PDE4 inhibitors. Accordingly, another aspect of the invention is the treatment in mammals of, for example, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthostatic hypotension, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth and cancerous invasion of normal tissues – maladies that are amenable to amelioration through inhibition of the PDE4 isoenzyme and the resulting elevated cAMP levels – by the administration of an effective amount of the compounds of this invention. The term "mammals" includes humans, as well as other animals such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than humans is the treatment of clinical correlating afflictions to those above recited examples that are human afflictions.

Further, as described above, the compound of this invention can be utilized in combination with other therapeutic compounds. In particular, the combinations of the PDE4 inhibiting compound of this invention can be advantageously used in combination with i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, or iii) M2/M3 antagonists.

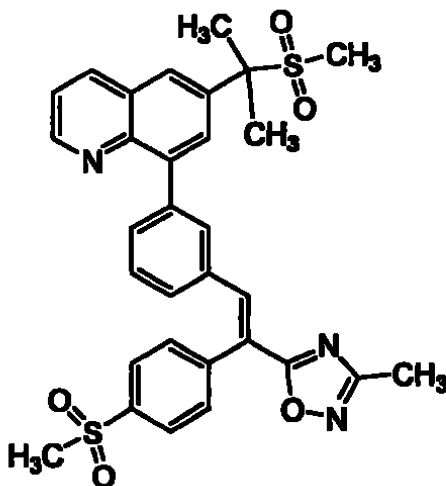
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In another aspect, it was found that the compound of this invention can be formed as a metabolite in the mammalian system. For example, Example 19, (5-((E)-2-(3-(6-(1-methyl-1-(methylsulfonyl)ethyl)-8-quinoliny)phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl)-1,2,4-oxadiazol-3-yl)methanol:



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which is a PDE4 inhibitor is formed *in vivo* as a metabolite when Example 14:



is administered. Accordingly, the present invention includes prodrugs that form PDE4 inhibitors *in vivo* as a metabolite after administering such prodrugs to a mammal. Further, this invention includes a method of treatment by a step of administering a prodrug to form *in vivo* an effective amount of a PDE4 inhibitor described by Formula I.

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The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

|                   |   |                                                                       |
|-------------------|---|-----------------------------------------------------------------------|
| Ac                | = | acetyl                                                                |
| Bn                | = | benzyl                                                                |
| CAMP              |   | cyclic adenosine-3',5'-monophosphate                                  |
| DBU               | = | 1,8-diazabicyclo[5.4.0]undec-7-ene                                    |
| DIBAL             | = | diisobutylaluminum hydride                                            |
| DMAP              | = | 4-(dimethylamino)pyridine                                             |
| DMF               | = | N,N-dimethylformamide                                                 |
| Et <sub>3</sub> N | = | triethylamine                                                         |
| GST               |   | glutathione transferase                                               |
| HMDS              |   | hexamethyldisilazide                                                  |
| LDA               | = | lithium diisopropylamide                                              |
| m-CPBA            | = | metachloroperbenzoic acid                                             |
| MMPP              | = | monoperoxyphthalic acid                                               |
| MPPM              | = | monoperoxyphthalic acid, magnesium salt 6H <sub>2</sub> O             |
| Ms                | = | methanesulfonyl = mesyl = SO <sub>2</sub> Ms                          |
| MsO               | = | methanesulfonate = mesylate                                           |
| NSAID             | = | non-steroidal anti-inflammatory drug                                  |
| o-Tol             | = | ortho-tolyl                                                           |
| OXONE®            | = | 2KHSO <sub>5</sub> ·KHSO <sub>4</sub> ·K <sub>2</sub> SO <sub>4</sub> |
| PCC               | = | pyridinium chlorochromate                                             |
| PDC               | = | pyridinium dichromate                                                 |
| PDE               |   | phosphodiesterase                                                     |
| Ph                | = | phenyl                                                                |
| Phe               | = | benzenediyl                                                           |
| PMB               | = | para-methoxybenzyl                                                    |
| Pye               | = | pyridinediyl                                                          |
| r.t.              | = | room temperature                                                      |
| Rac.              | = | racemic                                                               |
| SAM               | = | aminosulfonyl or sulfonamide or SO <sub>2</sub> NH <sub>2</sub>       |

|                               |   |                                 |
|-------------------------------|---|---------------------------------|
| SEM                           | = | 2-(trimethylsilyl)ethoxymethoxy |
| SPA                           | = | scintillation proximity assay   |
| TBAF                          | = | tetra-n-butylammonium fluoride  |
| Th                            | = | 2- or 3-thienyl                 |
| TFA                           | = | trifluoroacetic acid            |
| TFAA                          | = | trifluoroacetic acid anhydride  |
| THF                           | = | tetrahydrofuran                 |
| Thi                           | = | thiophenediyl                   |
| TLC                           | = | thin layer chromatography       |
| TMS-CN                        | = | trimethylsilyl cyanide          |
| TMSI                          |   | trimethylsilyl iodide           |
| Tz                            | = | 1H (or 2H)-tetrazol-5-yl        |
| C <sub>3</sub> H <sub>5</sub> | = | allyl                           |

|                     |          |                        |
|---------------------|----------|------------------------|
| <b>Me</b>           | <b>=</b> | <b>Methyl</b>          |
| <b>Et</b>           | <b>=</b> | <b>ethyl</b>           |
| <b><i>n</i>-Pr</b>  | <b>=</b> | <b>normal propyl</b>   |
| <b><i>i</i>-Pr</b>  | <b>=</b> | <b>isopropyl</b>       |
| <b><i>n</i>-Bu</b>  | <b>=</b> | <b>normal butyl</b>    |
| <b><i>i</i>-Bu</b>  | <b>=</b> | <b>isobutyl</b>        |
| <b><i>s</i>-Bu</b>  | <b>=</b> | <b>secondary butyl</b> |
| <b><i>t</i>-Bu</b>  | <b>=</b> | <b>tertiary butyl</b>  |
| <b><i>c</i>-Pr</b>  | <b>=</b> | <b>cyclopropyl</b>     |
| <b><i>c</i>-Bu</b>  | <b>=</b> | <b>cyclobutyl</b>      |
| <b><i>c</i>-Pen</b> | <b>=</b> | <b>cyclopentyl</b>     |
| <b><i>c</i>-Hex</b> | <b>=</b> | <b>cyclohexyl</b>      |

### ASSAYS DEMONSTRATING BIOLOGICAL ACTIVITY

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Whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as PDE4-selective inhibitors. Normal non-stimulated human blood does not contain detectable levels of TNF- $\alpha$  and LTB<sub>4</sub>. Upon stimulation with LPS, activated monocytes express and secrete TNF- $\alpha$  up to 8 hours and plasma levels remain stable for 24 hours. Published studies have shown that inhibition of TNF- $\alpha$  by increasing intracellular cAMP via PDE4 inhibition and/or enhanced adenylyl cyclase activity occurs at the transcriptional level. LTB<sub>4</sub> synthesis is also sensitive to levels of intracellular cAMP and can be completely inhibited by PDE4-selective inhibitors. As there is little LTB<sub>4</sub> produced during a 24 hour LPS stimulation of whole blood, an additional LPS stimulation followed by fMLP challenge of human whole blood is necessary for LTB<sub>4</sub> synthesis by activated neutrophils. Thus, by using the same blood sample, it is possible to evaluate the potency of a compound on two surrogate markers of PDE4 activity in the whole blood by the following procedure.

Fresh blood was collected in heparinized tubes by venipuncture from healthy human volunteers (male and female). These subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 4 days prior to blood collection. 500 $\mu$ L aliquots of blood were pre-incubated with either 2 $\mu$ L of vehicle (DMSO) or 2 $\mu$ L of test compound at varying concentrations for 15 minutes at 37°C. This was followed by the addition of either 10 $\mu$ L vehicle (PBS) as blanks or 10 $\mu$ L LPS (1 $\mu$ g/mL final concentration, #L-2630 (Sigma Chemical Co., St. Louis, MO) from *E. coli*, serotype 0111:B4; diluted in 0.1% w/v BSA (in PBS)). After 24 hours of incubation at 37°C, another 10 $\mu$ L of PBS (blank) or 10 $\mu$ L of LPS (1 $\mu$ g/mL final concentration) was added to blood and incubated for 30 minutes at 37°C. The blood was then challenged with either 10 $\mu$ L of PBS (blank) or 10 $\mu$ L of fMLP (1 $\mu$ M final concentration, #F-3506 (Sigma); diluted in 1% w/v BSA (in PBS)) for 15 minutes at 37°C. The blood samples were centrifuged at 1500xg for 10 minutes at 4°C to obtain plasma. A 50 $\mu$ L aliquot of plasma was mixed with 200 $\mu$ L methanol for protein precipitation and centrifuged as above. The supernatant was assayed for LTB<sub>4</sub> using an enzyme immunoassay kit (#520111 from Cayman Chemical Co., Ann Arbor, MI) according to the manufacturer's procedure. TNF- $\alpha$  was assayed in diluted plasma (in PBS) using an ELISA kit (Cistron Biotechnology, Pine Brook, NJ) according to manufacturer's procedure. The IC<sub>50</sub> values of Examples 1-42 generally ranged from 0.04 $\mu$ M to 8.71 $\mu$ M.

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### ANTI-ALLERGIC ACTIVITY *IN VIVO*

Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs. Guinea pigs were initially sensitized to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminum hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later. At six weeks, animals were challenged with aerosolized ovalbumin while under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

### SPA BASED PDE ACTIVITY ASSAY PROTOCOL

Compounds which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in a 96-well plate format as follows:

In a 96 well-plate at 30°C was added the test compound (dissolved in 2μL DMSO), 188μL of substrate buffer containing [2,8-<sup>3</sup>H] adenosine 3',5'-cyclic phosphate (cAMP, 100nM to 50μM), 10mM MgCl<sub>2</sub>, 1mM EDTA, 50mM Tris, pH 7.5. The reaction was initiated by the addition of 10μL of human recombinant PDE4 (the amount was controlled so that ~10% product was formed in 10min.). The reaction was stopped after 10min. by the addition of 1mg of PDE-SPA beads (Amersham Pharmacia Biotech, Inc., Piscataway, NJ). The product AMP generated was quantified on a Wallac Microbeta® 96-well plate counter (EG&G Wallac Co., Gaithersburg, MD). The signal in the absence of enzyme was defined as the background. 100% activity was defined as the signal detected in the presence of enzyme and DMSO with the background subtracted. Percentage of inhibition was calculated accordingly. IC<sub>50</sub> value was approximated with a non-linear regression fit

using the standard 4-parameter/multiple binding sites equation from a ten point titration.

The IC<sub>50</sub> values of Examples 1-42 were determined with 100nM cAMP using the purified GST fusion protein of the human recombinant phosphodiesterase IVa (met-248) produced from a baculovirus/Sf-9 expression system. The IC<sub>50</sub> values of Examples 1-42 generally ranged from 0.14nM to 10.24nM, although one example had an IC<sub>50</sub> value of 109nM.

The examples that follow are intended as an illustration of certain preferred embodiments of the invention and no limitation of the invention is implied.

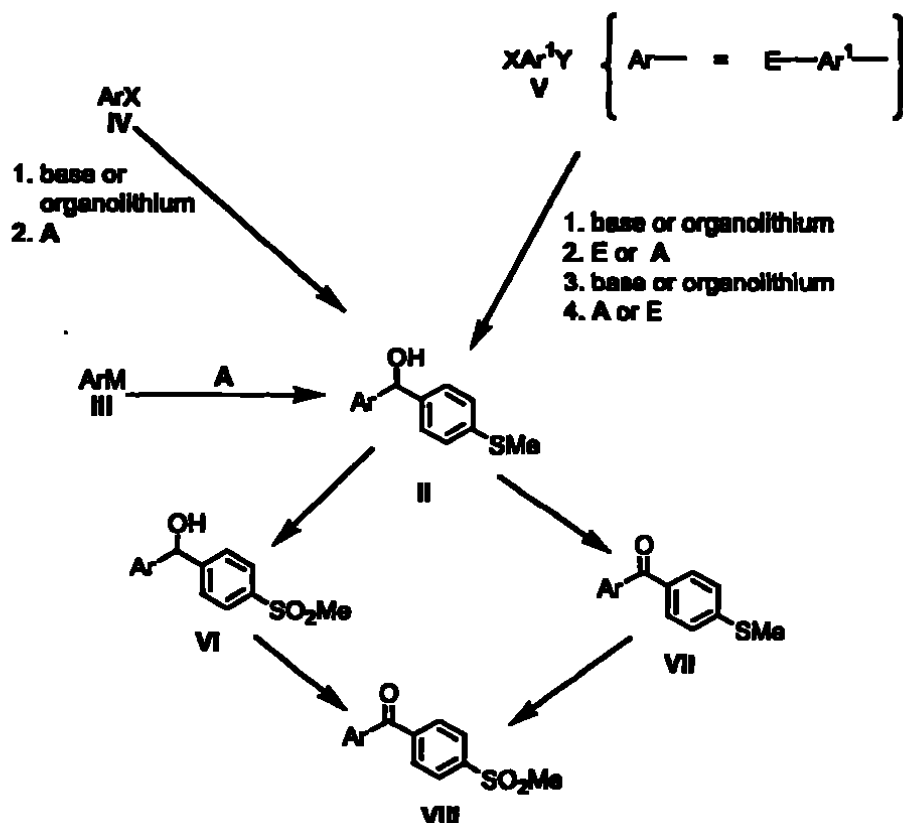
Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room or ambient temperature - that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. Yields are given for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz, 400 MHz or 500 MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations have also been used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

#### Methods of Synthesis

Compounds of the present invention can be prepared according to the following methods. The substituents are the same as in Formula I except where defined otherwise.

5

**SCHEME 1**  
**Ketone Synthesis**



Wherein X=halogen, H  
Y=halogen, H  
A=4-(methylthio)benzaldehyde  
E=electrophile  
Ar=aryl or heteroaryl

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Referring to Scheme 1 above, and Scheme 1 Table below, the alcohol intermediate II may be prepared by the reaction of an aryl or heteroaryl metallic species III such as an organomagnesium halide with 4-(methylthio)benzaldehyde (A)

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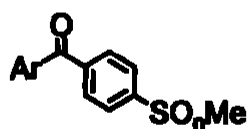
- in an organic solvent such as THF. The alcohol intermediate II may also be prepared by treatment an aryl or heteroaryl hydride or bromide IV with a base or an organometallic such as *n*-butyllithium in an organic solvent such as THF, followed by 4-(methylthio)benzaldehyde. Alternatively the alcohol intermediate II may also be
- 5 prepared by the following chemical transformations: 1) Treatment of an aryl or heteroaryl dihydride, halide-hydride or dihalide V with a base or an organometallic such as *n*-butyllithium in an organic solvent such as THF, followed by an electrophile such as acetone or 4-(methylthio)benzaldehyde; 2) Subsequent treatment with a base or an organometallic such as *n*-butyllithium in an organic solvent such as THF,
- 10 followed by an electrophile such as acetone or 4-(methylthio)benzaldehyde, where the first or the second transformation must use 4-(methylthio)benzaldehyde as the electrophile. The sulfone-alcohol VI may be prepared by the oxidation of the sulfide-alcohol II with an oxidizing agent such as oxone in a solvent such as a mixture of THF/MeOH/H<sub>2</sub>O. The ketones VII and VIII may be prepared by the oxidation of the
- 15 alcohols II and VI, respectively, with an oxidizing agent such as MnO<sub>2</sub> in a solvent such as CH<sub>2</sub>Cl<sub>2</sub>. The sulfone-ketone VIII may also be prepared by the oxidation of the sulfide-ketone VII with an oxidizing agent such as oxone in a solvent such as a mixture of THF/MeOH/H<sub>2</sub>O.

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## SCHEME 1 TABLE:

## Ketones



VII (n=0)

VIII (n=2)

| Ar | n | Ketone | Ar | n | Ketone |
|----|---|--------|----|---|--------|
|    | 2 | K1     |    | 2 | K7     |
|    | 0 | K2     |    | 2 | K8     |
|    | 2 | K3     |    | 2 | K9     |
|    | 0 | K4     |    | 2 | K10    |
|    | 2 | K5     |    | 2 | K11    |
|    |   |        |    |   |        |

5

## Ketone K1

(4-Fluorophenyl)[4-(methylsulfonyl)]phenyl ketone

Ketone K1 was prepared by the following procedure.

Step 1: (4-Fluorophenyl)[4-methylthio]phenyl]ketone

- To a -78°C solution of 4-(methylthio)benzaldehyde (2.5g, 16.4mmol)
- 10 in THF (100ml) was added 4-fluorophenylmagnesium bromide (1.0M in THF, 19.7ml, 19.7mmol) dropwise. The resulting solution was stirred at -78°C for 3h., and quenched with a saturated aqueous solution of NH<sub>4</sub>Cl. The mixture was then diluted with EtOAc and HCl 10%, extracted and washed (NaHCO<sub>3</sub> (sat.), brine). The organic

phase was dried over  $\text{MgSO}_4$  and concentrated. The residue was then treated with  $\text{MnO}_2$  (28.6g, 330mmol) in  $\text{CH}_2\text{Cl}_2$  (150ml) and the reaction was stirred at r.t. overnight. The mixture was filtered through a plug of silica (EtOAc) to yield 2.6g of the (4-Fluorophenyl)[4-methylthio]phenyl]ketone compound

5 Step 2: (4-Fluorophenyl)[4-(methylsulfonyl)phenyl]ketone

To a solution of the sulfide – in other words, the (4-Fluorophenyl)[4-methylthio]phenyl]ketone – from the present step 1 (2.0g, 8.1mmol) in THF/MeOH/ $\text{H}_2\text{O}$  (80/40/40 ml) was added oxone (7.5g, 12.2mmol). The mixture was stirred at r.t. for 4h, quenched with  $\text{NaHCO}_3$  (sat.), and diluted with EtOAc. The organic phase was washed with  $\text{NaHCO}_3$  (sat.), brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Crystallization ( $\text{CH}_2\text{Cl}_2$ /Hexanes) yielded (4-Fluorophenyl)[4-(methylsulfonyl)phenyl]ketone (2.2g), the K1 ketone compound, as a white solid.

Ketone K2

15 (1-Methyl-1H-imidazol-2-yl)[4-methylthio]phenyl]ketone

Ketone K2 was prepared by the following procedure.

Step 1: (1-Methyl-1H-imidazol-2-yl)[4-(methylthio)phenyl]methanol

To a solution of N-methylimidazole (10.0g, 122mmol) in 500mL THF at  $-78^\circ\text{C}$  was added *n*-butyllithium (2.5M in hexanes, 48.7ml, 118mmol) dropwise and the resulting solution was stirred at  $-78^\circ\text{C}$  for 30min. 4-(Methylthio)benzaldehyde (14.73ml, 110mmol) was then added at  $-78^\circ\text{C}$  and the mixture was stirred until completion by TLC, and quenched with  $\text{NH}_4\text{Cl}$  (sat). The mixture was then diluted with EtOAc, extracted and washed ( $\text{NaHCO}_3$  (sat.), brine). The organic phase was dried over  $\text{MgSO}_4$ , filtered and concentrated. Crystallisation (EtOAc/Hexanes) yielded (1-Methyl-1H-imidazol-2-yl)[4-(methylthio)phenyl]methanol (25.7g).

Step 2: (1-Methyl-1H-imidazol-2-yl)[4-(methylthio)phenyl]ketone

To a solution of the alcohol from the present step 1 (25.7g, 111mmol) in EtOAc (250ml) and  $\text{CH}_2\text{Cl}_2$  (250ml) was added  $\text{MnO}_2$  (140g, 1.66mol) and the

reaction was stirred at r.t. overnight. The mixture was filtered through a plug of silica (BtOAc) to yield 24.9g of ketone K2.

### Ketone K3

#### 5 (4-Methylsulfonyl)(phenyl)ketone

Ketone K3 was prepared by the following procedure.

##### Step 1: (4-Methylthio)(phenyl)methanol

To a solution of 4-(methylthio)benzaldehyde (1.0g, 6.5mmol) in THF (20mL) at 0°C was added phenylmagnesium chloride (2M, THF, 3.5mL, 7.0mmol).  
10 After 0.5h at r.t., the mixture was neutralised with saturated NH<sub>4</sub>Cl solution, diluted with water and extracted with Et<sub>2</sub>O. The organic extracts were washed (H<sub>2</sub>O), (brine), dried (MgSO<sub>4</sub>), filtered and concentrated. Purification by stirring vigorously in hexane/Et<sub>2</sub>O and filtration yielded (4-Methylthio)(phenyl)methanol as a white solid.

##### 15 Step 2: (4-Methylthio)(phenyl)ketone

(4-Methylthio)(phenyl)ketone was obtained by treating the (4-Methylthio)(phenyl)methanol from the present step 1 with MnO<sub>2</sub> as in step 2 of the procedure for K4 below.

##### Step 3: (4-Methylsulfonyl)(phenyl)ketone

To a solution of (4-Methylthio)(phenyl)ketone from the present step 2 (0.98g, 4.3mmol) in CHCl<sub>3</sub> (10mL) at 0°C was added mCPBA (m-chloroperbenzoic acid) (1.7g, 10mmol). After 0.5h at r.t., Ca(OH)<sub>2</sub> (1.7g, 23mmol) was added to the mixture which was stirred for 1h. Filtration on Celite® and concentration yielded  
20 ketone K3 as a white solid.

25

### Ketone K4

#### (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]ketone

Ketone K4 was prepared by the following procedure.

##### Step 1: (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]methanol

To a -78°C solution of thiazole (5.0g, 58.7mmol) in THF (250ml) was  
30 added *n*-butyllithium (2.5M in hexanes, 23.5ml, 58.7mmol) dropwise and the resulting solution was stirred at -78°C for 10min. 4-(Methylthio)benzaldehyde (7.1ml, 53.4mmol) was then added at -78°C. The resulting mixture was stirred until

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completion, and quenched with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ . The mixture was then diluted with EtOAc and HCl 10%, extracted and washed ( $\text{NaHCO}_3$  (sat.), brine). The organic phase was dried over  $\text{MgSO}_4$  and concentrated. The residue was then purified by flash chromatography (80%  $\text{CH}_2\text{Cl}_2$ / 20% EtOAc) to yield 10g of

5 (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]methanol.

Step 2: (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]ketone

To a solution of the (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]methanol from the present step 1 (10.0g, 42.1mmol) in EtOAc (250ml) was added  $\text{MnO}_2$  (70g, 843mmol) and the reaction was stirred at  $25^\circ\text{C}$  overnight. The mixture was filtered

10 through a plug of silica (EtOAc) to form 8.2g of the K4 ketone compound.

Ketone K5

(1,3-Thiazol-2-yl)[4-(methylsulfonyl)phenyl]ketone

Ketone K5 was prepared by the following procedure. To a solution of

15 K4 (1,3-Thiazol-2-yl)[4-(methylthio)phenyl]ketone (8.2g, 34.7mmol) in THF/MeOH/ $\text{H}_2\text{O}$  (350/175/175 ml) was added oxone (42.6g, 69.4mmol). The reaction was stirred at  $25^\circ\text{C}$  for 3h and quenched with a saturated aqueous solution of  $\text{NaHCO}_3$ . The resulting mixture was then diluted with EtOAc, extracted and washed ( $\text{NaHCO}_3$  (sat.), brine). The organic phase was dried over  $\text{MgSO}_4$  and concentrated.

20 The residue was then purified by crystallization (EtOAc/Hexanes) to yield 7.3g of (1,3-Thiazol-2-yl)[4-(methylsulfonyl)phenyl]ketone.

Ketone K6

[5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylsulfonyl)phenyl]ketone

25 Ketone K6 was prepared by the following procedure.

Step 1: [5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylthio)phenyl]ketone

To a  $-78^\circ\text{C}$  solution of thiazole (1.0g, 12.0mmol) in THF (100ml) was added *n*-butyllithium (2.3M in hexanes, 5.3ml, 12.3mmol) dropwise and the resulting

30 solution was stirred at  $-78^\circ\text{C}$  for 10min. 4-(Methylthio)benzaldehyde (7.1ml, 53.4mmol) was then added at  $-78^\circ\text{C}$ . The resulting mixture was stirred at r.t. 10min. and cooled at  $-78^\circ\text{C}$ . Then *n*-butyllithium (2.3M in hexanes, 5.3ml, 12.3mmol) was

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added dropwise and the resulting solution was stirred at 25°C for 10min and quenched with acetone (3.0ml). The mixture was then diluted with EtOAc and HCl 10%, extracted and washed (NaHCO<sub>3</sub> (sat.), brine). The organic phase was dried over MgSO<sub>4</sub> and concentrated. The residue was then treated with MnO<sub>2</sub> (20.4g, 235mmol) in CH<sub>2</sub>Cl<sub>2</sub> (250ml) and the reaction was stirred at r.t. overnight. The resulting mixture was then filtered through a plug of silica (EtOAc). Flash chromatography (90%CH<sub>2</sub>Cl<sub>2</sub>/10%EtOAc) yielded 1.7g of [5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylthio)phenyl]ketone.

Step 2: [5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylsulfonyl)phenyl]ketone

To a solution of the sulfide – that is, [5-(1-Hydroxy-1-Methylethyl)-1,3-thiazol-2-yl][4-(methylthio)phenyl]ketone – from present step 1 (1.7g, 5.8mmol) in THF/MeOH/H<sub>2</sub>O (100/50/50 ml) was added oxone (7.1g, 11.5mmol). The reaction was stirred at 25°C for 3h and quenched with a saturated aqueous solution of NaHCO<sub>3</sub>. The mixture was then diluted with EtOAc, extracted and washed (NaHCO<sub>3</sub> (sat.), brine). The organic phase was dried over MgSO<sub>4</sub> and concentrated. The residue was then purified by crystallization (EtOAc/Hexanes) to yield 1.6g of ketone K6.

Ketone K7

(6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]ketone

Ketone K7 was prepared by the following procedure.

Step 1: (6-Methyl-3-pyridinyl)[4-(methylthio)phenyl]methanol

To solution of 3-bromo-6-methylpyridine (760mg, 1eq) in THF (20mL) at -78°C, was added slowly *n*-butyllithium in hexane (1.1 eq). The solution was then stirred 30min. 4-(thiomethyl)benzaldehyde (738mg, 1.1eq) was then slowly added. The solution was warmed to rt. NH<sub>4</sub>Cl (sat.) was added, then water and EtOAc. The organic phase was separated, dried over MgSO<sub>4</sub>, and concentrated. The (6-Methyl-3-pyridinyl)[4-(methylthio)phenyl]methanol was obtained (550mg, 46%) by precipitation with ether/hexane and was used without further purification for the next step.

Step 2: (6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]methanol

Following the procedure of step 2 of ketone K1 above but substituting the sulfide (6-Methyl-3-pyridinyl)[4-(methylthio)phenyl]methanol from the present

step 1 for (4-fluorophenyl)[4-(methylthio)phenyl]ketone as the starting material, (6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]methanol was obtained.

Step 3: (6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]ketone

Following the procedure of step 2 of ketone K2 above but substituting the (6-Methyl-3-pyridinyl)[4-(methylsulfonyl)phenyl]methanol from the present step 2 for (1-methyl-1H-imidazol-2-yl)[4-(methylthio)phenyl]methanol as the starting material, ketone K7 was obtained.

#### Ketone K8

(5-Methyl-2-pyridinyl)[4-(methylsulfonyl)phenyl]ketone

Ketone K8 was prepared by following the procedure described for ketone K7 but substituting 2-bromo-5-methylpyridine for 3-bromo-6-methylpyridine.

#### Ketone K9

Bis-[(4-methylsulfonyl)phenyl]ketone

Ketone K9 was prepared by following the procedure described for ketone K7 but substituting 4-bromothioanisole for 3-bromo-6-methylpyridine and using twice the amount of Oxone in the sulfide-oxidation step.

#### Ketone K10

(2-Pyridinyl)[4-(methylsulfonyl)phenyl]ketone

Ketone K10 was prepared by following the procedure described for ketone K7 but substituting 2-bromopyridine for 3-bromo-6-methylpyridine.

#### Ketone K11

[5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]ketone

Ketone K11 was prepared by the following procedure.

Step 1: [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylthio)phenyl]methanol

To a suspension of 2,5-dibromopyridine (5.12g, 1eq) in ether at -78°C, was added *n*-butyllithium in hexane (1.05eq) slowly. The resulting yellow-orange precipitate was stirred 30min. Then acetone (1.54ml, 1.05eq) was added. The

solution was kept at -78°C for another 30min. *n*-Butyllithium in hexane (1.1eq) was slowly syringed to the resulting orange suspension. The suspension was then stirred 1h at -78°C. Following this, 4-(methylthio)benzaldehyde (2.85 ml, 1.1 eq.) was added. The resulting suspension was warmed to -35°C and quenched with a solution of NH<sub>4</sub>Cl (sat.). Water and EtOAc were added and the organic layer dried over MgSO<sub>4</sub>, evaporated and purified by flash chromatography (EtOAc) to give [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylthio)phenyl]methanol.

Step 2: [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]methanol

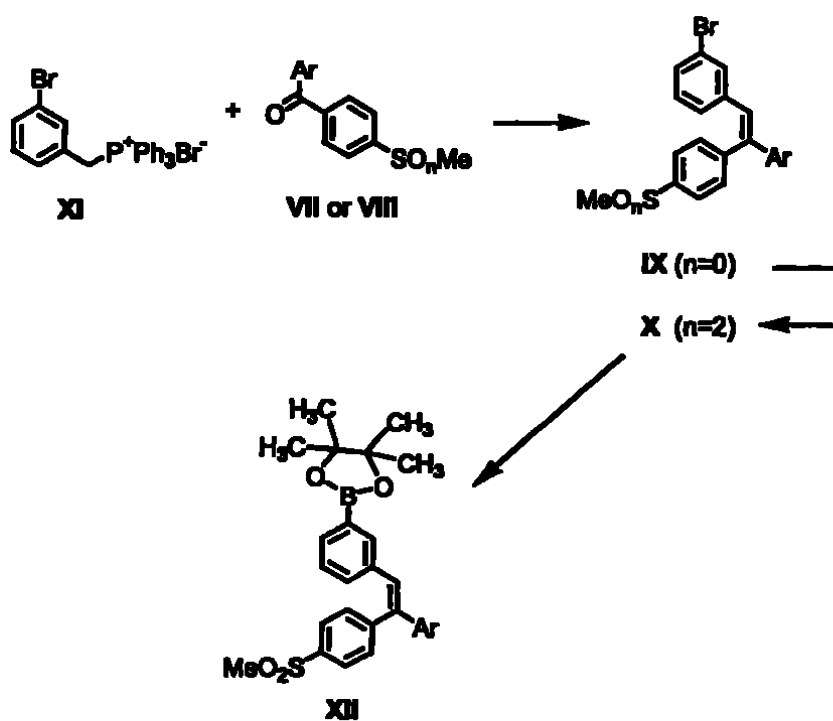
Following the procedure described above for step 2 of ketone K1 but substituting the sulfide - that is, [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylthio)phenyl]methanol - from the present step 1 for (4-fluorophenyl)[4-(methylthio)phenyl]ketone as the starting material, [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]methanol was obtained.

Step 3: [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]ketone

Following the procedure described above for step 2 for ketone K2 but substituting the [5-(1-Hydroxy-1-methylethyl)-2-pyridinyl][4-(methylsulfonyl)phenyl]methanol from the present step 2 for (1-methyl-1H-imidazol-2-yl)[4-(methylthio)phenyl]methanol as the starting material, ketone K11 was obtained.

The boronate compounds utilized to prepare the compounds of this invention can be made according to Scheme 2 shown below:

**SCHEME 2**  
**Boronate Synthesis**



| Ketone (VII or VIII) | Ar | n | Boronate (XII) |
|----------------------|----|---|----------------|
| K2                   |    | 0 | B1             |
| K4                   |    | 0 | B2             |
| K8                   |    | 2 | B3             |
| K11                  |    | 2 | B4             |

5

The aryl bromides IX and X may be prepared by treatment of the benzyl phosphonium bromide XI with a base such as *t*-BuOK or LiHMDS in an

organic solvent such as THF, followed by the addition of the ketone VII or VIII to the reaction mixture. The sulfide in IX may be converted to the sulfone X by treatment with oxone in a solvent such as a mixture of THF/MeOH/H<sub>2</sub>O. The boronate ester XII can be prepared by heating the aryl bromide X with pinacol  
 5 diborane in the presence of a base such as KOAc and a catalyst such as PdCl<sub>2</sub>(dppf) in a solvent such as DMF.

#### Boronate B1

10 Pinacol 3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenylboronate

Boronate B1 was prepared by the following procedure.

15 Step 1: (E/Z)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylthio)phenyl]ethene

To a solution of (3-bromobenzyl)(triphenyl)phosphonium bromide (10.2g, 19.9mmol) in THF (200mL) and CH<sub>3</sub>CN (50mL) at 25°C was added *t*-BuOK (1.0M in THF, 19.9mL, 19.9mmol) dropwise and the resulting red solution was stirred at r.t. for 20min. To this resulting ylide was then added at 25°C the ketone K2  
 20 (4.4g, 18.9mmol). The resulting mixture was stirred at 60°C for 2 days and quenched with NH<sub>4</sub>Cl (sat). The mixture was then diluted with EtOAc. The organic phase was washed with NaHCO<sub>3</sub> (sat.), brine, dried over MgSO<sub>4</sub>, filtered and concentrated, and used directly in the next present step 2.

25 Step 2: (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene

To a solution of the crude sulfide – that is, (E/Z)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylthio)phenyl]ethene – from present step 1 (18.9mmol) in THF/MeOH/H<sub>2</sub>O (200/100/100 ml) was added oxone (23.2g, 37.8mmol). The mixture was stirred at r.t. for 4h, quenched with NaHCO<sub>3</sub> (sat.), and  
 30 diluted with EtOAc. The organic phase was washed with NaHCO<sub>3</sub> (sat.), brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Flash chromatography (95%EtOAc/5% Et<sub>3</sub>N)

yielded (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene (3.5 g, single isomer) as a foam.

Step 3: Pinacol 3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenylboronate

- 5 A suspension of the bromide -- that is, (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene -- from present step 2 (2.0g; 4.8mmol), pinacol diborane (1.5g; 5.8mmol), KOAc (1.65g; 16.8mmol) and PdCl<sub>2</sub>(dppf) (0.2g; 0.24mmol) in 50mL of DMF was stirred at 90°C for 4h. The resulting mixture was cooled to r.t., diluted with EtOAc, washed with H<sub>2</sub>O (3x), brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Flash chromatography (95%EtOAc/5% Et<sub>3</sub>N) yielded boronate B1 (1.1g) as a foam.
- 10

#### Boronate B2

- Pinacol 3-((E/Z)-2-(1,3-thiazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenylboronate
- 15

Boronate B2 was prepared by the following procedure.

Step 1: (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylthio)phenyl]ethene

- To a solution of (3-bromobenzyl)(triphenyl)phosphonium bromide (44.5g, 86.9mmol) in THF (500mL) and DMF (200mL) at 0°C was added LiHMDS (1.0M in THF, 86.9mL, 86.9mmol) dropwise and the resulting red solution was stirred at r.t. for 20min. To the resulting ylide was then added at 0°C the ketone K4 (18.6g, 79.0mmol). The mixture was stirred until completion by TLC, and quenched with a NH<sub>4</sub>Cl (sat). The mixture was then diluted with EtOAc. The organic phase
- 20
- 25 was washed with NaHCO<sub>3</sub> (sat), brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>) yielded (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylthio)phenyl]ethene (24.8g, 1.5 to 1 mixture of isomers).

Step 2: (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene

- To a solution of the sulfide -- that is, (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylthio)phenyl]ethene -- from present step 1 (24.8g, 63.9mmol) in THF/MeOH/H<sub>2</sub>O (600/300/300 ml) was added Oxone (78.5g, 128mmol). The resulting reaction mixture was stirred at r.t. overnight. The resulting mixture was quenched with a NaHCO<sub>3</sub> (sat), and diluted with EtOAc. The organic phase was
- 30

washed with  $\text{NaHCO}_3$  (sat.), brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to yield (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene (21.5g, 3 to 2 mixture of isomers).

Step 3: Pinacol 3-((E/Z)-2-(1,3-thiazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenylboronate

A suspension of the bromide (E/Z)-2-(3-Bromophenyl)-1-(1,3-thiazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene from present step 2 (15.0g, 35.7mmol), pinacol diborane (10.9g, 42.8mmol), KOAc (12.3g, 125mmol) and  $\text{PdCl}_2(\text{dppf})$  (1.46g, 1.78mmol) in 350mL of DMF was stirred at  $90^\circ\text{C}$  for 4h. The resulting mixture was cooled to r.t., diluted with EtOAc, washed with  $\text{H}_2\text{O}$  (3x), brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Flash chromatography (Tol/Acetone, 9/1) yielded boronate B2 (7.4g, 3 to 1 mixture of isomers) as a foam.

#### Boronate B3

Pinacol 3-((E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenylboronate

Boronate B3 was prepared by the following procedure.

Step 1: (E)-2-(3-Bromophenyl)-1-(5-methyl-2-pyridinyl)-1-[4-(methylsulfonyl)phenyl]ethylene

Following the procedure described for step 1 for boronate B1 but substituting the ketone K8 for ketone K2 as the starting material, (E)-2-(3-Bromophenyl)-1-(5-methyl-2-pyridinyl)-1-[4-(methylsulfonyl)phenyl]ethylene was obtained after separation of the isomers by flash chromatography.

Step 2: Pinacol 3-((E)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenylboronate

Following the procedure described for step 3 for boronate B1 but substituting the bromide (E)-2-(3-Bromophenyl)-1-(5-methyl-2-pyridinyl)-1-[4-(methylsulfonyl)phenyl]ethylene from present step 1 for (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene as the starting material, boronate B3 was obtained.

#### Boronate B4

Pinacol 3-((E)-2-(5-(1-hydroxy-1-methylethyl)-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenylboronate

Boronate B4 was prepared by the following procedure.

Step 1: (E)-2-(3-Bromophenyl)-1-[5-(1-hydroxy-1-methylethyl)-2-pyridinyl]-1-[4-(methylsulfonyl)phenyl]ethene

Following the procedure described for step 1 for boronate B1 but substituting the ketone K11 for ketone K2 as the starting material, (E)-2-(3-Bromophenyl)-1-[5-(1-hydroxy-1-methylethyl)-2-pyridinyl]-1-[4-(methylsulfonyl)phenyl]ethene was obtained after separation of the isomers by flash chromatography.

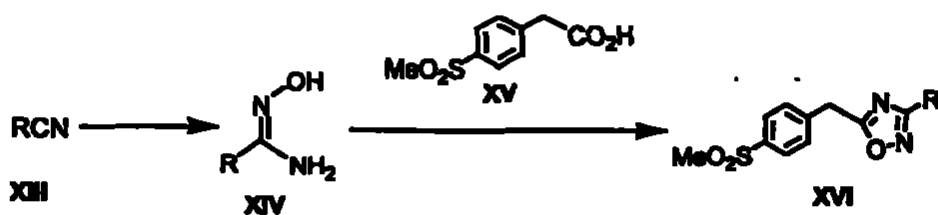
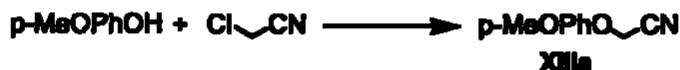
Step 2: Pinacol 3-((E)-2-(5-(1-hydroxy-1-methylethyl)-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenylboronate

Following the procedure described for step 3 for boronate B1 but substituting the bromide (E)-2-(3-Bromophenyl)-1-[5-(1-hydroxy-1-methylethyl)-2-pyridinyl]-1-[4-(methylsulfonyl)phenyl]ethene from present step 1 for (E)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylsulfonyl)phenyl]ethene as the starting material, boronate B4 was obtained.

The aryl bromide compounds utilized to prepare the compounds of this invention can be made according to Schemes 3 and 4 shown below:

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### SCHEME 3 Oxadiazole Synthesis



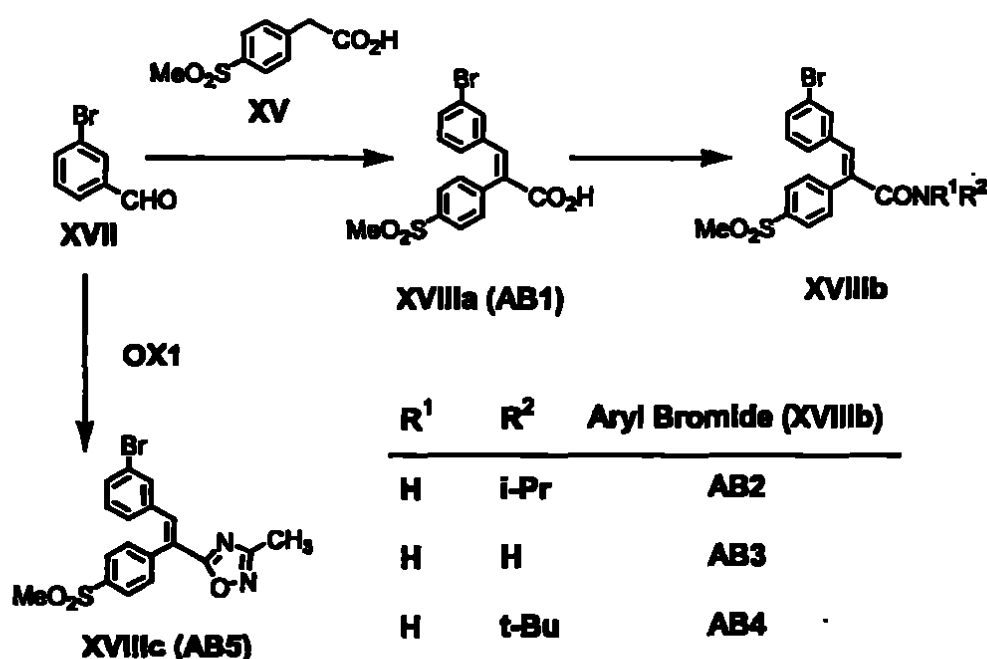
| R                       | Oxadiazole (XVI) |
|-------------------------|------------------|
| Me                      | OX1              |
| p-MeOPhOCH <sub>2</sub> | OX2              |

365

Referring to Scheme 3 above, the nitrile intermediate XIIIa may be prepared by the alkylation of 4-methoxyphenol with chloroacetonitrile in the presence of a base such as potassium carbonate in a solvent such as acetone. The amide-oxime XIV may be prepared by treatment of the nitrile XIII with hydroxyl amine in a solvent such as methanol in the presence of a base such as sodium acetate. Formation of the oxadizole XVI may be achieved by activation of the arylacetic acid XV with carbonyldiimidazole in a solvent such as DMF followed the addition of the amide-oxime XIV and subsequent heating of the reaction mixture.

10

**SCHEME 4**  
**Aryl Bromide Synthesis**



Referring to Scheme 4 above, condensation of the aldehyde XVII by heating with the arylacetic acid XV in the presence of a base such as piperidine in a solvent such as toluene produces the unsaturated acid XVIIIa. Formation of the acid chloride of XVIIIa *in situ* by treatment with thionyl chloride and a base such as triethylamine in a solvent such as toluene, is followed by the addition of an amine to the reaction mixture to yield the amide XVIIIb. The oxadizole-ethene XVIIIc may

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be formed by heating OX1 with XVII in the presence of a base such as piperidine in a solvent such as toluene.

5

#### Aryl Bromide AB1

(E)-3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid

Aryl Bromide AB1 was prepared by the following procedure. To a solution of 3-bromobenzaldehyde (12.9g, 70mmol) in toluene (100mL) was added 4-(methylsulfonyl)phenylacetic acid (15g, 70mmol) and piperidine (2mL). After overnight refluxing, the mixture was cooled down to r.t. To the slurry thus formed, toluene was added (10 mL). Filtration gave (E)-3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid as a white solid (25g).

15

#### Aryl Bromide AB2

(E)-N-Isopropyl-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide

Aryl Bromide AB2 was prepared by the following procedure. To a solution of AB1 (24.9g, 65mmol) in toluene (250mL) was added thionyl chloride (14.3mL, 196mmol) and triethylamine (34mL, 245mmol). After stirring at r.t. for 0.5h., isopropyl amine (28mL, 327mmol) was added. After a further 2h at r.t., the mixture was cooled to 0°C and was neutralised with saturated NH<sub>4</sub>Cl solution, then extracted with EtOAc. The organic extracts were washed (H<sub>2</sub>O, brine), dried (MgSO<sub>4</sub>), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 1:1 to pure EtOAc) yielded (E)-N-Isopropyl-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide (8.3 g)

25

#### Aryl Bromide AB3

(E)-3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide

30

Aryl Bromide AB3 was prepared by following the procedure described for aryl bromide AB2 but substituting ammonium hydroxide for isopropyl amine as the starting material.

## Aryl Bromide AB4

(E)-N-(*t*-Butyl)-3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide

- Aryl Bromide AB4 was prepared by following the procedure described  
5 for aryl bromide AB2 but substituting *t*-butyl amine for isopropyl amine as the  
starting material.

## Aryl Bromide AB5

- 10 (E)-1-(3-Bromophenyl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-  
(methylsulfonyl)phenyl]ethene

Aryl Bromide AB5 was prepared by the following procedure.

Step 1 (Scheme 3, Oxadiazole OX1): (3-Methyl-1,2,4-oxadiazol-5-yl)  
[4-(methylsulfonyl)phenyl]methane

- 15 To a solution of 4-(methylsulfonyl)phenylacetic acid (15g, 70mmol) in  
DMF (300mL) at r.t., was added carbonyldiimidazole (12.5g, 77mmol). After 0.5h at  
r.t., acetamide oxime (5.7g, 77mmol) was added. After stirring the resulting mixture  
overnight at r.t., the mixture was heated to 120°C for 6h. After cooling to r.t., the  
mixture was quenched with H<sub>2</sub>O, and extracted with EtOAc. The organic extracts  
20 were washed (H<sub>2</sub>O, brine), dried (MgSO<sub>4</sub>), filtered and concentrated. Purification by  
flash chromatography (Hex:EtOAc, 1:1) yielded (3-Methyl-1,2,4-oxadiazol-5-yl) [4-  
(methylsulfonyl)phenyl]methane (7.4 g).

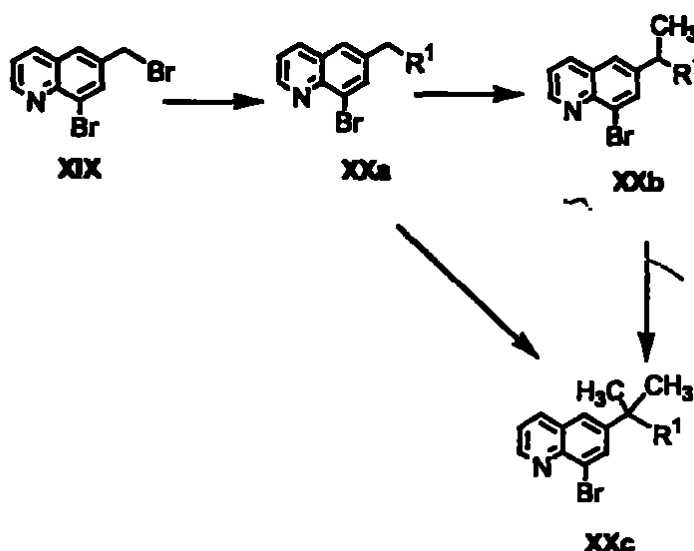
Step 2 (Scheme 4): (E)-1-(3-Bromophenyl)-2-(3-methyl-1,2,4-  
oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethene

- 25 To a solution of 3-bromobenzaldehyde (2.2g, 11.9mmol) in toluene  
(30mL) was added the product from step 1 (OX1) (3.0g, 11.9mmol) and piperidine  
(0.4mL). After overnight refluxing, the mixture was cooled down to r.t. To the  
resulting slurry, MeOH (30mL) was added. After further refluxing then cooling to  
0°C, filtration gave (E)-1-(3-Bromophenyl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-  
30 (methylsulfonyl)phenyl]ethene as a white solid (4.2g).

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The Bromoquinolines utilized to prepare the compounds of this invention can be made according to Scheme 5 shown below:

5  
SCHEME 5  
Preparation of Bromoquinolines

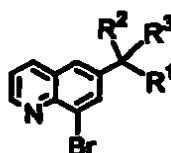


- Referring to Scheme 5 above and the Scheme 5 table below, treatment of the bromomethyl compound XIX with a nucleophile such as sodium methanesulfinate or potassium cyanide in a solvent such as DMF or a mixture of
- 10 DMF and water can be used to produce the compounds XXa. The compound XXb may be prepared by treatment of XXa with a base such as potassium *t*-butoxide (1.1 equivalents) in a solvent such as THF followed by the addition of the resulting mixture into a solution of methyl iodide in a solvent such as THF. The compound XXc may be prepared by treatment of XXb with a base such as potassium *t*-butoxide
- 15 (1.1 equivalents) in a solvent such as THF followed by the addition of the resulting mixture into a solution of methyl iodide in a solvent such as THF. The compound XXc (where R¹ = CN) may also be prepared by treatment of XXa with a base such as potassium *t*-butoxide (2.2 equivalents) and methyl iodide in a solvent such as THF. The compound XXc (where R¹ = SO₂Me) may also be prepared by treatment of XXa
- 20 with a base such as potassium *t*-butoxide (1.3 equivalents) and methyl iodide (1.6

equivalents) in a solvent such as THF, followed by an additional amount of methyl iodide (1.6 equivalents) and an additional amount of the same base (1.0 equivalents).

Scheme 5 Table

Bromoquinolines



XX

| R <sup>1</sup>     | R <sup>2</sup> | R <sup>3</sup> | Bromoquinoline (XX) |
|--------------------|----------------|----------------|---------------------|
| SO <sub>2</sub> Me | H              | H              | Q1                  |
| SO <sub>2</sub> Me | Me             | H              | Q2                  |
| SO <sub>2</sub> Me | Me             | Me             | Q3                  |
| CN                 | H              | H              | Q4                  |
| CN                 | Me             | Me             | Q5                  |

5

Bromoquinoline Q1

6-(methylsulfonyl)methyl- 8-bromoquinoline

Bromoquinoline Q1 was prepared by the following procedure. DMF (500mL) was added to 6-bromomethyl-8-bromoquinoline (60g, 200mmol) (described in International Patent Publication WO 94/22852) and sodium methanesulfinate (27.6g, 270mmol). After stirring overnight at r.t., the mixture was quenched with H<sub>2</sub>O (2000mL), stirred for one hour, isolated by filtration and washed with Et<sub>2</sub>O to yield (59 g) 6-(methylsulfonyl)methyl-8-bromoquinoline.

10

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**Bromoquinoline Q2****6-[1-(methylsulfonyl)ethyl]-8-bromoquinoline**

Bromoquinoline Q2 was prepared by the following procedure. To a solution of bromoquinoline Q1 (16.1g, 54mmol) in THF (500mL) at -78°C, was added potassium *t*-butoxide (59mL, 1N in THF). After 0.5h at -78°C, the resulting mixture was stirred at 0°C for 45min and then transferred by canula dropwise into a solution of MeI (16.7mL, 268.3mmol) in THF (160mL). After stirring overnight at r.t., the mixture was neutralised with saturated NH<sub>4</sub>Cl solution and extracted with EtOAc. The organic extracts were washed (H<sub>2</sub>O), (brine), dried (MgSO<sub>4</sub>), filtered and concentrated. Stirring in ether, followed by isolation by filtration gave 6-[1-(methylsulfonyl)ethyl]-8-bromoquinoline (15.7g).

**Bromoquinoline Q3****6-[1-methyl-1-(methylsulfonyl)ethyl]-8-bromoquinoline**

Bromoquinoline Q3 was prepared by the following procedure. To a solution of bromoquinoline Q2 (15.7g, 50mmol) in THF (500mL) at -78°C, was added potassium *t*-butoxide (55mL, 1N in THF). After stirring 0.5h at -78°C, the resulting mixture was stirred at 0°C for 45min and then transferred dropwise into a solution of MeI (15.6mL, 250mmol) in THF (40mL) at 0°C. After stirring overnight at r.t., the mixture was neutralised with saturated NH<sub>4</sub>Cl solution, and extracted with EtOAc. The organic extracts were washed (H<sub>2</sub>O, brine), dried (MgSO<sub>4</sub>), filtered and concentrated. Stirring in ether, followed by isolation by filtration gave 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-bromoquinoline (10.2 g).

**Bromoquinoline Q4****6-cyanomethyl-8-bromoquinoline**

Bromoquinoline Q4 was prepared by the following procedure. DMF (10mL) and H<sub>2</sub>O (5mL) were added to 6-bromomethyl-8-bromoquinoline (3g, 10mmol) (described in International Patent Publication WO 94/22852) and potassium cyanide (1.6g, 25mmol). After heating at 100°C for 1 hour, the resulting mixture was quenched with H<sub>2</sub>O (100mL) and extracted with EtOAc. The organic extracts were washed (H<sub>2</sub>O, brine), dried (MgSO<sub>4</sub>), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 3:1) yielded 6-cyanomethyl-8-bromoquinoline (2.2g)

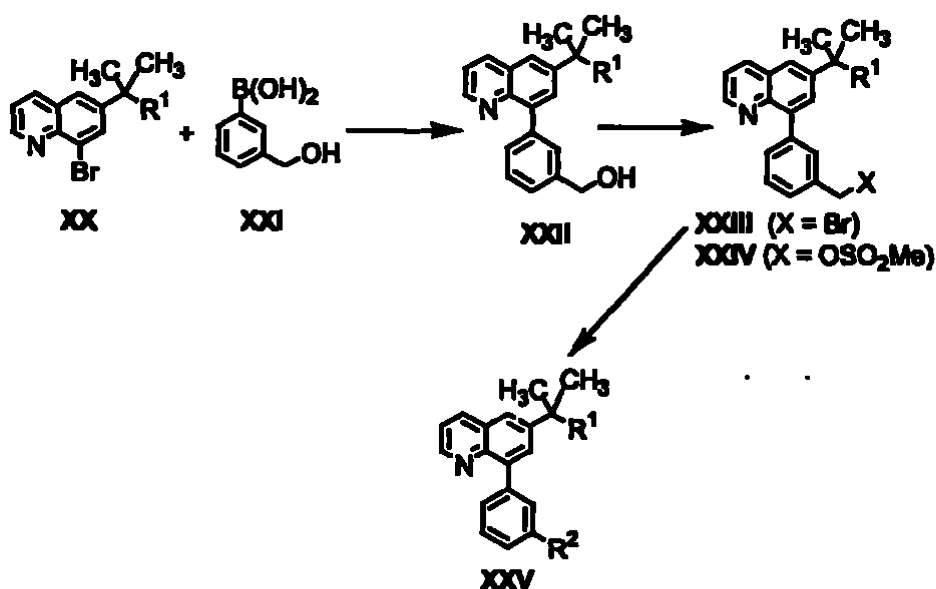
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**Bromoquinoline Q5**  
**6-[1-methyl-1-cyanoethyl]-8-bromoquinoline**

5                   Bromoquinoline Q5 was prepared by the following procedure. To a solution of bromoquinoline Q4 (3g, 12.1mmol) in THF (100mL) at  $-78^{\circ}\text{C}$ , was added MeI (1.7mL, 27mmol) followed by potassium *t*-butoxide (27mL, 27mmol). After 2h at  $-78^{\circ}\text{C}$ , the mixture was warmed to  $0^{\circ}\text{C}$  and was neutralised with saturated  $\text{NH}_4\text{Cl}$  solution then extracted with EtOAc. The organic extracts were washed ( $\text{H}_2\text{O}$ , brine),  
10                   dried ( $\text{MgSO}_4$ ), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 3:1) yielded 6-[1-methyl-1-cyanoethyl]-8-bromoquinoline (3.2g)

15                   The Benzyl Phosphorus Reagents utilized to prepare the compounds of this invention can be made according to Scheme 6 shown below:

**SCHEME 6**  
**Preparation of Benzyl Phosphorus Reagents**



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| R <sup>1</sup> | R <sup>2</sup>                                                  | Benz. Phos. Reag.(XXV) |
|----------------|-----------------------------------------------------------------|------------------------|
| H              | CH <sub>2</sub> P(Ph) <sub>3</sub> <sup>+</sup> Br <sup>-</sup> | P1                     |
| H              | CH <sub>2</sub> P(O)(OEt) <sub>2</sub>                          | P2                     |
| CN             | CH <sub>2</sub> P(O)(OEt) <sub>2</sub>                          | P3                     |

The arylquinolines of the formula XXII may be prepared by coupling bromoquinoline XX with the boronic acid XXI by heating in the presence of a catalyst such as Pd(PPh<sub>3</sub>)<sub>4</sub> and a base such as sodium carbonate (aqueous) in a solvent such as a DME. The alcohol XXII may be converted to the bromide XXIII by treatment with HBr (aq) in a solvent such as acetic acid. The alcohol XXII may be converted to the methyl sulfonate ester XXIV by methanesulfonyl chloride in the presence of a base such as triethylamine in a solvent such as dichloromethane. The benzyl phosphorous reagents XXV may be prepared either by heating XXIII in the presence of PPh<sub>3</sub> in a solvent such as acetonitrile or by treating XXIII or XXIV with diethylphosphite and a base such as potassium *t*-butoxide in a solvent such as THF.

#### Benzylphosphonium Bromide P1

[3-(6-Isopropyl-8-quinoliny)benzyl](triphenyl)phosphonium Bromide

Benzylphosphonium Bromide P1 was prepared by the following procedure.

Step 1: 6-Isopropyl-8-[3-(hydroxymethyl)phenyl]quinoline

A mixture of 6-isopropyl-8-Bromoquinoline (11.1g, 44.4mmol) (described in International Patent Publication WO 94/22852), 3-(hydroxymethyl)phenylboronic acid (8.70g, 57.2mmol), Na<sub>2</sub>CO<sub>3</sub> (2M, 71mL, 142mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (2.51mg, 2.17mmol) in 280mL of DME was stirred at 80°C for 5h. The resulting mixture was cooled to r.t., diluted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Flash chromatography (Hex/EtOAc, 1/1) and stirring in CH<sub>2</sub>Cl<sub>2</sub>/hexane (1/9) yielded 6-Isopropyl-8-[3-(hydroxymethyl)phenyl]quinoline (10.05g) as a white solid.

Step 2: 6-Isopropyl-8-[3-(bromomethyl)phenyl]quinoline

A suspension of the hydroxymethyl product compound from present step 1 (7.40g, 26.7mmol) in AcOH (50mL) and HBr (50mL, 48% aq) was stirred for

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12h at 100°C. The mixture was cooled to r.t., poured into NaOH (2N) in ice, the pH was adjusted to 8 and the mixture was diluted with ether. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to yield 6-Isopropyl-8-[3-(bromomethyl)phenyl]quinoline (8.70g) as a yellow solid.

5                    Step 3: [3-(6-Isopropyl-8-quinoliny)benzyl](triphenyl)phosphonium Bromide

To a solution of the bromomethyl product compound from present step 2 (3.807g, 11.1mmol) in 40mL of CH<sub>3</sub>CN was added triphenylphosphine (3.22g, 12.3mmol). The mixture was stirred at 60°C for 12h, cooled to r.t., diluted with ether, 10 filtered, and washed with ether to yield [3-(6-Isopropyl-8-quinoliny)benzyl](triphenyl)phosphonium Bromide (6.71g)

Benzyolphosphate P2

15                    Diethyl 3-(6-isopropyl-8-quinoliny)benzylphosphonate

Benzyolphosphate P2 was prepared by the following procedure. The bromomethyl compound from from step 2 above of the synthesis of P1 (11.34g, 1eq) was dissolved in THF (170mL). Diethylphosphite (3.87mL, 1.05eq) was added and the solution was cooled down to 0°C. Next, *t*-BuOK (3.87mL, 1N in THF) was added 20 slowly. The reaction was stirred 2h and the quenched by addition of NH<sub>4</sub>Cl(sat), water and EtOAc. The organic phase was separated and washed with brine, dried over MgSO<sub>4</sub> and concentrated. Purification by flash chromatography on silica gel (hexane:EtOAc 1/9) gave 9.5g of Diethyl 3-(6-isopropyl-8-quinoliny)benzylphosphonate as a clear oil.

25

Benzyolphosphate P3

Diethyl 3-[6-(1-cyano-1-methylethyl)-8-quinoliny]benzylphosphonate

Benzyolphosphate P3 was prepared by the following procedure.

30                    Step 1: 6-(1-Cyano-1-methylethyl)-8-[3-(hydroxymethyl)phenyl]quinoline

Following step 1 described above of the procedure for Benzyolphosphonium Bromide P1, but substituting the bromoquinoline Q5 for 6-

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isopropyl-8-bromoquinoline as the starting material, 6-(1-Cyano-1-methylethyl)-8-[3-(hydroxymethyl)phenyl]quinoline was obtained.

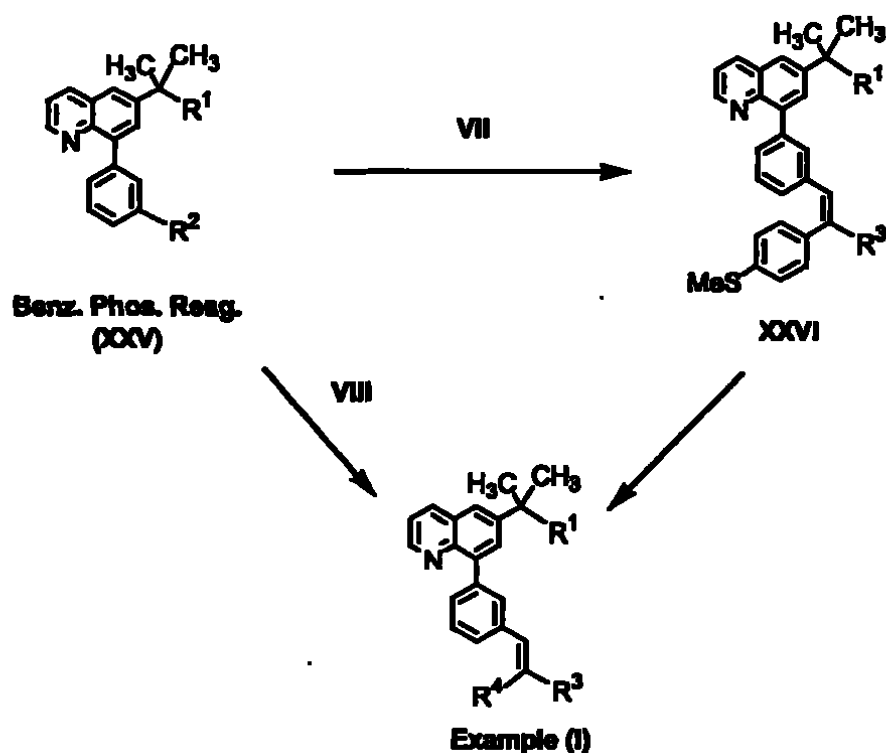
Step 2: 3-[6-(1-Cyano-1-methylethyl)-8-quinoliny]benzyl methanesulfonate

- 5 To a solution of the alcohol 6-(1-Cyano-1-methylethyl)-8-[3-(hydroxymethyl)phenyl]quinoline from present step 1 (5.15g, 17mmol) in  $\text{CH}_2\text{Cl}_2$  (150mL) at  $-78^\circ\text{C}$  was added  $\text{Et}_3\text{N}$  (3.6mL, 26mmol) and methanesulfonyl chloride ("MsCl") (1.6mL, 21mmol). After 0.5h at  $-78^\circ\text{C}$ , the mixture was neutralised with saturated  $\text{NH}_4\text{Cl}$  solution, diluted with water and extracted with ether. The organic
- 10 extracts were washed ( $\text{H}_2\text{O}$ , brine), dried ( $\text{MgSO}_4$ ), filtered and concentrated to yield 3-[6-(1-Cyano-1-methylethyl)-8-quinoliny]benzyl methanesulfonate as a white foam.

Step 3: Diethyl 3-[6-(1-cyano-1-methylethyl)-8-quinoliny]benzylphosphonate

- 15 To a solution of diethylphosphite (2.5mL, 18mmol) in THF (100mL) at  $-78^\circ\text{C}$  was added potassium *t*-butoxide (1M, THF, 16mL, 16mmol) and the mesylate compound 3-[6-(1-Cyano-1-methylethyl)-8-quinoliny]benzyl methanesulfonate from present step 2 (5.1g, 13.5mmol). After 0.5h at  $-78^\circ\text{C}$  and 12h at r.t., the resulting mixture was neutralised with saturated  $\text{NH}_4\text{Cl}$  solution, diluted with water and extracted with ether. The organic extracts were washed ( $\text{H}_2\text{O}$ , brine), dried ( $\text{MgSO}_4$ ),
- 20 filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 1:4 to 1:10) yielded Diethyl 3-[6-(1-cyano-1-methylethyl)-8-quinoliny]benzylphosphonate as an oil.

**SCHEME 7**  
**Benzylphosphorous Reagent – Ketone Coupling**



- Compounds corresponding to the formula I may be prepared using the reaction pathways outlined in Scheme 7 above. The compound XXVI may be obtained by adding a solution of the ketone VII in a solvent such as THF to a mixture of the benzylphosphorous reagent XXV and a base such as potassium *t*-butoxide in a solvent such as THF. The compounds corresponding to the formula I may then be prepared by treating XXVI with oxone in a mixture of solvents such as
- 5 THF/MeOH/water. Alternatively the compounds of formula I may be prepared by reacting the ketone VIII with XXV in the presence of a base such as potassium *t*-butoxide in a solvent such as THF.
- 10

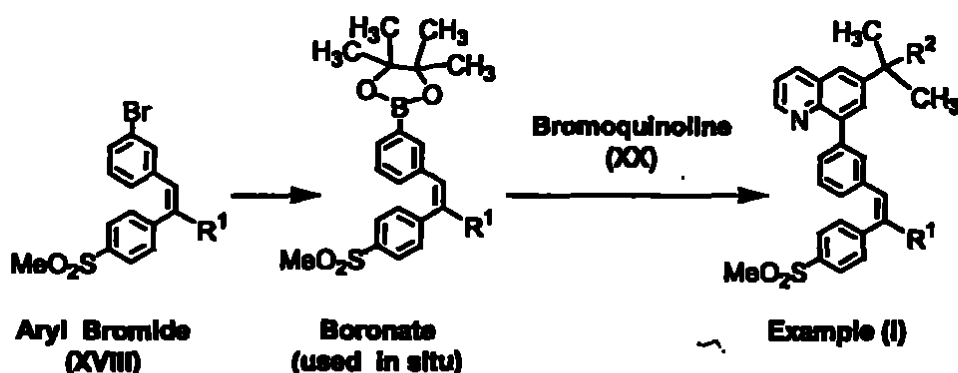
Referring to Scheme 7 above and Table 1 below, the coupling of the ketones with the benzyl phosphorous reagents resulted in the tabulated Examples.

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| Table1            |            |         |
|-------------------|------------|---------|
| Benz. Phos. Reag. | Ketone     | Example |
| P2                | K3         | 1       |
| P2                | K3         | 2       |
| P1                | K5         | 3       |
| P1                | K2         | 4       |
| P2                | K1         | 5       |
| P2                | K1         | 6       |
| P2                | K8         | 7       |
| P3                | K8         | 8       |
| P3                | K2         | 9       |
| P2                | Commercial | 30      |
| P2                | K7         | 31      |
| P2                | K7         | 32      |
| P2                | K8         | 33      |
| P2                | K8         | 34      |
| P2                | K9         | 35      |
| P3                | K8         | 36      |
| P3                | K8         | 37      |
| P3                | K9         | 38      |
| P3                | K10        | 39      |

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**SCHEME 8**  
**Aryl Bromide - Bromoquinoline Coupling**



- Referring to Scheme 8, compounds corresponding to the formula I may
- 5 be prepared by *in situ* conversion of the aryl bromide XVIII to the corresponding boronate ester by heating with diboron pinacol ester, a catalyst such as [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) and a base such as potassium acetate in a solvent such as DMF, followed by the addition of the bromoquinoline XX, an additional amount of the same catalyst, an additional amount of a base such as
- 10 sodium carbonate (aqueous) and an additional period of heating.

Referring to Scheme 8 above and Table 2 below, the coupling of the Aryl Bromide with the Bromoquinoline resulted in the tabulated Examples.

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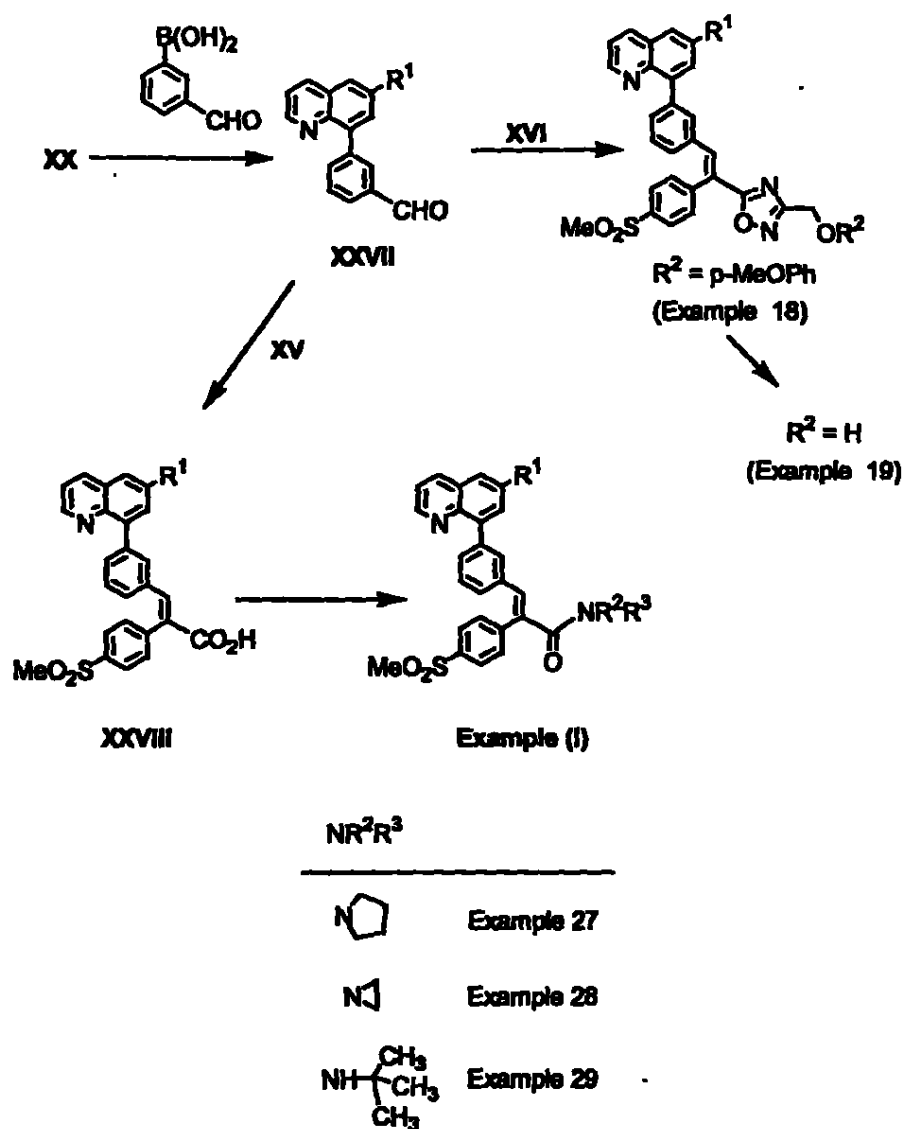
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| Table 2      |                |         |
|--------------|----------------|---------|
| Aryl Bromide | Bromoquinoline | Example |
| AB5          | Q3             | 14      |
| AB5          | Q3             | 15      |
| AB2          | Q5             | 16      |
| AB2          | Q5             | 17      |
| AB2          | Q3             | 20      |
| AB1          | Q5             | 21      |
| AB5          | Q5             | 22      |
| AB3          | Q5             | 23      |
| AB4          | Q5             | 24      |
| AB1          | WO 94/22852    | 25      |
| AB5          | WO 94/22852    | 26      |

Compounds of this invention can be prepared by following Scheme 9 shown below.

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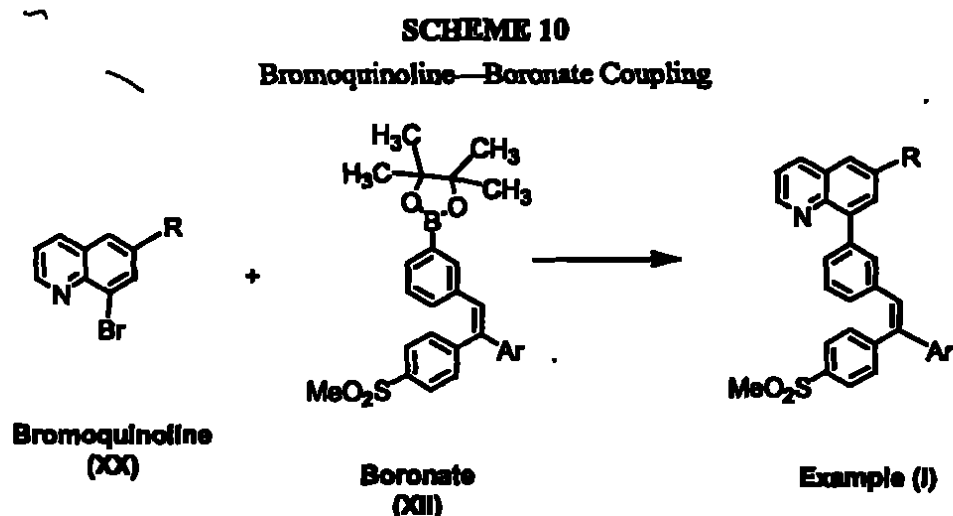
SCHEME 9



Scheme 9 outlines the preparation of compounds of formula I where  
 5 the aldehyde XXVII may be prepared by heating the bromoquinoline XX, 3-  
 formylphenylboronic acid, a catalyst such as  $\text{Pd(PPh}_3)_4$  and a base such as sodium  
 carbonate (aqueous) in a solvent such as DME. The aldehyde XXVII may be  
 converted to Example 18 by heating with XVI in the presence of a base such as  
 piperidine in a solvent such as toluene. Example 19 may be obtained by treatment of

- Example 18 with ceric ammonium nitrate ("CAN") in a mixture of solvents such as acetonitrile/water. Alternatively the aldehyde XXVII may be converted to the unsaturated acid XXVIII by heating with XV and a base such as piperidine in a solvent such as toluene. The acid XXVIII may then be converted to the amide I (Example 27, 28 and 29) by treatment with a coupling system such as EDCI, HOBT, and an amine in a solvent such as DMF.

- Compounds of this invention can be prepared by coupling Bromoquinoline compounds with Boronate compounds according to Scheme 10 below.



- Scheme 10 describes how compounds of formula I may be obtained by coupling the bromoquinoline XX with the boronate ester XII in the presence of a catalyst such as  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , and a base such as sodium carbonate (aqueous) in a solvent such as *n*-propanol. Referring to Table 3, the coupling of the Bromoquinoline with Boronate resulted in the tabulated Examples.

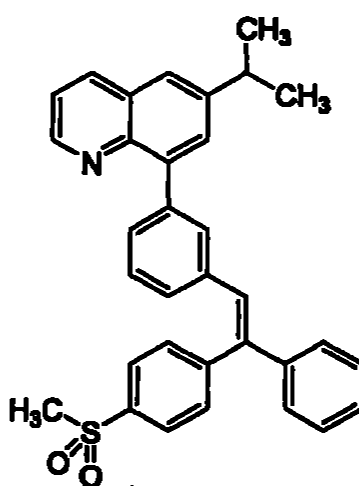
| Table 3        |          |         |
|----------------|----------|---------|
| Bromoquinoline | Boronate | Example |
| Q2             | B2       | 10      |
| Q3             | B2       | 11      |
| Q2             | B1       | 12      |

| Table 3        |          |         |
|----------------|----------|---------|
| Bromoquinoline | Boronate | Example |
| Q3             | B1       | 13      |
| Q3             | B3       | 40      |
| Q3             | B3       | 41      |
| Q3             | B4       | 42      |

EXAMPLES 1 and 2

6-isopropyl-8-(3-((Z/E)-2-[4-(methylsulfonyl)phenyl]-2-phenylethenyl)phenyl)quinoline

5



Example 1

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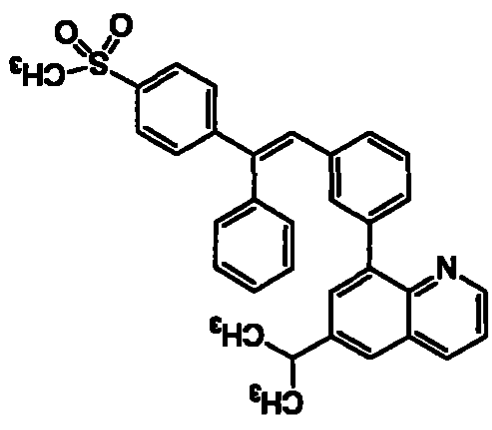
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Examples 1 and 2 were prepared by the following procedure. To a mixture of benzylphosphonate P2 (330mg, 0.83mmol) and ketone K3 (200mg, 0.77mmol) in THF (6mL) at r.t. was added potassium *t*-butoxide (1M, THF, 0.83mL, 0.83mmol). After 1h at r.t., the mixture was diluted with water and extracted with Et<sub>2</sub>O. The organic extracts were washed (H<sub>2</sub>O), (brine), dried (MgSO<sub>4</sub>), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 7:3) produced Examples 1 and 2 as white foams with one product being less polar than the other product. Example 1 was the less polar Z-isomer (120 mg) and Example 2 was the more polar E-isomer (80 mg).

Example 1: NMR <sup>1</sup>H (400MHz, Acetone-d<sub>6</sub>) δ 8.79 (q, 1H), 8.28 (q, 1H), 7.94 (d, 2H), 7.73 (d, 1H), 7.6-7.1 (m, 14H), 3.14 (m, 1H), 2.97 (q, 3H), 1.34 (d, 6H).

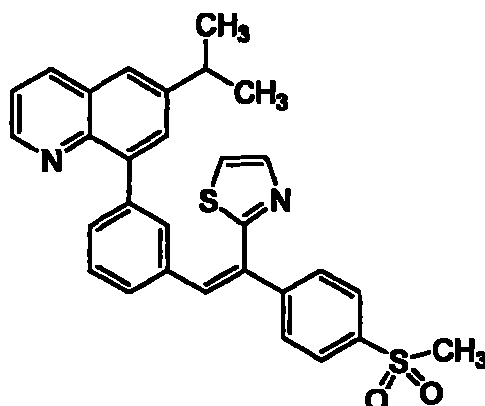
Example 2: NMR <sup>1</sup>H (400MHz, Acetone-d<sub>6</sub>) δ 8.78 (q, 1H), 8.25 (q, 1H), 7.89 (d, 2H), 7.71 (d, 1H), 7.6 (m, 3H), 7.45 (m, 3H), 7.39-7.2 (m, 8H), 3.11 (m, 4H), 1.34 (d, 6H).

Example 2



## EXAMPLE 3

6-isopropyl-8-{3-[(E/Z)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl}quinoline



5

Example 3 was prepared by the following procedure. To a suspension of the benzylphosphonium bromide P1 (320mg, 0.531mmol) in 2.5mL THF at -78°C was added *t*-BuOK (1.0M in THF, 0.55mL, 0.55mmol) dropwise and the resulting red solution was stirred 30min at 0°C. To this ylide at -78°C was then added ketone K5 (122mg, 0.455mmol) in 2mL of THF dropwise. The mixture was warmed to r.t., then stirred for 1h, quenched with a NH<sub>4</sub>Cl (sat.) and diluted with EtOAc. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Flash chromatography (Silica cartridge, Hex/EtOAc 10 to 100% in 20min) yielded Example 3 (150mg, 1.5 to 1 mixture of isomers).

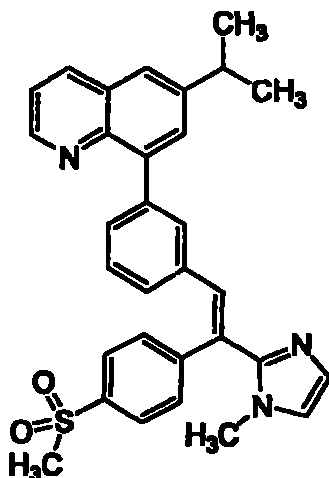
NMR <sup>1</sup>H (500MHz in acetone-*d*<sub>6</sub>) δ 8.79-8.78 (m, 1H), 8.26-8.23 (m, 1H), 8.01-7.92 (m, 3H), 7.84 (d, 0.4H, minor), 7.78 (d, 0.6H, major), 7.73-7.47 (m, 10H), 7.43 (dd, 1H), 7.34 (t, 0.6H, major), 7.27 (t, 0.4H, minor), 7.18 (d, 0.6H, major), 7.09 (d, 0.4H, minor), 3.12 (m, 1H), 3.11 (s, 1.8H, major), 2.99 (s, 1.2H, minor), 1.36-1.33 (m, 6H).

20

MS (M+1) 511.

382  
384**EXAMPLE 4**

**6-isopropyl-8-(3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)quinoline**



5      **Example 4 was prepared by the following procedure.**

**Step 1: 6-isopropyl-8-(3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylthio)phenyl]ethenyl)phenyl)quinoline**

Following the procedure for Example 3 but substituting the ketone K2 for K5 as the starting material, 6-isopropyl-8-(3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylthio)phenyl]ethenyl)phenyl)quinoline was obtained.

10      **Step 2: 6-isopropyl-8-(3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)quinoline**

Following the procedure used for the preparation of the boronate B1 (step 2 of Scheme 2) but substituting the sulfide obtained in the present step 1 for (E/Z)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylthio)phenyl]ethene as the starting material, Example 4 was obtained.

NMR <sup>1</sup>H (500 MHz in acetone-*d*<sub>6</sub>) δ 8.77 (dd, 1H), 8.24 (dd, 1H), 7.88 (d, 2H), 7.71 (d, 1H), 7.59 (d, 1H), 7.53 (d, 2H), 7.48 (d, 2H), 7.41 (dd, 1H), 7.28 (t, 1H), 7.23 (s, 1H), 7.15 (d, 1H), 7.07 (d, 1H), 6.95 (d, 1H), 3.51 (s, 3H), 3.10 (m, 1H),  
20      2.99 (s, 3H), 1.32 (d, 6H).

MS: (m+2): 509.4

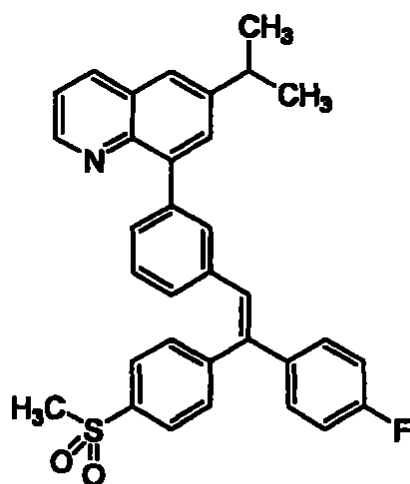
388

385

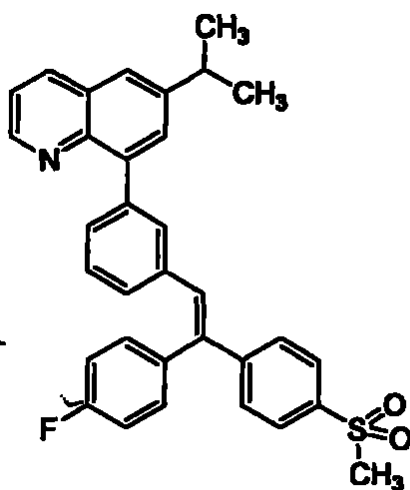
**EXAMPLES 5 and 6**

**6-isopropyl-8-(3-((Z/E)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)quinoline**

5



**Example 5**



**Example 6**

10

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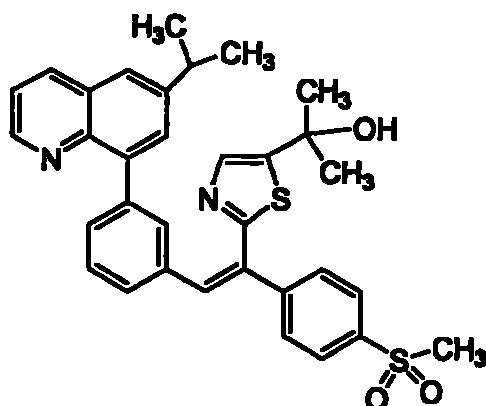
382  
386

Examples 5 and 6 were prepared by the following procedure.  
Following the procedure for Example 1 but substituting the ketone K1 for K3 as the starting material, and purification by flash chromatography (50%EtOAc/50%Hexanes) yielded Examples 5 and 6 (55mg and 65mg).

- 5 NMR <sup>1</sup>H (500MHz in acetone-*d*<sub>6</sub>) Example 5: Major (Z) isomer: δ 8.78 (dd, 1H), 8.25 (dd, 1H), 7.93 (d, 2H), 7.72 (d, 1H), 7.55-7.40 (m, 6H), 7.35 (m, 2H), 7.25 (t, 1H), 7.23 (s, 1H), 7.11 (t, 2H), 7.05 (d, 1H), 3.12 (m, 1H), 2.96 (s, 3H), 1.34 (d, 6H).
- 10 NMR <sup>1</sup>H (500MHz in acetone-*d*<sub>6</sub>) Example 6: Minor (E) isomer: δ 8.78 (dd, 1H), 8.35 (dd, 1H), 7.93 (d, 2H), 7.72 (d, 1H), 7.65-7.55 (m, 3H), 7.45 (dd, 1H), 7.35-7.15 (m, 9H), 3.12 (m, 4H), 1.34 (d, 6H).

# EXAMPLE 7

- 15 2-(2-((E/Z)-2-[3-(6-isopropyl-8-quinoliny)phenyl]-1-[4-(methylsulfonyl)phenyl]ethenyl)-1,3-thiazol-5-yl)-2-propanol



- Example 7 was prepared by following the procedure for Example 1 but substituting the ketone K6 for K3 as the starting material. Purification by flash chromatography (100%EtOAc) yielded Example 7 as a mixture of isomers.

NMR <sup>1</sup>H (400MHz in acetone-*d*<sub>6</sub>) δ 8.80 (m, 1H), 8.30 (m, 1H), 8.05 (d(major), 1.44H), 7.93 (d(minor), 0.55H), 7.85 (s(major), 0.72H), 7.77 (s(minor), 0.28H), 7.75-7.45 (m, 7H) 7.35 (t(minor), 0.28H), 7.28 (t(major), 0.72H), 7.21

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320  
387

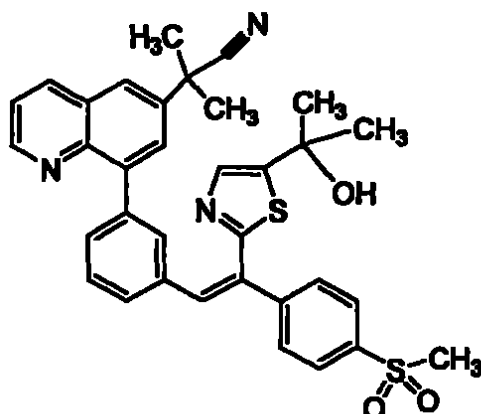
(d(minor), 0.28H), 7.10 (d(major), 0.72H), 4.7 (m, 1H), 3.15 (m, 1H), 3.15 (s(minor), 0.84), 2.99 (s(major), 2.16H), 1.60 (m, 6H), 1.35 (m, 6H).

MS (m+1): 569.6

5

# EXAMPLE 8

2-[8-(3-((E/Z)-2-[5-(1-hydroxy-1-methylethyl)-1,3-thiazol-2-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-quinoliny]-2-methylpropanenitrile



10

Example 8 was prepared by following the procedure for Example 1 but substituting the ketone K6 for K3 and the benzyl phosphonate P3 for P2 as the starting materials. Purification by flash chromatography (20%CH<sub>2</sub>Cl<sub>2</sub>/80%EtOAc) yielded Example 8 as a mixture of isomers.

NMR <sup>1</sup>H (400MHz in acetone-d<sub>6</sub>) δ 8.92 (m, 1H), 8.45 (m, 1H), 8.10 (m, 1H), 8.05 (m, 1H), 7.93 (m, 1H), 7.85 (m, 2H), 7.77-7.55 (m, XH), 7.40 (t(minor), 0.43H), 7.28 (t(major), 0.57H), 7.21 (d(minor), 0.43H), 7.10(d(major), 0.57H), 4.67 (s(major), 0.57H), 4.63 (s(minor), 0.43H), 3.15 (s(minor), 1.3H), 2.99 (s(major), 1.7H), 1.90 (m, 6H), 1.65 (s(major), 3.4H), 1.45 (s(minor), 2.6H).

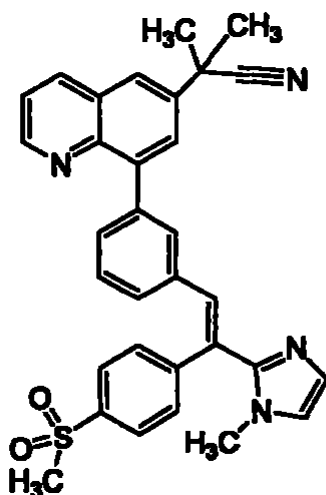
20

MS (m+1): 594.6

60171522.1222

## EXAMPLE 9

2-methyl-2-[8-(3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-quinoliny]propanenitrile



5 Example 9 was prepared by the following procedure.

Step 1: 2-methyl-2-[8-(3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylthio)phenyl]ethenyl)phenyl)-6-quinoliny]propanenitrile was prepared by following the procedure for Example 1 but substituting the ketone K2 for K3 and the benzyl phosphonate P3 for P2 as the starting materials.

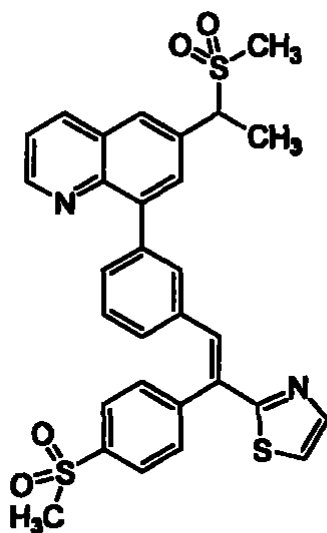
10 Step 2: 2-methyl-2-[8-(3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-quinoliny]propanenitrile, Example 9, was prepared by following the procedure used for the preparation of the boronate B1 (step 2 of Scheme 2) but substituting the sulfide obtained in present step 1 for (E/Z)-2-(3-Bromophenyl)-1-(1-methyl-1H-imidazol-2-yl)-1-[4-(methylthio)phenyl]ethene as the starting material. Example 9 was obtained after purification by flash chromatography (97% EtOAc/3% Et<sub>3</sub>N).

NMR <sup>1</sup>H (400MHz in acetone-*d*<sub>6</sub>) δ 8.92 (dd, 1H), 8.45 (dd, 1H), 8.10 (d, 1H), 7.93 (d, 2H), 7.76 (d, 1H), 7.60-7.50 (m, 5H), 7.38 (t, 1H), 7.35 (s, 1H), 7.19 (m, 1H), 7.10 (m, 1H), 6.95 (m, 1H), 3.55 (s, 3H), 3.00 (s, 3H), 1.85 (s, 6H).

20 MS (m+1): 533.3

## EXAMPLE 10

6-[1-(methylsulfonyl)ethyl]-8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl}quinoline



5

Example 10 was prepared by the following procedure. A mixture of bromoquinoline Q2 (105mg, 0.33mmol), boronate B2 (236mg, 0.51mmol),  $\text{Na}_2\text{CO}_3$  (2M, 0.65mL, 1.3mmol),  $\text{Pd}(\text{OAc})_2$  (6.3mg, 0.028mmol) and  $\text{PPh}_3$  (28mg, 0.11mmol) in 4mL of *n*-propanol was stirred at 90°C for 2h. The mixture was cooled to r.t., diluted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Flash chromatography (Tol/Acetone; 4/1) and stirring in Hexane/EtOAc yielded Example 10 (152mg, single isomer) as a white solid.

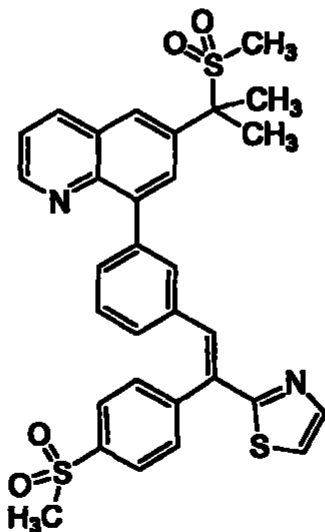
NMR  $^1\text{H}$  (400MHz, Acetone- $d_6$ )  $\delta$  8.89 (dd, 1H), 8.39 (dd, 1H), 8.07 (d, 1H), 8.03 (d, 2H), 7.94 (s, 1H), 7.86 (d, 1H), 7.71-7.68 (m, 3H) 7.62-7.60 (m, 2H), 7.55 (dd, 1H), 7.45 (s, 1H) 7.34 (t, 1H), 7.18 (d, 1H), 4.67 (q, 1H), 3.04 (s, 3H), 2.86 (s, 3H) 1.88 (s, 3H)

15

MS ( $M + 1$ ) 576.

## EXAMPLE 11

6-[1-methyl-1-(methylsulfonyl)ethyl]-8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl}quinoline



5            Example 11 was prepared by following the procedure described in Example 10 but substituting bromoquinoline Q3 for Q2 and using boronate B2. Flash chromatography (Tol/Acetone; 9/1) and stirring in EtOAc/Hex yielded Example 11 (single isomer) as a white solid.

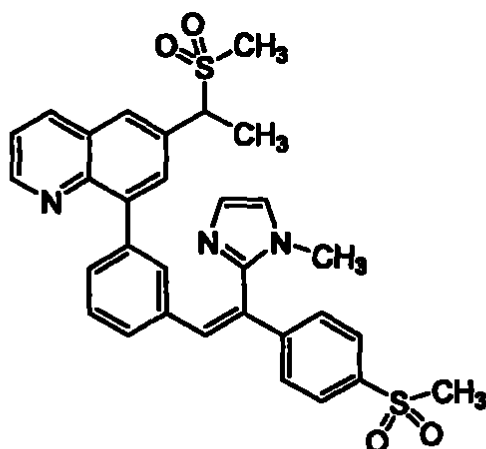
10            NMR <sup>1</sup>H (400MHz, Acetone-d<sub>6</sub>): δ 8.90 (dd, 1H), 8.41 (dd, 1H), 8.23 (s, 1H), 8.02-7.99 (d, 3H), 7.95 (s, 1H), 7.86 (d, 1H), 7.70 (d, 2H), 7.60-7.54 (m, 4H), 7.32 (t, 1H), 7.13 (d, 1H), 3.00 (s, 3H), 2.69 (s, 3H), 1.96 (s, 6H)

MS (M+1) 523.

391

## EXAMPLE 12

5 8-(3-((Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-[1-(methylsulfonyl)ethyl]quinoline



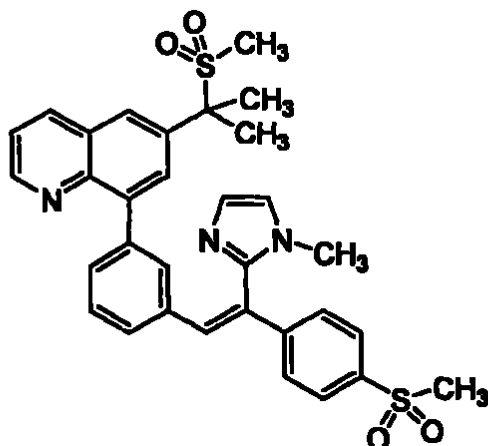
Example 12 was prepared following the procedure described in Example 10 using the bromoquinoline Q2 but substituting the boronate B1 for boronate B2. Flash chromatography (95%CH<sub>2</sub>Cl<sub>2</sub>/5%EtOH) yielded the Example 12 compound.

NMR <sup>1</sup>H (400MHz in acetone-d<sub>6</sub>) δ 8.92 (dd, 1H), 8.45 (dd, 1H), 8.10 (s, 1H), 7.93 (d, 2H), 7.76-7.65 (m, 4H), 7.59 (dd, 1H), 7.39 (t, 1H), 7.26 (s, 1H), 7.18 (s, 1H), 7.05 (m, 2H), 4.70 (q, 1H), 3.40 (s, 3H), 3.13 (s, 3H), 2.93 (s, 3H), 1.87 (d, 3H).

15 MS (m+1): 572.4

## EXAMPLE 13

8-(3-((Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline



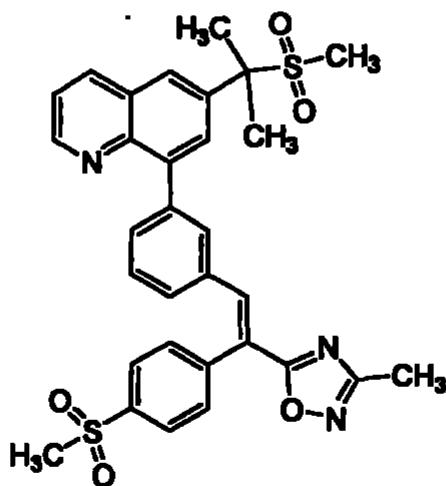
Example 13 was prepared following the procedure described in Example 10 but substituting the bromoquinoline Q3 for Q2 and substituting the boronate B1 for boronate B2. Flash chromatography (95% EtOAc/5% Et<sub>3</sub>N) produced Example 13 (single isomer) as a foam.

NMR <sup>1</sup>H (400MHz in acetone-*d*<sub>6</sub>) δ 8.92 (dd, 1H), 8.45 (dd, 1H), 8.37 (d, 1H), 8.05 (d, 1H), 7.93 (d, 2H), 7.76 (d, 1H), 7.69 (d, 2H), 7.65 (d, 1H), 7.59 (dd, 1H), 7.38 (t, 1H), 7.31 (s, 1H), 7.18 (s, 1H), 7.05 (m, 2H), 3.40 (s, 3H), 3.13 (s, 3H), 2.70 (s, 3H), 1.95 (s, 6H).

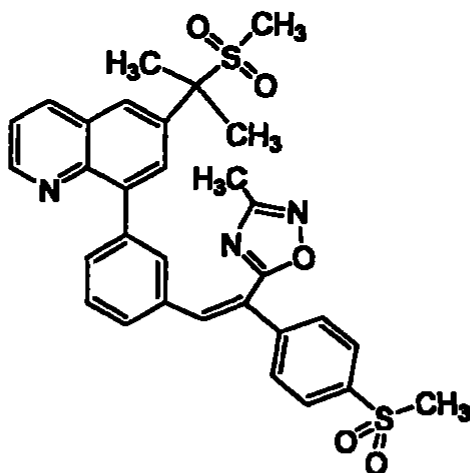
MS (m+1): 586.2

## EXAMPLES 14 and 15

6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-[(E/Z)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl)quinoline



Example 14



Example 15

Examples 14 and 15 were prepared by the following procedure. A

- 10 solution of the aryl bromide AB5 (249mg, 0.57mmol), diboron pinacol ester (167mg, 0.66mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (12mg, 0.015mmol) and potassium acetate (176mg, 1.8mmol) in DMF (*N,N*-

Dimethylformamide) (10mL) was degassed and stirred at 80°C for 3h. To that resulting mixture at 25°C was then added the bromoquinoline Q3 (150mg, 0.46mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (12mg, 0.015mmol) and sodium carbonate (0.6mL, 2M). After degassing, the mixture was heated at 80°C overnight. The mixture was then cooled to r.t. quenched with H<sub>2</sub>O, and extracted with EtOAc. The organic extracts were washed (H<sub>2</sub>O, brine), dried (MgSO<sub>4</sub>), filtered and concentrated. Purification by flash chromatography (hexane:EtOAc:Et<sub>3</sub>N, 22:68:10 then hexane:EtOAc, 3:1) yielded both isomers (126mg of Example 14, 30mg of Example 15).

10 NMR <sup>1</sup>H (500MHz, Acetone-*d*<sub>6</sub>) Major(E) isomer (Example 14): δ 8.91 (dd, 1H), 8.42 (dd, 1H), 8.25 (d, 1H), 8.12 (s, 1H), 8.02 (d, 1H), 8.00 (d, 2H), 7.70 (m, 3H), 7.64 (s, 1H), 7.55 (dd, 1H), 7.38 (t, 1H), 7.23 (d, 1H), 3.03 (s, 3H), 2.69 (s, 3H), 2.33 (s, 3H), 1.96 (s, 6H).

MS (M+1): 588.2

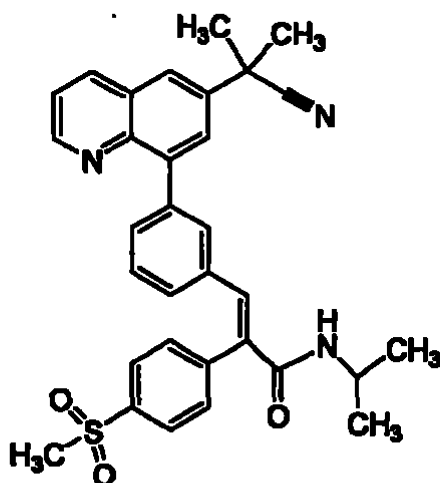
15 Minor(Z) isomer (Example 15): δ 8.92 (dd, 1H), 8.45 (dd, 1H), 8.29 (d, 1H), 8.07 (d, 1H), 7.99 (d, 2H), 7.88 (s, 1H), 7.75 (m, 3H), 7.62 (s, 1H), 7.58 (q, 1H), 7.48 (t, 1H), 7.24 (d, 1H) 3.16 (s, 3H), 2.70 (s, 3H), 2.38 (s, 3H), 2.00 (s, 6H).

MS (M+1): 588.2

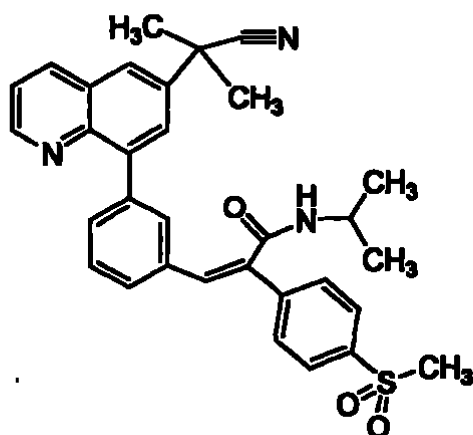
20

## EXAMPLES 16 and 17

(E/Z)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinoliny]phenyl}-N-isopropyl-2-[4-(methylsulfonyl)phenyl]-2-propenamide



Example 16



Example 17

Examples 16 and 17 were prepared following the procedure described previously for Examples 14 and 15 but substituting the aryl bromide AB2 for AB5 and the bromoquinoline Q5 for Q3 as the starting materials. Examples 16 and 17 were obtained as a 4:1 mixture.

NMR  $^1\text{H}$  (500 MHz, Acetone- $d_6$ ) Major(E) isomer (Example 16):  $\delta$  8.89 (dd, 1H), 8.43 (dd, 1H), 8.09 (d, 1H), 7.90 (d, 2H), 7.81 (d, 1H), 7.68 (s, 1H), 7.57 (m, 4H), 7.45 (s, 1H), 7.29 (t, 1H), 7.04 (d, 1H), 6.71 (bd, 1H), 4.13 (m, 1H) 2.92 (s, 3H), 1.87 (s, 6H), 1.12 (d, 6H).

5

MS (M+1): 538.3

Minor(Z) isomer (Example 17):  $\delta$  8.93 (dd, 1H), 8.48 (dd, 1H), 8.14 (d, 1H), 7.94 (m, 4H), 7.85 (d, 2H), 7.70 (dd, 2H), 7.59 (q, 1H), 7.50 (m, 2H), 7.28 (s, 1H), 4.15 (m, 1H) 3.13 (s, 3H), 1.91 (s, 6H), 1.04 (d, 6H).

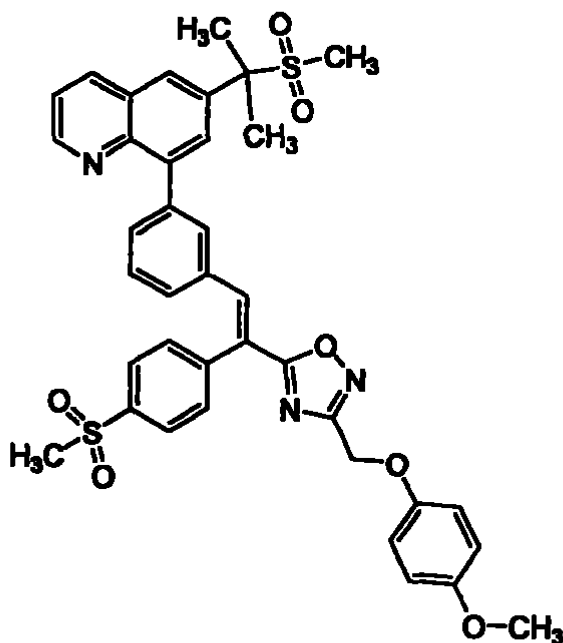
MS (M+1): 538.3

10

**EXAMPLE 18**

8-(3-((E)-2-(3-((4-methoxyphenoxy)methyl)-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline

15



Example 18 was prepared by the following procedure.

Step 1 (Scheme 3): (4-methoxyphenoxy)acetonitrile

A mixture of 4-methoxyphenol (10g, 80mmol), chloroacetonitrile (7.0mL, 111mmol) and  $K_2CO_3$  (26g, 188mmol) in acetone (150 mL) was stirred at r.t. for 18h. The mixture was filtered, concentrated and purified by flash chromatography (Hex:EtOAc, 4:1) to yield (4-methoxyphenoxy)acetonitrile as a clear oil.

**Step 2 (Scheme 3): (4-methoxyphenoxy)acetamide oxime**

A mixture of the (4-methoxyphenoxy)acetonitrile product (5.0g, 31mmol) from step 1, hydroxylamine hydrochloride (4.3g, 62mmol) and sodium acetate (5.1g, 62mmol) in MeOH (100mL) was stirred at r.t. for 2h. The resulting mixture was filtered on Celite®, concentrated, stirred in  $CHCl_3$  for 18h and filtered. The resulting solution was concentrated to yield (4-methoxyphenoxy)acetamide oxime as a gum.

**Step 3 (Scheme 3, Oxadiazole OX2): 3-[(4-methoxyphenoxy)methyl]-5-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazole**

3-[(4-methoxyphenoxy)methyl]-5-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazole was prepared following the procedure as described in Scheme 3 for AB5 step 1 (OX1) but substituting the (4-methoxyphenoxy)acetamide oxime from step 2 above for acetamide oxime and heating the reaction at 90°C for 2h. Purification by flash chromatography (Hex:EtOAc, 3:2 to 1:4) yielded the desired material as a pale brown solid.

**Step 4: 3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinoliny}benzaldehyde**

To bromoquinoline Q3 (10.1g, 30.9mmol) 3-formylbenzeneboronic acid (5.8g, 38.7mmol), tetrakis(triphenylphosphine)-palladium (0) (2.1g 1.86mmol) and sodium carbonate (39mL, 2M ) was added DME (330mL). After degassing, the mixture was heated at 80°C overnight. After cooling to r.t. the resulting mixture was quenched with  $H_2O$ , and extracted with EtOAc. The organic extracts were washed ( $H_2O$ , brine), dried ( $MgSO_4$ ), filtered and concentrated. Stirring in ether, followed by isolation by filtration gave 3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinoliny}benzaldehyde (8.3g).

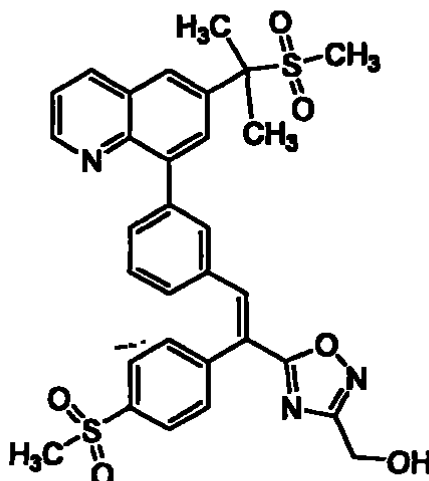
Step 5: 8-(3-((E)-2-{3-[(4-methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl}-2-[4-(methylsulfonyl)phenyl]ethenyl}phenyl)-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline

A mixture of the product from present step 4 (150mg, 0.42mmol), the oxadiazole OX2 from present step 3 above (175mg, 0.47mmol) and piperidine (0.1mL, 1.0mmol) in toluene (0.6mL) was heated at 120°C for 3h. The mixture was purified by flash chromatography (Hex:EtOAc, 3:2 to 1:4) to yield Example 18 as a foam.

NMR <sup>1</sup>H (400MHz, Acetone-*d*<sub>6</sub>) δ 8.90 (q, 1H), 8.42 (q, 1H), 8.24 (d, 1H), 8.20 (s, 1H), 8.02 (m, 3H), 7.75-7.66 (m, 4H), 7.55 (q, 1H), 7.39 (t, 1H), 7.25 (d, 1H), 7.00 (d, 2H), 6.87 (d, 2H), 5.17 (s, 2H), 3.73 (s, 3H), 3.03 (s, 3H), 2.80 (s, 3H), 1.96 (s, 6H).

#### EXAMPLE 19

(5-((E)-2-(3-(6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl)phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl)-1,2,4-oxadiazol-3-yl)methanol



Example 19 was prepared by the following procedure. To a solution of the Example 18 compound (250mg, 0.35mmol) in acetonitrile:water (4:1, 8 mL) was added CAN (330mg, 0.62mmol) in two portions at r.t. After 3h at r.t., the

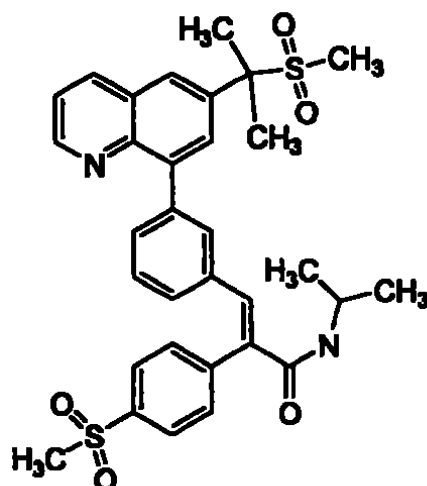
mixture was diluted with saturated  $\text{NaHCO}_3$  solution, diluted with water and extracted with EtOAc. The organic extracts were washed ( $\text{H}_2\text{O}$ ), (brine), dried ( $\text{MgSO}_4$ ), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 3:7) yielded (5-((E)-2-(3-(6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl)phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl)-1,2,4-oxadiazol-3-yl)methanol as a pale yellow foam (138mg).

NMR  $^1\text{H}$  (400MHz, Acetone- $d_6$ )  $\delta$  8.90 (q, 1H), 8.42 (q, 1H), 8.25 (d, 1H), 8.15 (s, 1H), 8.02 (m, 3H), 7.73-7.65 (m, 4H), 7.55 (q, 1H), 7.38 (t, 1H), 7.23 (d, 1H), 4.67 (m, 3H), 3.04 (s, 3H), 2.82 (s, 3H), 1.96 (s, 6H).

10

# EXAMPLE 20

(E)-N-isopropyl-3-(3-(6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl)phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide



Example 20 was prepared by following the procedure described above for Examples 14 and 15 but substituting the aryl bromide AB2 for AB5, and using the bromoquinoline Q3, as the starting materials.

NMR  $^1\text{H}$  (300MHz, Acetone- $d_6$ )  $\delta$  8.89 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.99 (d, 1H), 7.88 (d, 2H), 7.67 (s, 1H), 7.53 (m, 4H), 7.43 (s, 1H), 7.28 (t, 1H), 7.05 (d, 1H), 6.71 (bd, 1H), 4.14 (m, 1H) 2.9 (s, 3H), 1.95 (s, 6H), 1.13 (d, 6H).

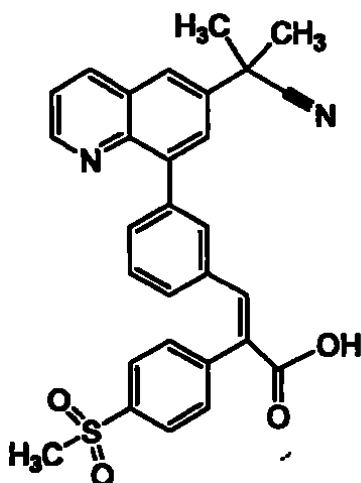
20

MS(M+1): 591.3

400

## EXAMPLE 21

(E)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinoliny]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid



5

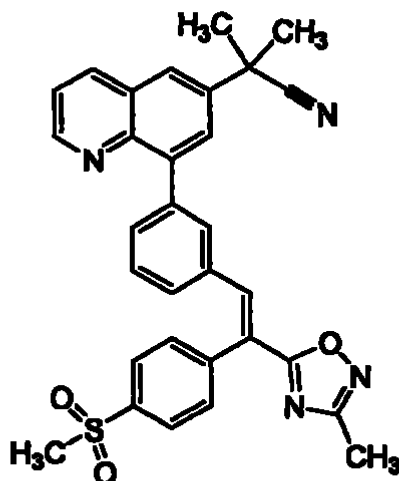
Example 21 was prepared by following the procedure described above for Examples 14 and 15 but substituting the aryl bromide AB1 for AB5 and the bromoquinoline Q5 for Q3 as the starting materials.

10 NMR  $^1\text{H}$  (500MHz, Methanol)  $\delta$  8.8 (dd, 1H), 8.38 (dd, 1H), 8.04 (d, 2H), 7.88 (d, 2H), 7.66 (d, 1H), 7.55 (m, 4H), 7.36 (t, 1H), 7.29 (s, 1H), 7.18 (d, 1H), 2.93 (s, 3H), 1.88 (s, 6H).

MS (M-CO<sub>2</sub>): 451.4 (negative ion).

## EXAMPLE 22

2-methyl-2-[8-(3-((E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-quinoliny]propanenitrile



5 Example 22 was prepared by following the procedure described for Examples 14 and 15 using the aryl bromide ABS and substituting the bromoquinoline Q5 for Q3 as the starting materials.

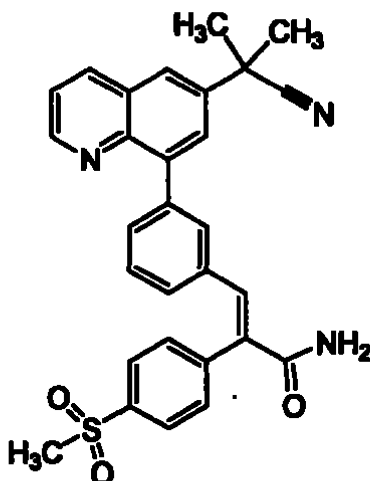
NMR <sup>1</sup>H (500 MHz, Acetone-*d*<sub>6</sub>) δ 8.90 (dd, 1H), 8.43 (dd, 1H), 8.1 (d, 2H), 8.01 (d, 2H), 7.83 (d, 1H), 7.71 (t, 3H), 7.66 (s, 1H), 7.56 (q, 1H), 7.55 (dd, 10 1H), 7.38 (t, 1H), 7.22 (d, 1H), 3.03 (s, 3H), 2.33 (s, 3H), 1.87 (s, 6H)

MS (M+1): 535.2

402

## EXAMPLE 23

(E)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinoliny]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenamide



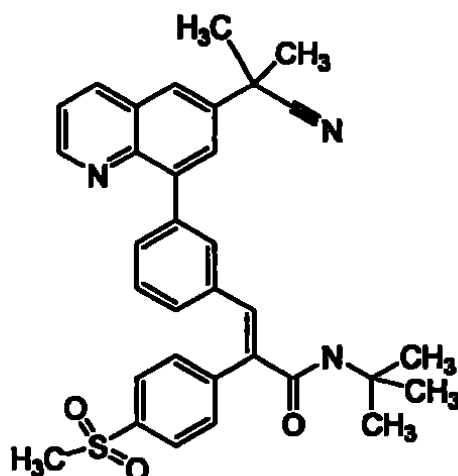
5            Example 23 was prepared by following the procedure described above for Examples 14 and 15 but substituting the aryl bromide AB3 for ABS and the bromoquinoline Q5 for Q3 as the starting materials, the title compound was obtained.

          NMR <sup>1</sup>H (500MHz, Acetone-*d*<sub>6</sub>) δ 8.89 (dd, 1H), 8.43 (dd, 1H), 8.08 (d, 1H), 7.93 (d, 2H), 7.8 (d, 2H), 7.6 (m, 4H), 7.48 (s, 1H), 7.31 (t, 1H), 7.08 (d, 10 1H), 6.6 (bs, 1H), 6.7 (bs, 1H), 2.93 (s, 3H), 1.87 (s, 6H)

403

## EXAMPLE 24

(E)-N-(tert-butyl)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinolinyl]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenamide



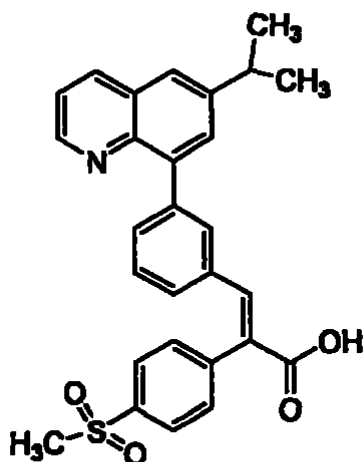
5            Example 24 was prepared by following the procedure described for Examples 14 and 15 but substituting the aryl bromide AB4 for AB5 and the bromoquinoline Q5 for Q3 as the starting materials.

             NMR <sup>1</sup>H (500MHz, Acetone-*d*<sub>6</sub>) δ 8.89 (dd, 1H), 8.43 (dd, 1H), 8.08 (d, 1H), 7.92 (d, 2H), 7.79 (d, 1H), 7.58 (m, 5H), 7.45 (s, 1H), 7.29 (t, 1H), 7.04 (d, 10   1H), 6.4 (bs, 1H), 2.93 (s, 3H), 1.87 (s, 6H), 1.36 (s, 9H).

             MS (M + 1) 553.

## EXAMPLE 25

(E)-3-[3-(6-isopropyl-8-quinolinyl)phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid



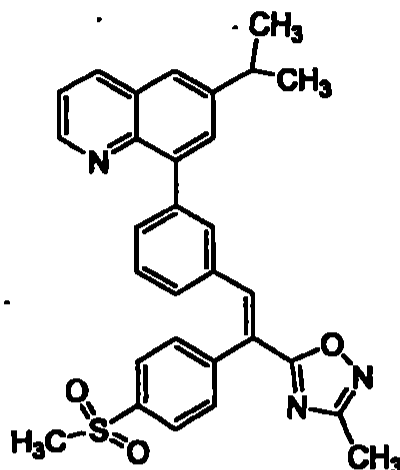
5 Example 25 was prepared by following the procedure described for Examples 14 and 15 but substituting the aryl bromide AB1 for AB5, and 5-isopropyl-8-bromoquinoline (described in International Patent Publication WO9422852) for Q3, as the starting materials.

10 NMR  $^1\text{H}$  (500MHz, Acetone- $d_6$ )  $\delta$  8.69 (dd, 1H), 8.26 (dd, 1H), 7.85 (s, 1H), 7.83 (d, 2H), 7.68 (s, 1H), 7.51 (d, 2H), 7.49 (m, 2H), 7.36 (dd, 1H), 7.31 (t, 1H), 7.20 (s, 1H), 7.13 (d, 1H), 3.1 (m, 1H), 2.93 (s, 3H), 1.36 (d, 6H).

MS (M + 1) 472.

## EXAMPLE 26

6-isopropyl-8-(3-((E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)quinoline



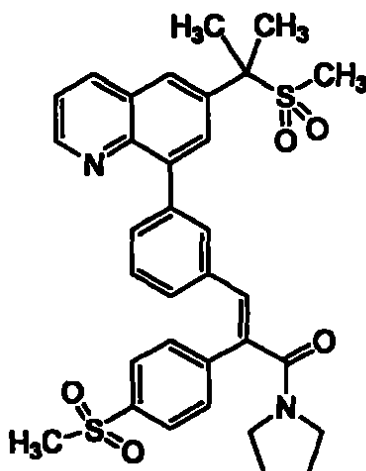
5 Example 26 was prepared by following the procedure described for Examples 14 and 15 using the aryl bromide ABS, and substituting 5-isopropyl-8-bromoquinoline (described in International Patent Publication WO9422852) for Q3 as the starting materials.

10 NMR  $^1\text{H}$  (500MHz, Acetone- $d_6$ )  $\delta$  8.80 (dd, 1H), 8.29 (dd, 1H), 8.12 (s, 1H), 8.03 (d, 2H), 7.76 (s, 1H), 7.73 (m, 3H), 7.59 (s, 1H), 7.53 (d, 1H), 7.47 (q, 1H), 7.36 (t, 1H), 7.22 (d, 1H), 3.1 (m, 1H), 2.93 (s, 3H), 2.33 (s, 3H) 1.36 (d, 6H).

MS (M+1) 510.

## EXAMPLE 27

(E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidinyl)-2-propen-1-one



5 Example 27 was prepared by the following procedure.

Step 1: (E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid

A mixture of 3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}benzaldehyde from step 4 of Example 18 (2.33g, 6.60mmol), 4-(methylsulfonyl)phenyl acetic acid (1.71g, 7.98mmol) and piperidine (0.20ml, 1.98mmol) in 10mL of toluene was refluxed for 2 days. The mixture was cooled to r.t., diluted with CH<sub>2</sub>Cl<sub>2</sub>, subjected to flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc/AcOH, 50/50/1) and finally stirred with (Et<sub>3</sub>O/CH<sub>2</sub>Cl<sub>2</sub>) and isolated to give (E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid (1.31mg; single isomer) as a white solid.

NMR <sup>1</sup>H (400MHz, Acetone-d<sub>6</sub>): δ 8.89 (dd, 1H), 8.39 (dd, 1H), 8.07 (d, 1H), 8.03 (d, 2H), 7.94 (s, 1H), 7.86 (d, 1H), 7.71-7.68 (m, 3H), 7.62-7.60 (m, 2H), 7.55 (dd, 1H), 7.45 (s, 1H), 7.34 (t, 1H), 7.18 (d, 1H), 4.67 (q, 1H), 3.04 (s, 3H), 2.86 (s, 3H), 1.88 (s, 3H).

20 MS (M + 1) 576.

Step 2: (E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidinyl)-2-propen-1-one

407

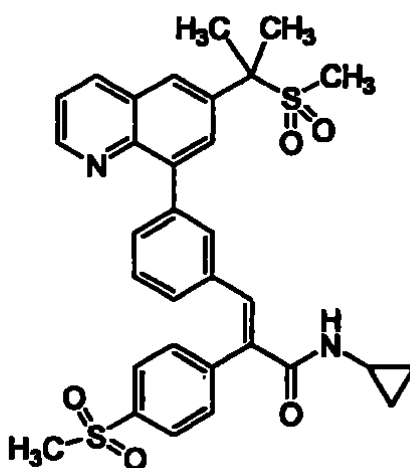
A mixture of (E)-3-(3-(6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl)phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid (104mg, 0.19mmol) from the present step 1 above, pyrrolidine (24 $\mu$ L, 0.29mmol), EDCI (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) (55mg, 0.29mmol) and HOBt (1-Hydroxybenzotriazole hydrate) (34mg, 0.25mmol) in 1ml of DMF was stirred at r.t. for 12h. The mixture was diluted with EtOAc, washed with NH<sub>4</sub>Cl (sat), H<sub>2</sub>O (3x), brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Stirring in EtOAc/Hex yielded Example 27 (81mg) as a white solid.

NMR <sup>1</sup>H (400MHz, Acetone-d<sub>6</sub>):  $\delta$  8.88 (dd, 1H), 8.40 (dd, 1H), 8.22 (d, 1H), 8.98 (d, 1H), 7.88 (d, 2H), 7.67 (d, 2H), 7.60 (d, 1H) 7.55-7.52 (m, 2H) 7.34 (t, 1H), 7.18 (d, 1H), 7.03 (bs, NH) 3.58 (bs, 2H), 3.44 (bs, 2H), 3.02 (s, 3H), 2.69 (s, 3H) 1.95 (s, 6H), 1.88 (bs, 4H).

MS (M + 1) 603.

#### EXAMPLE 28

(E)-N-cyclopropyl-3-(3-(6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl)phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide



Example 28 was prepared by following the procedure for step 2 of Example 27 but substituting cyclopropyl amine for pyrrolidine, thus yielding a white solid.

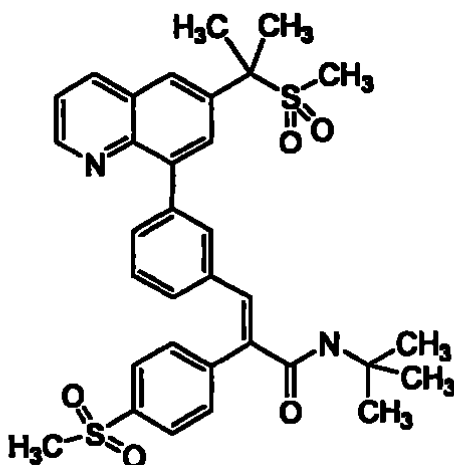
60171522-12229

NMR  $^1\text{H}$  (400 MHz, acetone- $d_6$ ):  $\delta$  8.89 (dd, 1H), 8.41 (dd, 1H), 8.23 (d, 1H), 7.98 (d, 1H), 7.87 (d, 2H), 7.68 (s, 1H), 7.59-7.53 (m, 4H), 7.43 (s, 1H), 7.29 (t, 1H), 7.04 (d, 1H), 6.94 (bs, 1H), 2.89 (s, 3H), 2.84-2.80 (m, 1H), 2.69 (s, 3H), 1.96 (s, 6H), 0.67-0.63 (m, 2H), 0.49-0.45 (m, 2H).

5 MS (M + 1) 589.

#### EXAMPLE 29

(E)-N-(tert-butyl)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl}phenyl)-  
10 2-[4-(methylsulfonyl)phenyl]-2-propenamide



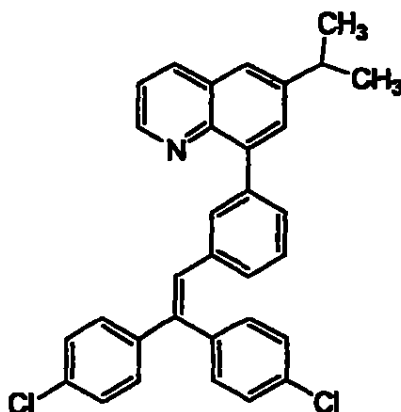
Example 29 was prepared as a white solid by following the procedure for step 2 of Example 27 but substituting *t*-butyl amine for pyrrolidine.

15 NMR  $^1\text{H}$  (400MHz, acetone- $d_6$ ):  $\delta$  8.89 (dd, 1H), 8.41 (dd, 1H), 8.23 (d, 1H), 7.98 (d, 1H), 7.90 (d, 2H), 7.59-7.53 (m, 5H), 7.43 (s, 1H), 7.30 (t, 1H), 7.05 (d, 1H), 6.43 (bs, 1H), 2.94 (s, 3H), 2.69 (s, 3H), 1.96 (s, 6H), 1.36 (s, 9H)

MS (M+1) 606.

## EXAMPLE 30

8-{3-[2,2-bis(4-chlorophenyl)vinyl]phenyl}-6-isopropylquinoline

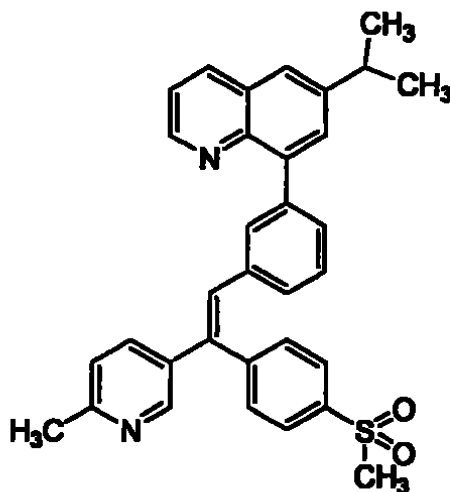


- Example 30 was prepared by the following procedure. To a mixture of the benzylphosphonate P2 (100mg, 0.25mmol), 4,4'-dichlorobenzophenone (63mg, 0.25mmol), in THF (2mL) at r.t. was added potassium *t*-butoxide (1M, THF, 0.35mL, 0.35mmol). After 1h at r.t., the mixture was diluted with water/NH<sub>4</sub>Cl and extracted with EtOAc. The organic extracts were washed (H<sub>2</sub>O), (brine), dried (MgSO<sub>4</sub>), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 8:2) yielded Example 30 as a white foam (50mg).

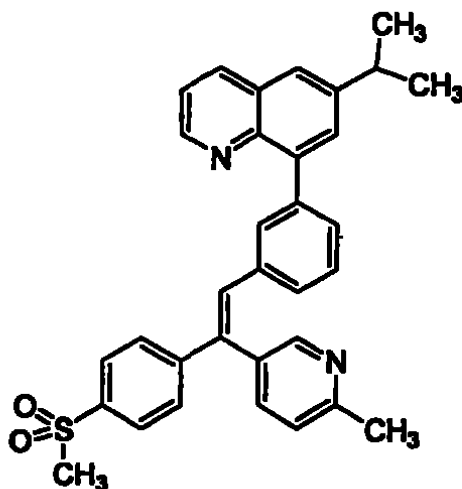
NMR <sup>1</sup>H (300MHz, acetone-*d*<sub>6</sub>) δ 8.79 (dd, 1H), 8.28 (dd, 1H), 7.74 (d, 1H), 7.60 (d, 1H), 7.48-7.25 (m, 12H), 7.20-7.16 (m, 2H) 3.13 (hept, 1H), 1.36 (d, 6H).

## EXAMPLES 31 AND 32

6-isopropyl-8-(3-((E/Z)-2-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)quinoline



Example 31



Example 32

Examples 31 and 32 were prepared by following the procedure described for Example 30 but substituting the ketone K7 for 4,4'-dichlorobenzophenone and using the benzylphosphonate P2 as the starting materials.

411

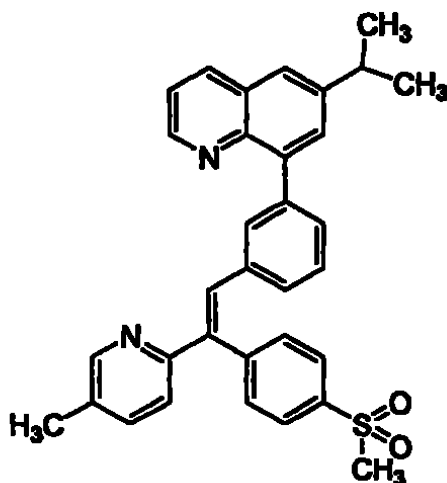
NMR  $^1\text{H}$  (300MHz, Acetone- $d_6$ ) (E) isomer (Example 31):  $\delta$  8.79 (dd, 1H), 8.43 (d, 1H), 8.27 (dd, 1H), 7.95 (d, 2H), 7.73 (d, 1H), 7.57-7.43 (m, 7H), 7.32-7.19 (m, 3H), 7.10 (d, 1H), 3.15 (hept, 1H), 2.98 (s, 3H), 1.34 (d, 6H).

(Z) isomer (Example 32):  $\delta$  8.79 (dd, 1H), 8.35 (d, 1H), 8.28 (dd, 1H), 7.92 (d, 2H), 7.74 (d, 1H), 7.61-7.30 (m, 10H), 7.19 (d, 1H), 3.13 (s, 3H), 3.11 (hept, 1H), 1.35 (d, 6H).

10

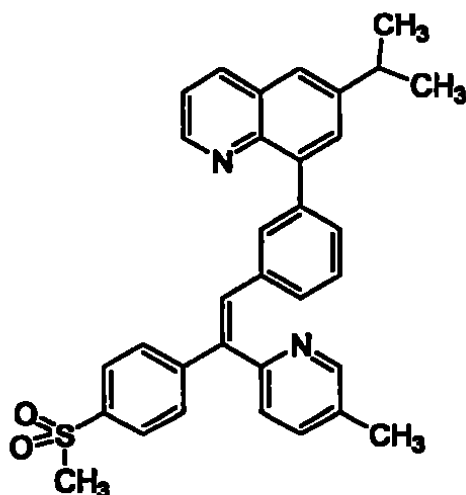
# EXAMPLES 33 AND 34

6-isopropyl-8-(3-((E/Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)quinoline



Example 33

412



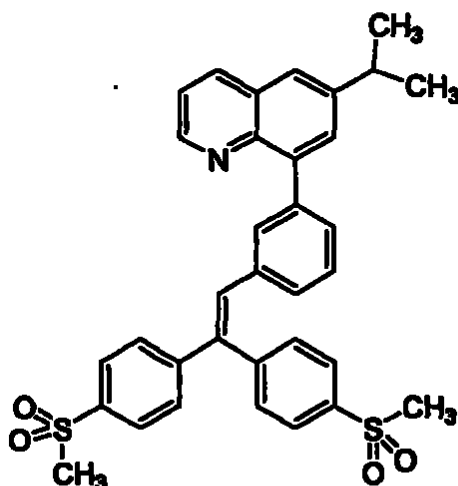
#### Example 34

Examples 33 and 34 were prepared by following the procedure described for Example 30 but substituting the ketone K8 for 4,4'-

5 dichlorobenzophenone and using the benzylphosphonate P2 as the starting materials.

NMR <sup>1</sup>H (300MHz, Acetone-d<sub>6</sub>) (E) isomer (Example 33): δ 8.80 (dd, 1H), 8.48 (s, 1H), 8.28 (dd, 1H), 7.99-7.96 (m, 3H), 7.97 (m, 1H), 7.74 (d, 1H), 7.61-7.44 (m, 6H), 7.27 (t, 1H), 7.07 (d, 1H), 6.97 (d, 1H), 3.15 (hept, 1H), 2.96 (s, 3H), 1.36 (d, 6H).

10 NMR <sup>1</sup>H (300MHz, Acetone-d<sub>6</sub>) (Z) isomer (Example 34): δ 8.79 (dd, 1H), 8.52 (s, 1H), 8.29 (dd, 1H), 7.89 (d, 2H), 7.75 (d, 1H), 7.65-7.54 (m, 4H), 7.47 (dd, 1H), 7.42-7.23, (m, 5H), 7.11 (d, 1H), 3.12 (s, 3H), 3.12 (hept, 1H), 1.36 (d, 6H).

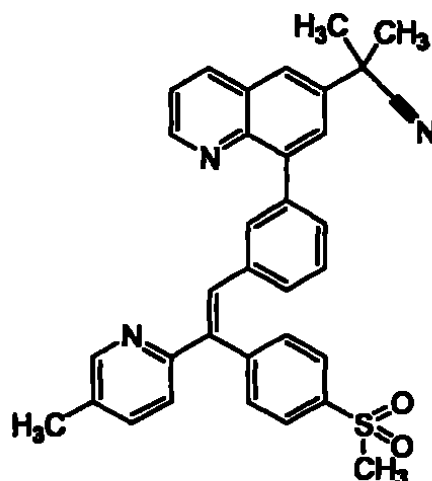
**EXAMPLE 35****8-(3-(2,2-bis[4-(methylsulfonyl)phenyl]vinyl)phenyl)-6-isopropylquinoline**

Example 35 was prepared by following the procedure described for Example 30 but substituting the ketone K9 for 4,4'-dichlorobenzophenone and using the benzylphosphonate P2 as the starting materials.

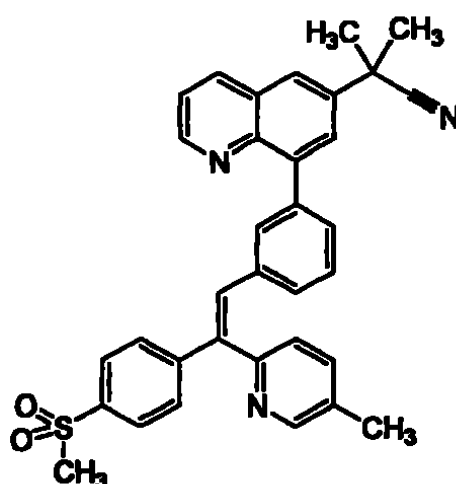
NMR  $^1\text{H}$  (500MHz, Acetone- $d_6$ ):  $\delta$  8.80 (dd, 1H), 8.29 (dd, 1H), 7.98 (d, 2H), 7.93 (d, 2H), 7.75 (d, 1H), 7.61 (d, 2H), 7.59-7.56 (m, 3H), 7.50 (d, 1H), 7.48-7.44 (m, 3H) 7.30 (t, 1H), 7.12 (d, 1H), 3.14 (hept, 1H), 3.13 (s, 3H), 2.97 (s, 3H), 1.35 (d, 6H).

## EXAMPLES 36 AND 37

2-methyl-2-[8-(3-((E/Z)-2-(5-methyl-2-pyridinyl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-quinolinyl]propanenitrile



Example 36



Example 37

Examples 36 and 37 were prepared by following the procedure described for Example 30 but substituting the ketone K8 for 4,4'-

415

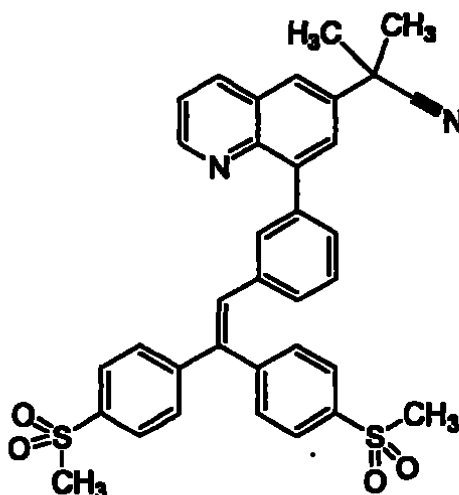
dichlorobenzophenone and substituting the benzyphosphonate P3 for P2 as the starting materials.

NMR  $^1\text{H}$  (500MHz, Acetone- $d_6$ ) (E) isomer (Example 36):  $\delta$  8.90 (dd, 1H), 8.47 (s, 1H), 8.43 (dd, 1H), 8.08 (d, 1H), 8.00 (s, 1H), 7.97 (d, 2H), 7.83 (d, 1H) 7.57-7.53 (m, 5H), 7.50 (s, 1H), 7.28 (t, 1H), 7.06 (d, 1H), 6.96 (d, 1H), 2.96 (s, 3H), 2.33 (s, 3H), 1.88 (s, 6H).

NMR  $^1\text{H}$  (300MHz, Acetone- $d_6$ ) (Z) isomer (Example 37):  $\delta$  8.89 (dd, 1H), 8.51 (s, 1H), 8.45 (dd, 1H), 8.09 (d, 1H), 7.89 (d, 2H), 7.72 (d, 1H), 7.62-7.56 (m, 5H), 7.43-7.42 (m, 2H) 7.30 (t, 1H), 7.25 (d, 1H), 7.10 (d, 1H), 3.11 (s, 3H), 2.34 (s, 3H), 1.87 (s, 6H).

### EXAMPLE 38

2-[8-(3-(2,2-bis[4-(methylsulfonyl)phenyl]vinyl)phenyl)-6-quinoliny]-2-methylpropanenitrile



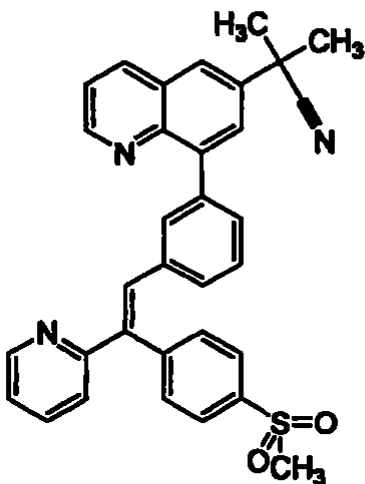
Example 38 was prepared by following the procedure described for Example 30 but substituting the ketone K9 for 4,4'-dichlorobenzophenone and substituting the benzyphosphonate P3 for P2 as the starting materials.

NMR  $^1\text{H}$  (500MHz, Acetone- $d_6$ ):  $\delta$  8.90 (dd, 1H), 8.44 (dd, 1H), 8.09 (d, 1H), 7.97 (d, 2H), 7.92 (d, 2H), 7.81 (d, 1H), 7.61 (d, 2H) 7.58-7.55 (m, 3H), 7.53 (s, 1H), 7.44 (s, 1H), 7.32 (t, 1H), 7.13 (d, 1H), 6.96 (d, 1H), 3.13 (s, 3H), 2.97 (s, 3H), 1.86 (s, 6H).

60171522.122299

## EXAMPLE 39

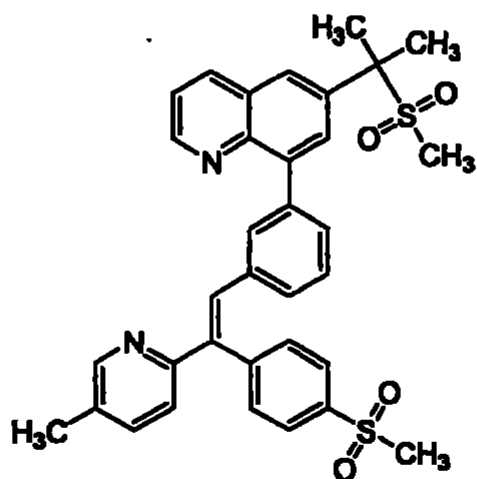
2-methyl-2-(8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(2-pyridinyl)ethenyl]phenyl}-6-quinolinyl)propanenitrile



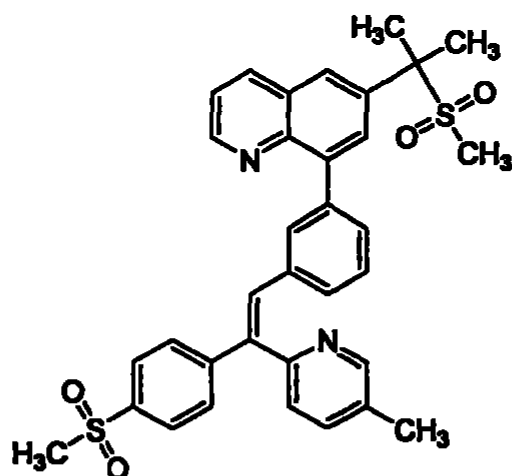
Example 39 was prepared by following the procedure described for Example 30 but substituting the ketone K10 for 4,4'-dichlorobenzophenone and substituting the benzylphosphonate P3 for P2 as the starting materials.

NMR  $^1\text{H}$  (300MHz, Acetone- $d_6$ ):  $\delta$  8.90 (dd, 1H), 8.45 (dd, 1H), 8.11-8.09 (m, 2H), 7.84-7.80 (m, 3H), 7.72-7.69 (m, 1H), 7.63-7.52 (m, 5H), 7.43-7.38 (m, 2H), 7.33 (t, 1H), 7.28 (s, 1H), 7.14 (d, 1H), 2.97 (s, 3H), 1.86 (s, 6H)

**6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-((E/Z)-2-(5-methyl-2-pyridinyl)-2-(4-(methylsulfonyl)phenyl)ethenyl)phenyl)quinoline**



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### Example 41

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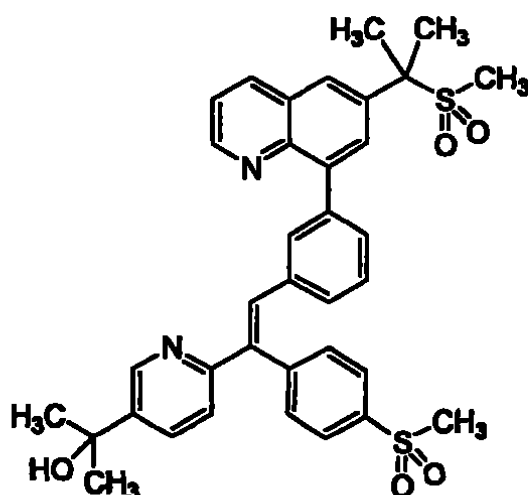
NMR <sup>1</sup>H (400MHz, Acetone-*d*<sub>6</sub>) (E) isomer (Example 40): δ 8.91 (dd, 1H), 8.45 (s, 1H), 8.41 (dd, 1H), 8.23 (d, 1H), 8.01-8.00 (m, 2H), 7.95 (d, 2H), 7.57-7.54 (m, 4H), 7.51 (d, 1H), 7.49 (s, 1H), 7.28 (t, 1H), 7.07 (d, 1H), 6.96 (d, 1H), 2.94 (s, 3H), 2.69 (s, 3H), 2.33 (s, 3H), 1.97 (s, 6H).

5 NMR <sup>1</sup>H (400MHz, Acetone-*d*<sub>6</sub>) (Z) isomer (Example 41): δ 8.88 (dd, 1H), 8.49 (s, 1H), 8.42 (dd, 1H), 8.24 (dd, 1H), 7.94 (d, 1H), 7.88 (d, 2H), 7.61-7.55 (m, 5H), 7.47 (s, 1H), 7.40 (s, 1H), 7.29 (t, 1H), 7.24 (d, 1H), 7.06 (d, 1H), 3.12 (s, 3H), 2.68 (s, 3H), 2.33 (s, 3H), 1.96 (s, 6H).

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# EXAMPLE 42

2-(6-((E)-2-(3-(6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinolinyl)phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl)-3-pyridinyl)-2-propanol



15 Example 42 was prepared by following the procedure described in Example 10 but substituting bromoquinoline Q3 for Q2 and substituting boronate B4 for boronate B2.

20 NMR <sup>1</sup>H (500 MHz, Acetone-*d*<sub>6</sub>): δ 8.91 (dd, 1H), 8.80 (d, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.03-8.01 (m, 2H), 7.96 (d, 1H), 7.82 (dd, 1H), 7.58-7.54 (m, 4H), 7.51 (s, 1H), 7.29 (t, 1H), 7.08 (d, 1H), 7.01 (d, 1H), 4.31 (s, 1H), 2.96 (s, 3H), 2.70 (s, 3H), 1.96 (s, 6H), 1.56 (s, 6H).

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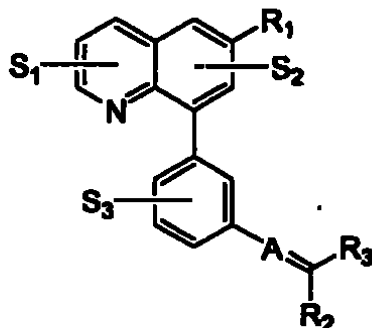
Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

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## WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl), -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -C<sub>1</sub>-C<sub>6</sub>alkyl-SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH, C-ester, or C-R<sub>4</sub>;

R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or

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-C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

5 one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system;

R<sub>4</sub> is an aryl, heteroaryl, -CN, carbonyl, carbamoyl, -C(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 10 1-5 substituents, wherein each substituent is independently a carbonyl, -CN, halogen, -C(O)(C<sub>0</sub>-C<sub>6</sub>alkyl), -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) group; and

n is independently 0, 1, or 2.

15 2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, 20 -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>2</sub>NH(aryl), -SO<sub>2</sub>NH(heteroaryl), -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or 25 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

30 A is CH;

R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with

1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and

n is independently 0, 1, or 2.

3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a -C<sub>1</sub>-C<sub>6</sub>alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and

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n is independently 0, 1, or 2.

4. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

5 S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -C<sub>1</sub>-C<sub>6</sub>alkyl-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and

n is independently 0, 1, or 2.

5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

30 S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a -C<sub>1</sub>-C<sub>6</sub>alkenyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy,

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cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN,

- 5 -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -C<sub>1</sub>-C<sub>6</sub>alkyl-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl,
- 10 -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and
- 15 R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and

n is independently 0, 1, or 2.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein
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S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a heteroaryl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-

25 C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN,

- 30 -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -C<sub>1</sub>-C<sub>6</sub>alkyl-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl,

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- C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and
- n is independently 0, 1, or 2.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein
- S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;
- R<sub>1</sub> is a an -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, or
- (C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);
- A is CH;
- R<sub>2</sub> and R<sub>3</sub> independently is an aryl, heteroaryl, H, halogen, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, carbonyl, carbamoyl, -COOH, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), or -C<sub>1</sub>-C<sub>6</sub>alkylacylamino group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); one of R<sub>2</sub> and R<sub>3</sub> must be an aryl or heteroaryl, optionally substituted; and when R<sub>2</sub> and R<sub>3</sub> are both an aryl then R<sub>2</sub> and R<sub>3</sub> are optionally connected by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three ring system; and
- n is independently 0, 1, or 2.

8. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

- S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;
- R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl), -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

- R<sub>2</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

- R<sub>3</sub> is a heteroaryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and n is independently 0, 1, or 2.

9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

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S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl), -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl; -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

R<sub>2</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and

n is independently 0, 1, or 2.

10. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

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**R<sub>1</sub>** is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl),  
 5 -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl,  
 10 alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

**A** is CH;

**R<sub>2</sub>** is a carbonyl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);  
 15  
 20 **R<sub>3</sub>** is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and  
 25

**n** is independently 0, 1, or 2.

11. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

**S<sub>1</sub>**, **S<sub>2</sub>**, and **S<sub>3</sub>** are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

**R<sub>1</sub>** is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino,

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- C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl), -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or
- 5 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl; aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);
- 10 A is CH;  
R<sub>2</sub> is a carbamoyl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or
- 15 -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);  
R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and
- 20  
25 n is independently 0, 1, or 2.

12. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

- S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;
- 30 R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl),

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-SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl),  
 -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or  
 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally  
 substituted with 1-5 substituents; wherein each substituent is independently a halogen,  
 5 -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl,  
 alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl,  
 heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

10 R<sub>2</sub> and R<sub>3</sub> are each independently an aryl, optionally substituted,  
 connected to each other by a thio, oxy, or (C<sub>1</sub>-C<sub>4</sub>alkyl) bridge to form a fused three  
 ring system; and

n is independently 0, 1, or 2.

13. The compound according to claim 1, or a pharmaceutically  
 15 acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl,  
 -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl,  
 -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino,  
 20 -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl,  
 -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl),  
 -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl),  
 -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or  
 -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally  
 25 substituted with 1-5 substituents; wherein each substituent is independently a halogen,  
 -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl,  
 alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl,  
 heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl);

A is CH;

30 R<sub>2</sub> is a -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), optionally substituted with  
 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH,  
 carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl,  
 -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or  
 -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently

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is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and

n is independently 0, 1, or 2.

14. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy,

R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl), -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl);

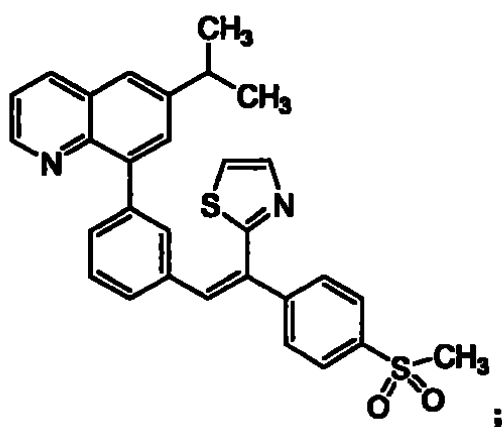
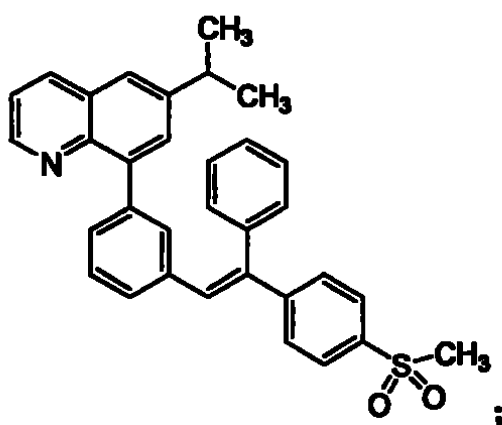
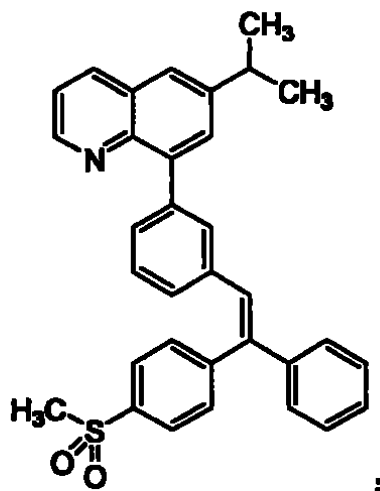
A is CH;

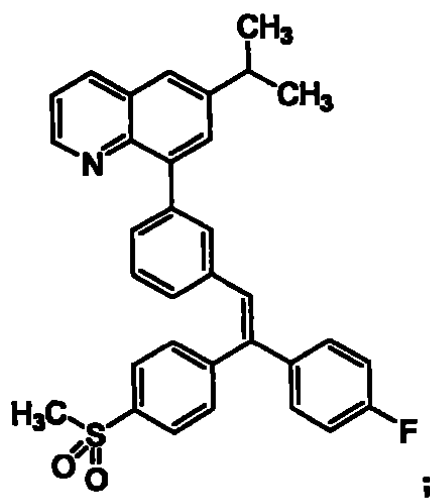
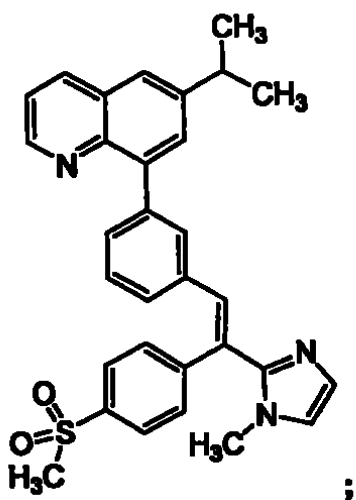
R<sub>2</sub> is a -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl);

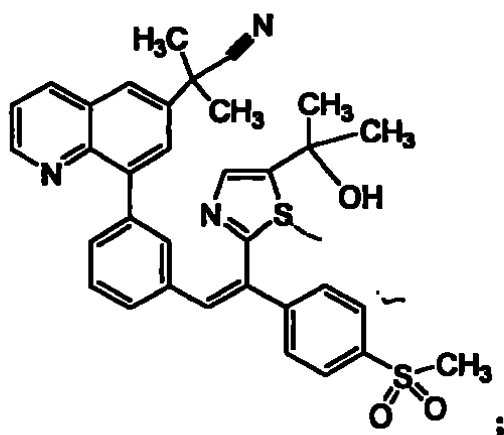
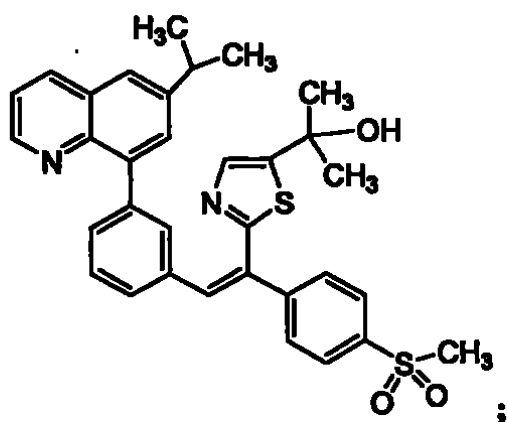
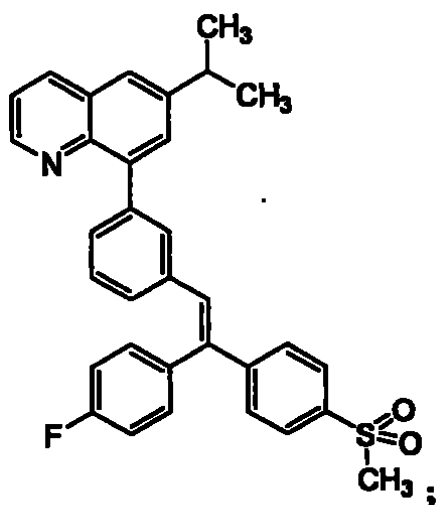
- R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and n is independently 0, 1, or 2.

15. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub> are independently H, -OH, halogen, -C<sub>1</sub>-C<sub>6</sub>alkyl, -NO<sub>2</sub>, -CN, or -C<sub>1</sub>-C<sub>6</sub>alkoxy, R<sub>1</sub> is a halogen, carbonyl, -C<sub>1</sub>-C<sub>6</sub>alkyl, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, -C<sub>1</sub>-C<sub>6</sub>alkenyl, -C<sub>1</sub>-C<sub>6</sub>alkoxy, aryl, heteroaryl, -CN, -heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -amino, -C<sub>1</sub>-C<sub>6</sub>alkylamino, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, -C<sub>1</sub>-C<sub>6</sub>alkyl(oxy)C<sub>1</sub>-C<sub>6</sub>alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO<sub>n</sub>NH(aryl), -SO<sub>n</sub>NH(heteroaryl), -SO<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl), -NH-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -carbamoyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-C(CN)-dialkylamino, or -(C<sub>1</sub>-C<sub>6</sub>alkyl)-SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C(O)(heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl), -C(O)-O-(C<sub>0</sub>-C<sub>6</sub>alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC<sub>3</sub>-C<sub>6</sub>alkyl, heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, aryl, heteroaryl, carbonyl, carbamoyl, or -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl); A is CH; R<sub>2</sub> is -CN; R<sub>3</sub> is an aryl, optionally substituted with 1-5 substituents, wherein each substituent is independently a halogen, -NO<sub>2</sub>, -COOH, carbonyl, -CN, -C<sub>1</sub>-C<sub>6</sub>alkyl, -SO<sub>n</sub>-(C<sub>1</sub>-C<sub>6</sub>alkyl), -O-aryl, -O-heteroaryl, -C(O)-heterocycloC<sub>3</sub>-C<sub>6</sub>alkyl, -NH-cycloC<sub>3</sub>-C<sub>6</sub>alkyl, amino, -OH, or -C<sub>1</sub>-C<sub>6</sub>alkyl(amino) substituent group, wherein each substituent group independently is optionally substituted with -OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(aryl), -COOH, -COO(C<sub>1</sub>-C<sub>6</sub>alkyl), halogen, -NO<sub>2</sub>, -CN, or -C(O)-N(C<sub>0</sub>-C<sub>6</sub>alkyl)(C<sub>0</sub>-C<sub>6</sub>alkyl); and n is independently 0, 1, or 2.

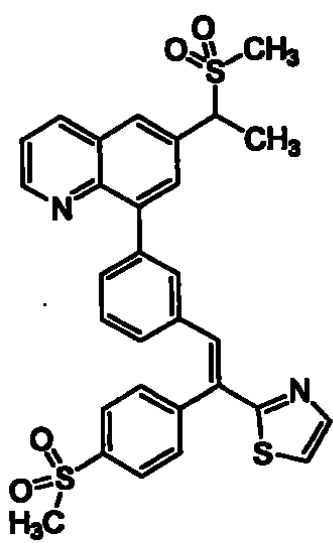
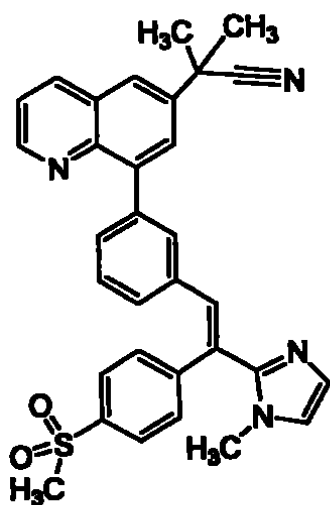
16. The compound according to claim 1, comprising



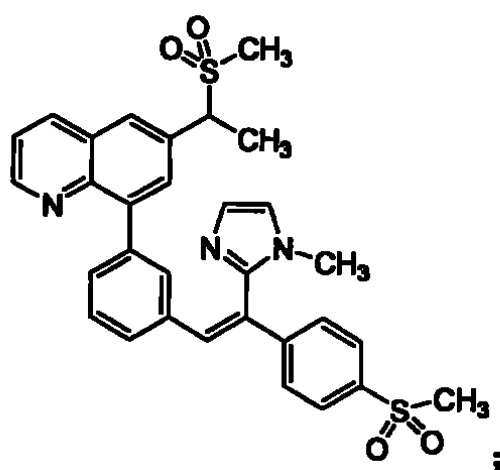
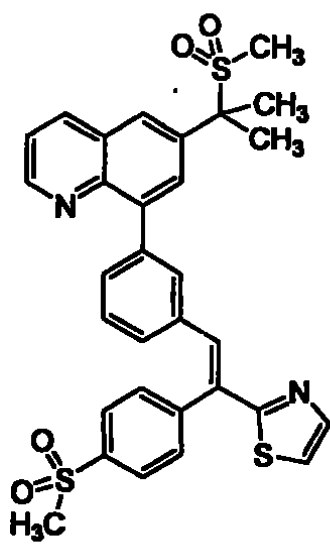


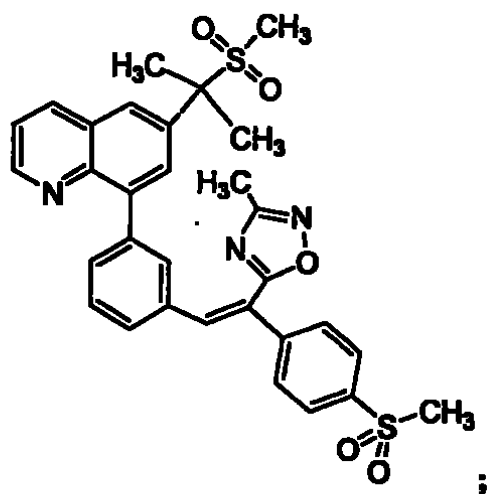
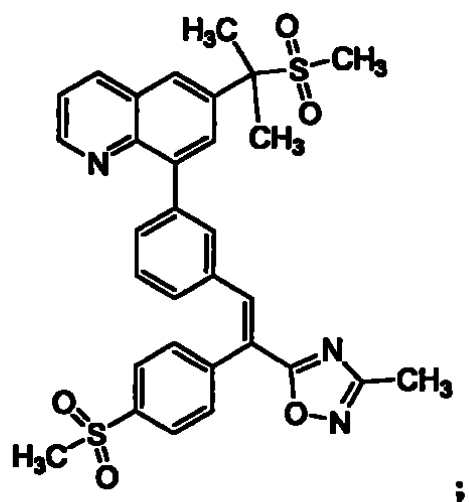
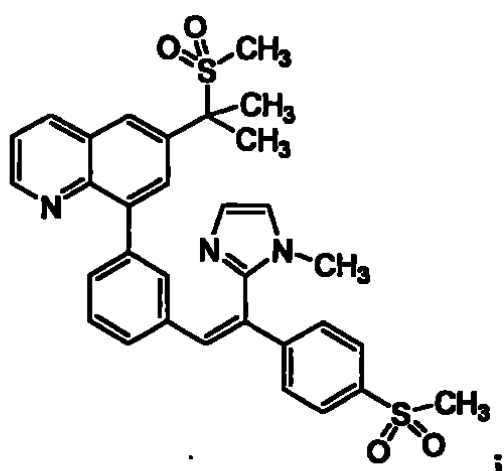


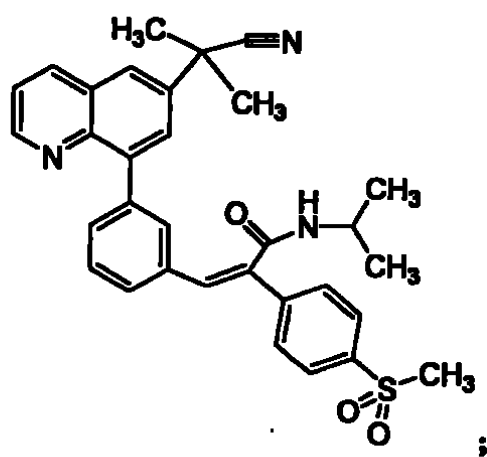
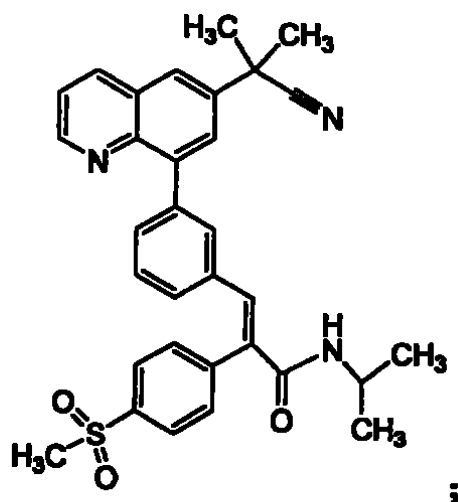
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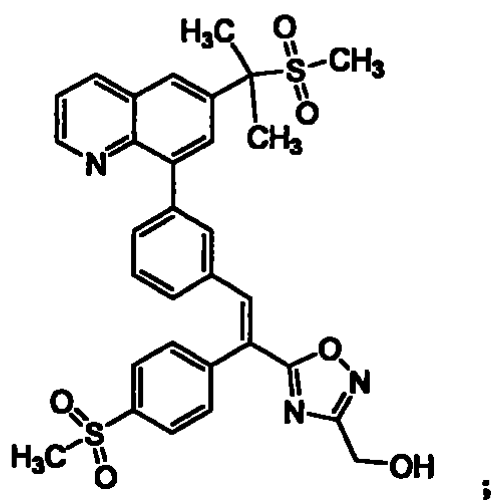
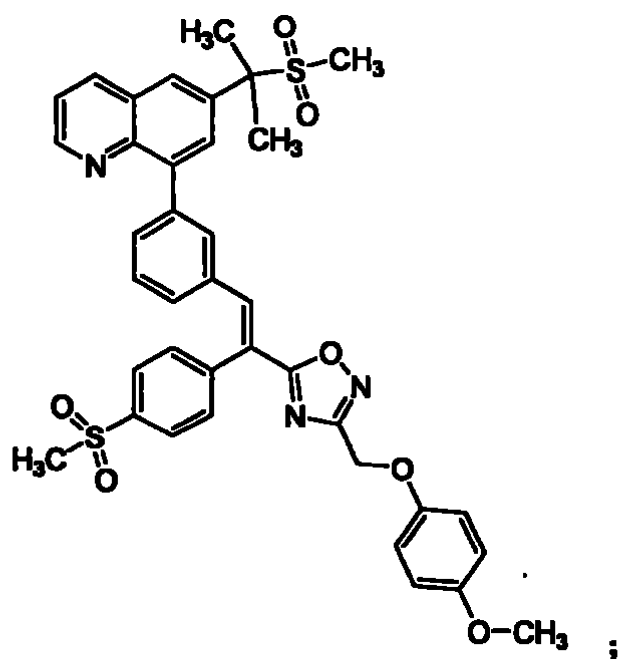


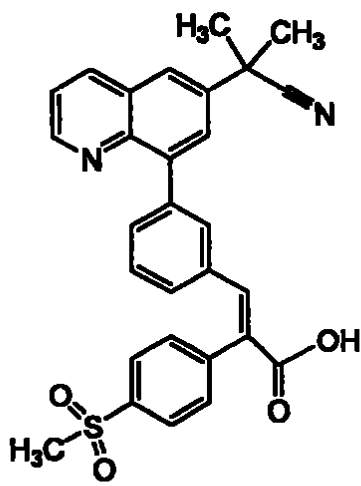
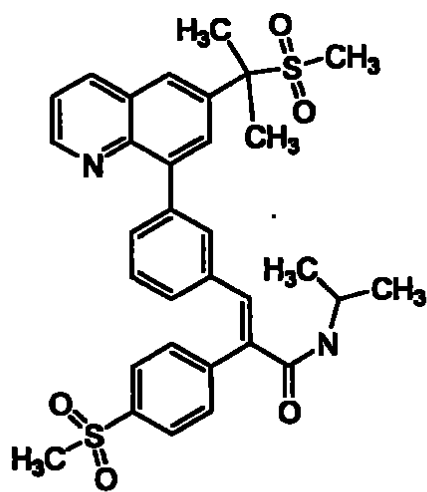
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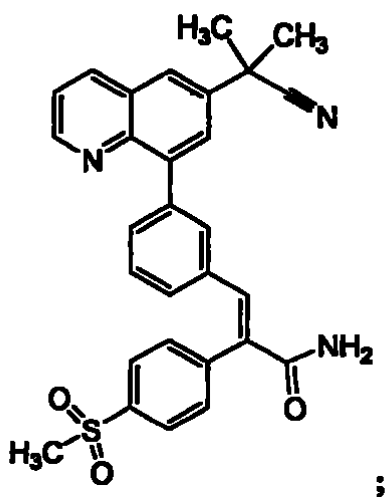
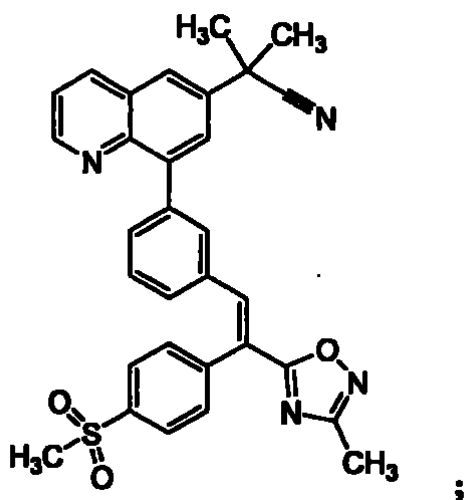




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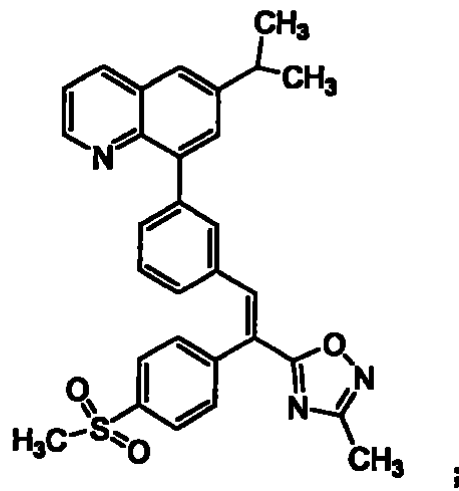
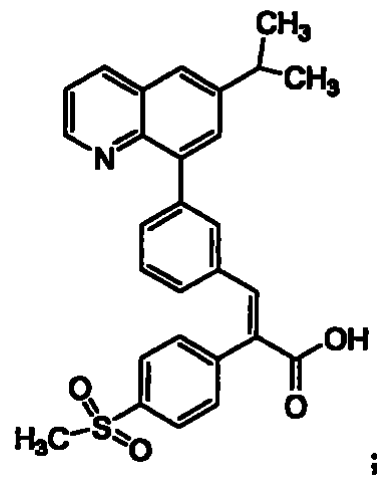
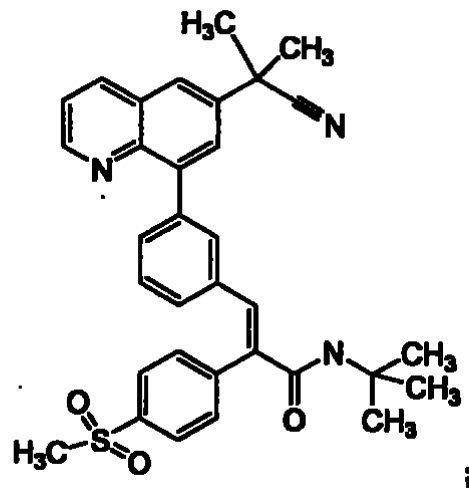
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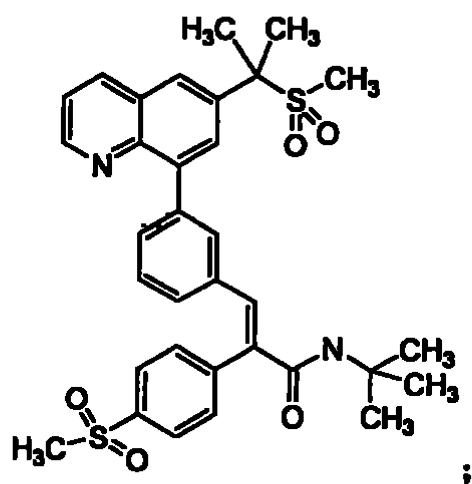
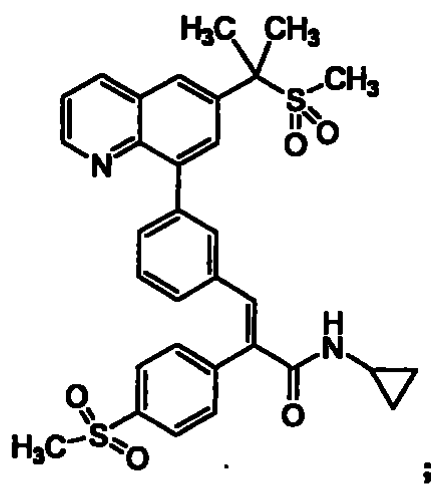
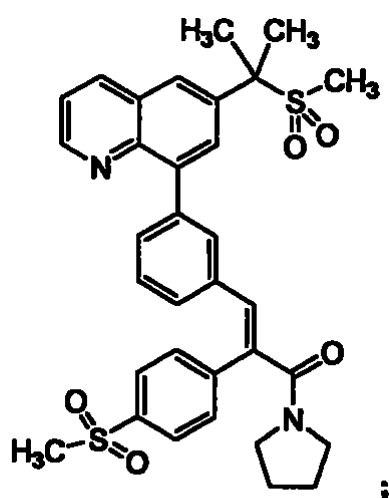
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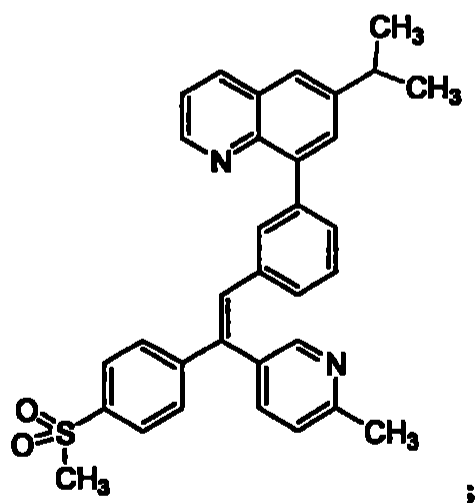
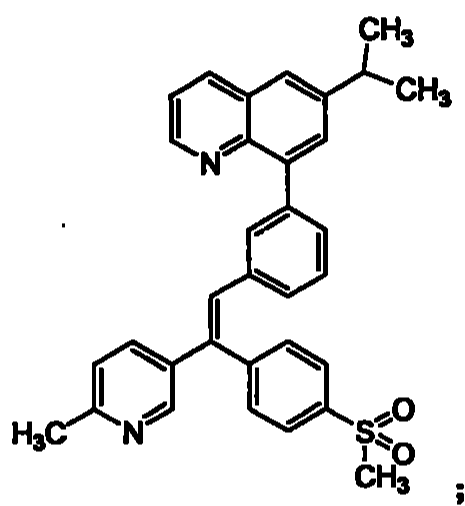
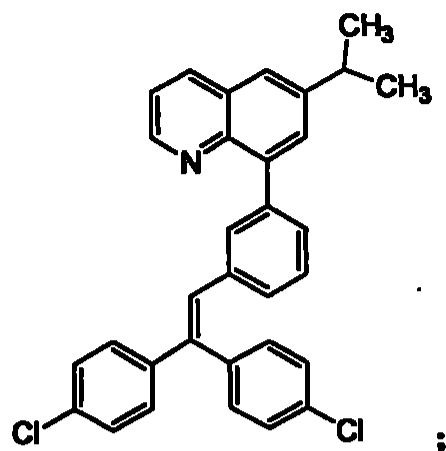


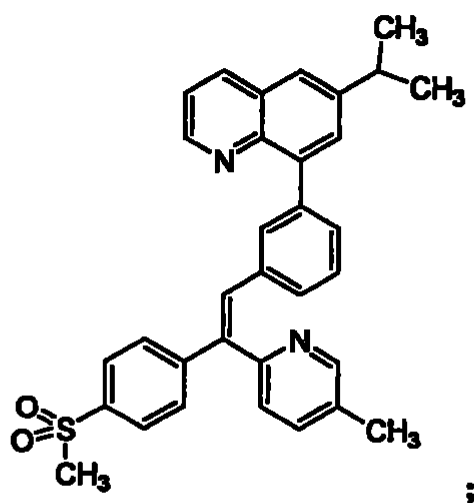
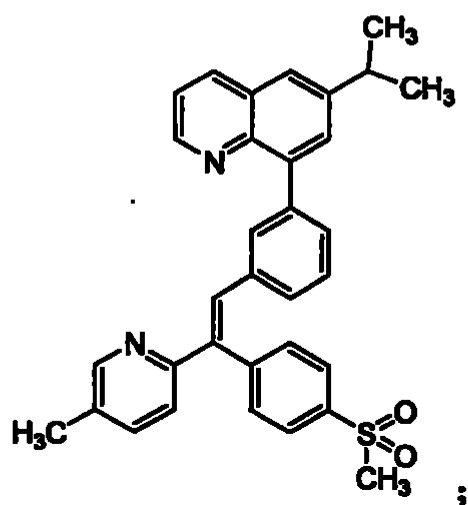
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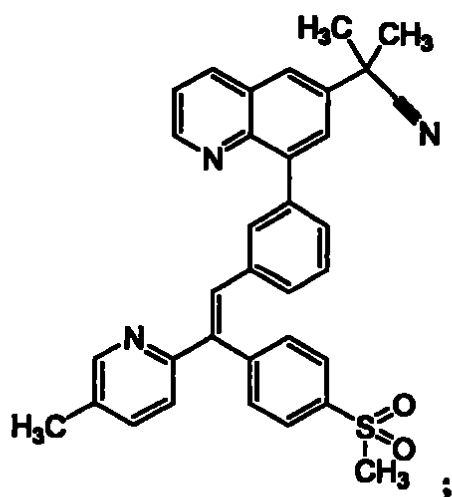
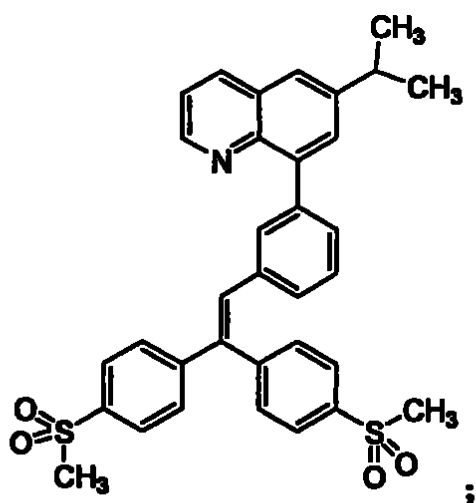






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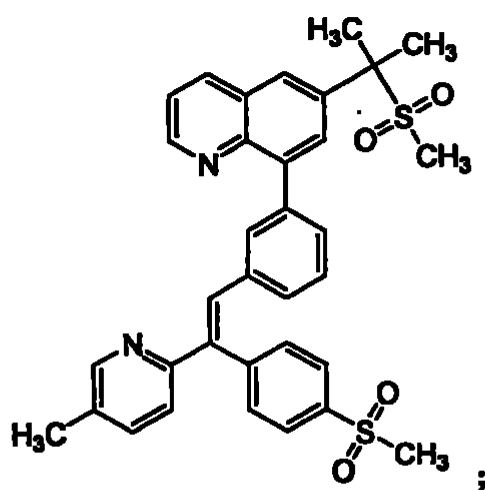
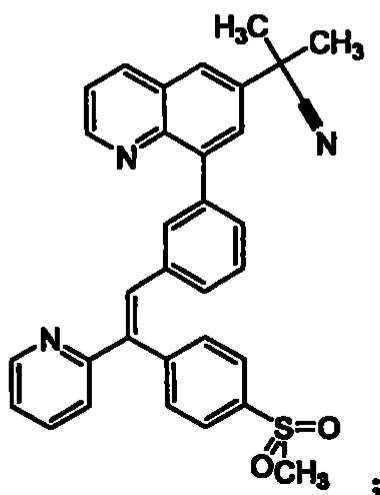


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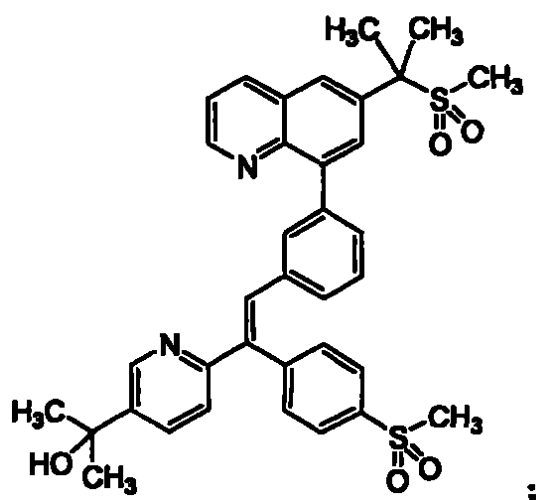
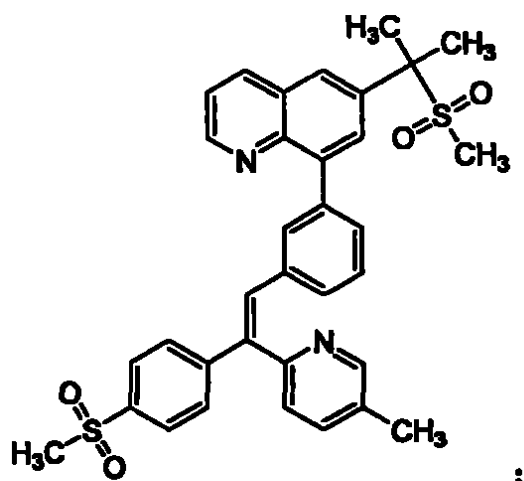
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or a pharmaceutically acceptable salt thereof.

- 5                    17.    The compound according to claim 1, comprising  
 6-isopropyl-8-(3-((Z/E)-2-[4-(methylsulfonyl)phenyl]-2-  
 phenylethenyl)phenyl)quinoline;  
 6-isopropyl-8-(3-[(E/Z)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-  
 yl)ethenyl]phenyl)quinoline;  
 10    6-isopropyl-8-(3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-  
 (methylsulfonyl)phenyl]ethenyl)phenyl)quinoline;

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- 6-isopropyl-8-(3-((Z/E)-2-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)quinoline;  
 2-(2-((E/Z)-2-[3-(6-isopropyl-8-quinoliny]phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl)-1,3-thiazol-5-yl)-2-propanol;  
 5 2-[8-(3-((E/Z)-2-[5-(1-hydroxy-1-methylethyl)-1,3-thiazol-2-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-quinoliny]-2-methylpropanenitrile;  
 2-methyl-2-[8-(3-((E)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-quinoliny]propanenitrile;  
 10 6-[1-(methylsulfonyl)ethyl]-8-(3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl)quinoline;  
 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(1,3-thiazol-2-yl)ethenyl]phenyl)quinoline;  
 8-(3-((Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-[1-(methylsulfonyl)ethyl]quinoline;  
 15 8-(3-((Z)-2-(1-methyl-1H-imidazol-2-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline;  
 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-((E/Z)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)quinoline;  
 20 (E/Z)-3-[3-[6-(1-cyano-1-methylethyl)-8-quinoliny]phenyl]-N-isopropyl-2-[4-(methylsulfonyl)phenyl]-2-propenamide;  
 8-(3-((E)-2-[3-[(4-methoxyphenoxy)methyl]-1,2,4-oxadiazol-5-yl]-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline;  
 25 (5-((E)-2-(3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinoliny]phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl)-1,2,4-oxadiazol-3-yl)methanol;  
 (E)-N-isopropyl-3-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinoliny]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenamide;  
 (E)-3-[3-[6-(1-cyano-1-methylethyl)-8-quinoliny]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid;  
 30 2-methyl-2-[8-(3-((E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl)phenyl)-6-quinoliny]propanenitrile;  
 (E)-3-[3-[6-(1-cyano-1-methylethyl)-8-quinoliny]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenamide;

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- (E)-N-(tert-butyl)-3-{3-[6-(1-cyano-1-methylethyl)-8-quinoliny]phenyl}-2-[4-(methylsulfonyl)phenyl]-2-propenamide;  
 (E)-3-[3-(6-isopropyl-8-quinoliny]phenyl]-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid;
- 5 6-isopropyl-8-(3-[(E)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl)quinoline;  
 (E)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinoliny]phenyl)-2-[4-(methylsulfonyl)phenyl]-1-(1-pyrrolidiny)-2-propen-1-one;  
 (E)-N-cyclopropyl-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinoliny]phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide;
- 10 (E)-N-(tert-butyl)-3-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinoliny]phenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide;  
 8-(3-[2,2-bis(4-chlorophenyl)vinyl]phenyl)-6-isopropylquinoline;  
 6-isopropyl-8-(3-[(E/Z)-2-(6-methyl-3-pyridiny)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl)quinoline;
- 15 6-isopropyl-8-(3-[(E/Z)-2-(5-methyl-2-pyridiny)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl)quinoline;  
 8-(3-{2,2-bis[4-(methylsulfonyl)phenyl]vinyl}phenyl)-6-isopropylquinoline;  
 2-methyl-2-[8-(3-[(E/Z)-2-(5-methyl-2-pyridiny)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl)-6-quinoliny]propanenitrile;
- 20 2-[8-(3-{2,2-bis[4-(methylsulfonyl)phenyl]vinyl}phenyl)-6-quinoliny]-2-methylpropanenitrile;  
 2-methyl-2-(8-{3-[(E)-2-[4-(methylsulfonyl)phenyl]-2-(2-pyridiny)ethenyl]phenyl)-6-quinoliny]propanenitrile;
- 25 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-[(E/Z)-2-(5-methyl-2-pyridiny)-2-[4-(methylsulfonyl)phenyl]ethenyl]phenyl)quinoline;  
 2-(6-[(E)-2-(3-{6-[1-methyl-1-(methylsulfonyl)ethyl]-8-quinoliny]phenyl)-1-[4-(methylsulfonyl)phenyl]ethenyl]-3-pyridiny)-2-propanol;  
 or a pharmaceutically acceptable salt thereof.

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18. A pharmaceutical composition comprising a therapeutically effective amount of  
 the compound according to claim 1 or a pharmaceutically acceptable salt thereof; and

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a pharmaceutically acceptable carrier.

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19. The pharmaceutical composition according to claim 18, further comprising a Leukotriene receptor antagonist, a Leukotriene biosynthesis inhibitor, or an M2/M3 antagonist.

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20. A method of treatment or prevention of asthma, chronic bronchitis, chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock, laminitis in horses, colic in horses, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthrosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection, graft versus host disease, hypersecretion of gastric acid, bacterial, fungal induced sepsis, viral induced sepsis, fungal induced septic shock, viral induced septic shock, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

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21. A precursor compound which forms *in vivo* the compound according to claim 1.

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22. A method of treatment or prevention of asthma, chronic bronchitis, chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock, laminitis in horses, colic in horses, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthrosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis,

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- ankylosing spondylitis, transplant rejection, graft versus host disease, hypersecretion of gastric acid, bacterial, fungal induced sepsis, viral induced sepsis, fungal induced septic shock, viral induced septic shock, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer,
- 5 cachexia, muscle wasting, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues comprising the step of forming *in vivo* a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1.

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**TITLE OF THE INVENTION**

**SUBSTITUTED 8-ARYLQUINOLINE PHOSPHODIESTERASE-4 INHIBITORS**

**ABSTRACT OF THE DISCLOSURE**

5 Novel substituted 8-arylquinolines, wherein the aryl group at the 8-position contains a substituent substituted-alkenyl group, are PDE4 inhibitors.

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