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mismo, donde:

Q se selecciona entre el grupo compuesto por CO, CR<sup>11</sup>R<sup>12</sup>, NR<sup>11</sup> y S(O)<sub>n</sub>, donde n es un número entero de 0 a 2;

A es un enlace, arilo C<sub>6</sub>-C<sub>10</sub>, anillo heteroaromático de 5 a 13 miembros, alquilo C<sub>3</sub>-C<sub>8</sub> y anillo heteroalquilo de 3 a 8 miembros y cada uno de los anteriores grupos A está opcionalmente sustituido con de 1 a 5 grupos R<sup>5</sup>;

L es -(CH<sub>2</sub>)<sub>p</sub>- donde p es un número entero de 0 a 5; -O-; -S-; -S(O)-; -S(O)<sub>2</sub>-; -N(R)-; N(C(O)OR)-; -N(C(O)R)-; -N(SO<sub>2</sub>R)-; -CH<sub>2</sub>O-; -CH<sub>2</sub>S-; -CH<sub>2</sub>N(R)-; -C(NR)-; -CH<sub>2</sub>N(C(O)R)-; -CH<sub>2</sub>N(C(O)OR)-; -CH<sub>2</sub>N(SO<sub>2</sub>R)-; -CH(NHR)-; -CH(NHC(O)R)-; -CH(NHSO<sub>2</sub>R)-; -CH(NHC(O)OR)-; -CH(OC(O)R)-; -CH(OC(O)NHR)-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-; -C(O)N(R)-; -N(R)C(O)-; -N(R)S(O)-; -N(R)S(O)<sub>2</sub>-; -OC(O)N(R)-; -N(R)C(O)N(R)-; -NRC(O)O-; -S(O)N(R)-; -S(O)<sub>2</sub>N(R)-; -N(C(O)R)S(O)-; -N(C(O)R)S(O)<sub>2</sub>-; -N(R)S(O)N(R)-; -N(R)S(O)<sub>2</sub>N(R)-; -C(O)N(R)C(O)-; -S(O)N(R)C(O)-; -S(O)<sub>2</sub>N(R)C(O)-; -OS(O)N(R)-; -OS(O)<sub>2</sub>N(R)-; -N(R)S(O)O-; -N(R)S(O)<sub>2</sub>O-; -N(R)S(O)C(O)-; -N(R)S(O)<sub>2</sub>C(O)-; -SON(C(O)R)-; -SO<sub>2</sub>N(C(O)R)-; -N(R)SON(R)-; -N(R)SO<sub>2</sub>N(R)-; -C(O)O-; -N(R)P(OR<sup>x</sup>)O-; -N(R)P(OR<sup>x</sup>)-; -N(R)P(O)(OR<sup>x</sup>)O-; -N(R)P(OR<sup>x</sup>)-; -N(C(O)R)P(OR<sup>x</sup>)O-; -N(C(O)R)P(OR<sup>x</sup>)-; -N(C(O)R)P(O)(OR<sup>x</sup>)O-; -N(C(O)R)P(OR<sup>x</sup>)-; -CH(R)S(O)-; -CH(R)S(O)<sub>2</sub>-; -CH(R)N(C(O)OR)-; -CH(R)N(C(O)R)-; -CH(R)N(SO<sub>2</sub>R)-; -CH(R)O-; -CH(R)S-; -CH(R)N(R)-; -CH(R)N(C(O)R)-; -CH(R)N(C(O)OR)-; -CH(R)N(SO<sub>2</sub>R)-; -CH(R)C(=NOR)-; -CH(R)C(O)-; -CH(R)CH(OR)-; -CH(R)C(O)N(R)-; -CH(R)N(R)C(O)-; -CH(R)N(R)S(O)-; -CH(R)N(R)S(O)<sub>2</sub>-; -CH(R)OC(O)N(R)-; -CH(R)N(R)C(O)N(R)-; -CH(R)N(R)C(O)O-; -CH(R)S(O)N(R)-; -CH(R)S(O)<sub>2</sub>N(R)-; -CH(R)N(C(O)R)S(O)-; -CH(R)N(C(O)R)S(O)<sub>2</sub>-; -CH(R)N(R)S(O)N(R)-; -CH(R)N(R)S(O)<sub>2</sub>N(R)-; -CH(R)C(O)N(R)C(O)-; -CH(R)S(O)N(R)C(O)-;

CH(R)S(O)<sub>2</sub>N(R)C(O)-; -CH(R)OS(O)N(R)-; -CH(R)OS(O)<sub>2</sub>N(R)-; CH(R)N(R)S(O)O-;  
 ; -CH(R)N(R)S(O)<sub>2</sub>O-; -CH(R)N(R)S(O)C(O)-; -CH(R)N(R)S(O)<sub>2</sub>C(O)-; -  
 CH(R)SON(C(O)R)-; -CH(R)S(O)<sub>2</sub>N(C(O)R)-; -CH(R)N(R)SON(R)-; -  
 CH(R)N(R)S(O)<sub>2</sub>N(R)-; -CH(R)C(O)O-; -CH(R)N(R)P(OR<sup>x</sup>)O-; -CH(R)N(R)P(OR<sup>x</sup>)-;  
 5 -CH(R)N(R)P(O)(OR<sup>x</sup>)O-; -CH(R)N(R)P(O)(OR<sup>x</sup>)-; -CH(R)N(C(O)R)P(OR<sup>x</sup>)O-; -  
 CH(R)N(C(O)R)P(OR<sup>x</sup>)-; -CH(R)N(C(O)R)P(O)(OR<sup>x</sup>)O- o -CH(R)N(C(O)R)P(OR<sup>x</sup>)-,  
 donde cada uno de R y R<sup>x</sup> se selecciona independientemente entre H, acilo C<sub>1</sub>-C<sub>6</sub>,  
 alquilo C<sub>1</sub>-C<sub>6</sub>, grupo C<sub>6</sub>-aromático y grupo heteroaromático de 5 ó 6 miembros, donde  
 cada uno de los grupos R y R<sup>x</sup> anteriores está opcionalmente sustituido  
 10 independientemente con 1-3 átomos halo, alquilo C<sub>1</sub>-C<sub>6</sub> y alcoxi C<sub>1</sub>-C<sub>6</sub>;

R<sup>1</sup> es H, alquilo C<sub>1</sub>-C<sub>6</sub>, cicloalquilo C<sub>3</sub>-C<sub>8</sub>, bicicloalquilo sustituido,  
 cicloalqueno de 5 a 8 miembros, grupo aromático de 6 a 10 miembros, grupo  
 heteroaromático de 5 a 13 miembros, grupo heterocicloalquilo de 3 a 8 miembros, y  
 grupo heterobicicloalquilo, y cada uno de los grupos R<sup>1</sup> anteriores está opcionalmente  
 15 sustituido con de 1 a 5 grupos R<sup>10</sup>;

R<sup>2</sup> es H, halo, alquilo C<sub>1</sub>-C<sub>6</sub>, cicloalquilo C<sub>3</sub>-C<sub>8</sub>, grupo aromático de 6 a 10  
 miembros, grupo heteroaromático de 5 a 13 miembros, heterocicloalquilo de 3 a 8  
 miembros, -(CH<sub>2</sub>)<sub>0-3</sub>NR<sup>6</sup>R<sup>7</sup> y -(CH<sub>2</sub>)<sub>0-3</sub>C(O)NR<sup>6</sup>R<sup>7</sup>, y cada uno de los grupos R<sup>2</sup>  
 anteriores está opcionalmente sustituido con de 1 a 5 grupos R<sup>5</sup>;

20 R<sup>3</sup> es H, alquilo C<sub>1</sub>-C<sub>6</sub>, cicloalquilo C<sub>3</sub>-C<sub>8</sub>, grupo aromático -(CH<sub>2</sub>)<sub>1</sub>C<sub>6</sub>-C<sub>10</sub>, -  
 (CH<sub>2</sub>)<sub>1</sub>(grupo heteroaromático de 5 a 13 miembros) y heterocicloalquilo de 3 a 8  
 miembros, y cada uno de los grupos R<sup>3</sup> anteriores está opcionalmente sustituido con de  
 1 a 5 grupos R<sup>5</sup>;

cada R<sup>5</sup> se selecciona independientemente entre el grupo compuesto por halo,  
 25 ciano, trifluorometoxi, trifluorometilo, -C(O)R<sup>8</sup>, -NR<sup>6</sup>C(O)R<sup>7</sup>, -C(O)NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, -

$OR^9$ ,  $-SO_2NR^6R^7$ ,  $-SO_2R^6$ ,  $-NR^6SO_2R^7$ , alquilo  $C_1-C_6$ , alquenilo  $C_2-C_6$ , alquinilo  $C_2-C_6$ ,  
 $-(CH_2)_jO(CH_2)_qNR^6R^7$ ,  $-(CH_2)_tO(CH_2)_qOR^9$ ,  $-(CH_2)_tOR^9$ ,  $-S(O)_j$ (alquilo  $C_1-C_6$ ), -  
 $(CH_2)_t$ (arilo  $C_6-C_{10}$ ),  $-(CH_2)_t$ (heterociclilo de 5 a 10 miembros), -  
 $(CH_2)_tO(CH_2)_q$ (heterociclilo de 5 a 10 miembros),  $-C(O)(CH_2)_t$ (heterociclilo de 5 a 10  
5 miembros),  $-(CH_2)_jNR^7(CH_2)_qNR^6R^7$ ,  $-(CH_2)_jNR^7CH_2C(O)NR^6R^7$ , -  
 $(CH_2)_jNR^7(CH_2)_qNR^9C(O)R^8$ ,  $-(CH_2)_jNR^7(CH_2)_tO(CH_2)_qOR^9$ , -  
 $(CH_2)_jNR^7(CH_2)_qS(O)_j$ (alquilo  $C_1-C_6$ ),  $-(CH_2)_jNR^7(CH_2)_tR^6$ ,  $-SO_2(CH_2)_t$ (arilo  $C_6-C_{10}$ ) y  
 $-SO_2(CH_2)_t$ (heterociclilo de 5 a 10 miembros), donde j es un número entero de 0 a 2, t es  
un número entero de 0 a 6, q es un número entero de 2 a 6, los restos  $-(CH_2)_q$ - y  $-(CH_2)_t$ -  
10 de los grupos  $R^5$  anteriores incluyen opcionalmente un doble o triple enlace carbono-  
carbono donde t es un número entero de 2 a 6, y los restos alquilo, arilo y heterociclilo  
de los grupos  $R^5$  anteriores están opcionalmente sustituidos con de 1 a 3 sustituyentes  
seleccionados independientemente entre halo, ciano, trifluorometilo,  $-C(O)R^8$ , -  
 $NR^6C(O)R^7$ ,  $-C(O)NR^6R^7$ ,  $-(CH_2)_tNR^6R^7$ ,  $-SO_2R^6$ ,  $-SO_2NR^6R^7$ , alquilo  $C_1-C_6$ , -  
15  $(CH_2)_t$ (heterociclilo de 5 a 10 miembros),  $-(CH_2)_tO(CH_2)_qOR^9$  y  $-(CH_2)_tOR^9$ , donde t es  
un número entero de 0 a 6 y q es un número entero de 2 a 6;

cada uno de  $R^6$  y  $R^7$  se selecciona independientemente entre H, alquilo  $C_1-C_6$ , -  
 $(CH_2)_t$ (arilo  $C_6-C_{10}$ ),  $-(CH_2)_t$ (heterociclilo de 5 a 10 miembros),  $-(CH_2)_tO(CH_2)_qOR^9$  y -  
 $(CH_2)_tOR^9$ , donde t es un número entero de 0 a 6 y q es un número entero de 2 a 6, y los  
20 restos alquilo, arilo y heterociclilo de los grupos  $R^6$  y  $R^7$  anteriores están opcionalmente  
sustituidos con de 1 a 3 sustituyentes seleccionados independientemente entre halo,  
ciano, trifluorometilo,  $-C(O)R^8$ ,  $-NR^9C(O)R^{10}$ ,  $-C(O)NR^9R^{10}$ ,  $-NR^9R^{10}$ , alquilo  $C_1-C_6$ , -  
 $(CH_2)_t$ (arilo  $C_6-C_{10}$ ),  $-(CH_2)_t$ (heterociclilo de 5 a 10 miembros),  $-(CH_2)_tO(CH_2)_qOR^9$  y -  
 $(CH_2)_tOR^9$ , donde t es un número entero de 0 a 6 y q es un número entero de 2 a 6, con  
25 la condición de que donde  $R^6$  y  $R^7$  están ambos unidos al mismo nitrógeno, entonces  $R^6$

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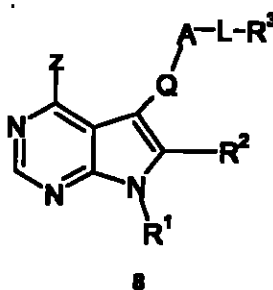
y  $R^7$  no están ambos unidos al nitrógeno directamente a través de un oxígeno;

cada  $R^8$  se selecciona independientemente entre H, alquilo  $C_1-C_{10}$ ,  $-(CH_2)_t$ (arilo  $C_6-C_{10}$ ) y  $-(CH_2)_t$ (heterociclilo de 5 a 10 miembros), donde t es un número entero de 0 a 6;

5 cada uno de  $R^9$  y  $R^{10}$  se selecciona independientemente entre H y alquilo  $C_1-C_6$ ; y

$R^{11}$  y  $R^{12}$  se seleccionan independientemente entre el grupo compuesto por H, alquilo  $C_1-C_6$ , cicloalquilo  $C_3-C_6$ , alcoxi  $C_1-C_6$  o  $R^{11}$  y  $R^{12}$  tomados juntos forman un anillo alquilo o heteroalquilo de 3 a 7 miembros,

10 que comprende tratar un compuesto de fórmula 8 en la que Z es halo

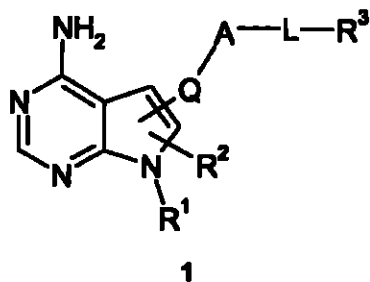


con un compuesto de fórmula  $H_3N$ .

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Resumen

La invención se refiere a compuestos de fórmula 1



5 o una sal, profármaco o hidrato farmacéuticamente aceptable del mismo, en la que Q, A, L, R<sup>1</sup>, R<sup>2</sup> y R<sup>3</sup> son como se han definido anteriormente. La invención también se refiere a composiciones farmacéuticas que contienen los compuestos de fórmula 1 y a procedimientos para tratar trastornos hiperproliferativos en un mamífero por la administración de los compuestos de fórmula 1.

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**TRATADO DE COOPERACIÓN DE PATENTES**  
**PCT**  
**NOTIFICACIÓN DE TRANSMISIÓN DEL REPORTE DE EXAMEN**  
**PRELIMINAR INTERNACIONAL**  
**(PCT Regla 71.1)**

**De: AUTORIDAD DE REVISION PRELIMINAR INTERNACIONAL**

**Para:**

**LUMB, J. Trevor**  
**c/o Jackie Lawrence**  
**PFIZER INC**  
**Eastern Point Road,**  
**Mailstop 8260-1615**  
**Groton, Connecticut 06340**  
**Estados Unidos de América.**

**Sello de recibido 22 de marzo de 2005, PFIZER INC. Departamento de Patentes,**  
**Presentaciones extranjeras Groton.**

**Fecha de envío: 17.03.2005**

**Referencia del solicitante o representante: PC25088A**

**No. de Solicitud Internacional: PCT/IB03/05841**

**Fecha de presentación internacional: 08.12.2003**

**Fecha de prioridad: 19.12.2002**

**Solicitante: PFIZER PRODUCTS INC. et. al.**

1. Por la presente se notifica al solicitante que esta Autoridad de Revisión Preliminar Internacional transmite adjunto a la presente el reporte de examen preliminar internacional y sus anexos, si existen, existentes en la solicitud internacional.

2. Una copia del reporte y sus anexos, si los hay, serán transmitidos a la Oficina Internacional para dar comunicación a todas las Oficinas designadas.

3. Donde se requiera por cualquiera de las Oficinas designadas, la Oficina Internacional preparará una traducción al inglés del reporte (pero no de sus anexos) y transmitirá tal traducción a aquellas Oficinas.

**4. RECORDATORIO**

El solicitante deberá entrar en la fase nacional ante cada Oficina designada realizando ciertos actos (presentando traducciones y cancelando tarifas nacionales) dentro de 30 meses a partir de la fecha de prioridad (o después en algunas Oficinas) (Artículo 39 (1)) (ver también el recordatorio enviado por la Oficina Internacional con el Formulario PCT/IB/301).

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Donde se deba presentar una traducción de la solicitud internacional ante una Oficina designada, la traducción deberá contener una traducción de cualquier anexo del reporte de examen preliminar internacional. Es responsabilidad del solicitante preparar y presentar tal traducción directamente a cada Oficina designada.

Para más información con respecto a los plazos y requisitos de las Oficinas designadas, ver el Volumen II de la Guía del Solicitante PCT.

Se llama la atención del solicitante al Artículo 33(5), el cual estipula que los criterios de novedad, nivel inventivo y aplicación industrial descritos en el Artículo 33(2) a (4) sirven meramente para propósitos del examen preliminar internacional y que "cualquier estado miembro puede aplicar criterios adicionales o diferentes para los propósitos de decidir si, en ese estado, los inventos reivindicados son patentables o no" (ver también Artículo 27(5)). Tales criterios adicionales pueden estar relacionados, por ejemplo, con excepciones a partir de la patentabilidad, requerimientos para permitir la divulgación, claridad y soporte para las reivindicaciones.

Nombre y dirección de correspondencia de la Autoridad de Revisión Preliminar Internacional:

Oficina de Patentes Europea

D-80298 – Munich

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Fax: +49-89 2399 – 4465.

Funcionario Autorizado: Ullrich, J.

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**REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL**  
(PCT Artículo 36 y Regla 70)

Referencia del solicitante o representante: PC25088A  
No. de Solicitud Internacional: PCT/IB03/05841  
Fecha de presentación internacional: 08.12.2003  
Fecha de prioridad: 19.12.2002  
Clasificación Internacional de Patentes (IPC) o ambas, clasificación nacional e IPC:  
C07D487/04  
Solicitante: PFIZER PRODUCTS INC et. al.

1. El reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Revisión Preliminar Internacional y es transmitido al solicitante según el Artículo 36.

2. Este REPORTE consta de 6 hojas, incluyendo esta cubre hoja.  
Este reporte también está acompañado de ANEXOS, es decir, hojas de la descripción, reivindicaciones, y/o dibujos los cuales han sido modificados y son la base para este reporte y/o hojas que contengan rectificaciones hechas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT).

Estos anexos constan de \_\_hojas.

3. Este reporte contiene indicaciones con relación a los siguientes ítems:

- I. ☒ Base para el reporte
- II. ☐ Prioridad
- III. ☒ Ninguna opinión con respecto a la novedad, nivel inventivo y aplicación industrial.
- IV. ☐ Falta de unidad inventiva
- V. ☒ Declaración razonada bajo la Regla 66.2(a) (ii) con respecto a la novedad, nivel inventivo o aplicación industrial; citas y explicaciones soportando dicha declaración.
- VI. ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos en la solicitud internacional
- VIII ☐ Ciertas observaciones sobre la solicitud internacional

Fecha de radicación de la demanda: 28.01.2004  
Fecha de elaboración de este reporte: 17.03.2005  
Nombre y dirección de correspondencia de la Autoridad de Revisión Preliminar Internacional:  
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## **REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL**

No. de Solicitud Internacional: PCT/IB03/05841

### **I. Base del reporte**

1. Con respecto a los elementos de la solicitud internacional (Hojas de reemplazo, entregadas a la Oficina receptora en respuesta a un requerimiento según el Artículo 14, son referidas en este reporte como “presentadas originalmente” y no están anexadas al presente puesto que no contienen enmiendas (Reglas 70.16 y 70.17)):

#### **Descripción, páginas:**

1-133                      tal como se presentó originalmente

#### **Reivindicaciones, Nos.:**

1-15                      tal como se presentó originalmente

2. Con respecto al idioma, todos los elementos marcados anteriormente estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma en el cual fue presentada la solicitud internacional, a menos que se indique de otra manera bajo este punto.

Estos elementos estuvieron disponibles o fueron suministrados a esta Autoridad en el siguiente idioma: , el cual es:

- ☐ el idioma de una traducción suministrada con fines de la búsqueda internacional (bajo Regla 23.1(b)).
- ☐ el idioma de la publicación de la solicitud internacional (bajo Regla 48.3 (b)).
- ☐ el idioma de una traducción suministrada con fines del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Con respecto a cualquier secuencia nucleótida y/o de amino ácidos divulgada en la solicitud internacional, el examen preliminar internacional fue realizado con base en el listado de secuencias:

- ☐ contenido en la solicitud internacional por escrito.
- ☐ presentado junto con la solicitud internacional en forma electrónica
- ☐ suministrado subsecuentemente a esta Autoridad por escrito
- ☐ suministrado subsecuentemente a esta Autoridad en forma electrónica
- ☐ Ha sido suministrada la declaración donde indica que el listado suministrado de secuencias escrito no va más allá de la divulgación encontrada en la solicitud internacional tal como se presentó

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☐ Ha sido suministrada la declaración que indica que la información registrada en forma electrónica es idéntica al listado de secuencias escrito.

4. Las enmiendas han resultado en la cancelación de:

- ☐ la descripción, páginas:
- ☐ las reivindicaciones, Nos.:
- ☐ los dibujos, hojas:

5. Este reporte ha sido establecido como si no estuvieran hechas las enmiendas, puesto que se consideró que iban más allá de la divulgación tal como se presentó (Regla 70.2(c)).

*(Cualquier hoja de reemplazo que contenga tales enmiendas debe referirse al ítem 1 y estar adjunto a este reporte.)*

6. Observaciones adicionales, si son necesarias:

**III. Ninguna formulación de opinión con respecto a la novedad, nivel inventivo, y aplicación industrial**

1. Las preguntas con respecto a si el invento reivindicado parece ser novedoso, tener nivel inventivo (no ser obvio), o ser industrialmente aplicable no han sido examinadas con respecto a:

- ☐ toda la solicitud internacional,
- ☒ reivindicaciones Nos. 11-13 con respecto a la aplicabilidad industrial

puesto que:

- ☒ dicha solicitud internacional, o dichas reivindicaciones Nos. 11-13 se relacionan con el siguiente tema el cual no requiere examen preliminar internacional (especifique):

**ver página adjunta**

- ☐ la descripción, reivindicaciones, o dibujos (indique elementos en particular a continuación) o tales reivindicaciones Nos. están tan ambiguas que ninguna opinión significativa pudo formularse (especifique):
- ☐ las reivindicaciones, o dichas reivindicaciones No. están tan inapropiadamente soportadas que no se pudo formar una opinión significativa.
- ☐ no se ha establecido ninguna búsqueda internacional para dichas reivindicaciones Nos.

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2. Un examen preliminar internacional significativo no puede efectuarse debido a que el listado de secuencias nucleótidas y/o de amino ácidos no cumple con el estándar suministrado en el Anexo C de las Instrucciones Administrativas:

- ☐ la forma escrita no ha sido suministrada o no cumple con el estándar
- ☐ la forma electrónica no ha sido suministrada o no cumple con el estándar

**V. Declaración razonada según el Artículo 35(2) con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración**

**1. Declaración**

|                            |     |                                    |
|----------------------------|-----|------------------------------------|
| Novedad (N)                | Si: | Reivindicaciones 5, 6, 8, 10-13,15 |
|                            | No: | Reivindicaciones 1-4, 7, 9, 14     |
| Nivel Inventivo (NI)       | Si: | Reivindicaciones 6, 8              |
|                            | No: | Reivindicaciones 1-5, 7, 9, 11-15  |
| Aplicación Industrial (AI) | Si: | Reivindicaciones 1-10, 14,-15      |
|                            | No: | Reivindicaciones                   |

**2. Anterioridades y explicaciones**

**Ver hoja adjunta**

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**Sección III:**

Las reivindicaciones 11-13 se relacionan con materia considerada por esta Autoridad cubierta por las provisiones encontradas en la Regla 67.1 (iv) del PCT. Por lo tanto, no se formulará ninguna opinión con respecto a la aplicación industrial de la materia de estas reivindicaciones (Artículo 34(4)(a)(I) del PCT).

**Sección V:**

1. Los siguientes documentos han sido citados en el reporte de búsqueda:

- D1: US-A-6 051 577 (ALTMANN EVA) 18 de abril de 2000 (2000-04-18)  
D2: WO 97/32879 A (CIBA GEIGY AG; ALTMANN EVA (CH);  
MISSBACH MARTIN (CH); WILDER LEO (CH) 12 de septiembre de 1997  
D3: THOMAS E RENA U ET AL: "Síntesis de análogos no nucleósidos de  
toyocamicina, sangivamicina, y tiosangivamicina: influencia de varios 7-sustituyentes  
sobre actividad antiviral" JOURNAL OF MEDICINAL CHEMISTRY, SOCIEDAD  
AMERICANA DE QUÍMICA. WASHINGTON, US, vol. 39, no. 4, 1996, páginas  
873-880, XP002139583 ISSN: 0022-2623  
D4: ADDELHAMID A O ET AL: "REACCIONES CON  
ENAMINONITRILOS HETEROCÍCLICOS: SÍNTESIS DE DERIVADOS DE  
PIRROLO-2,3-BIPYRIDINA, PIRROLO-2,3-DIPYRIDINA Y PIRROL"  
HETEROCYCLOS, XX, XX, vol. 27, no. 8, 1988, páginas 1861-1866, XP000973572  
ISSN: 0385-5414  
D5: WO 00/17202 A (BASF AG; MAZDIYASNI HORMOZ (US); DENG  
BOJUAN B (US); HIRST GAVIN (US)) 30 MARCH 2000  
D6: DE 31 45 287 A (TROPONWERKE GMBH & CO KG) 19 de mayo de  
1983  
D7: STEINHILBER D ET AL: "NUEVA CLASE DE INHIBIDORES DE LA  
5-LIPOXIGENASA: CORRELACIÓN ENTRE LA INHIBICIÓN DE LA  
PRODUCCIÓN DE LTB4 Y LA QUIMIOLUMINISENCIA DE GRANULOCITOS  
POLIMORFONUCLEARES HUMANOS" INVESTIGACIÓN FARMACÉUTICA,  
NUEVA YORK, NY, US, vol. 3, no. 5, 1986, páginas 271-277, XP009004659 ISSN:  
0724-8741  
D8: FOLKERS G ET AL: "MODELAJE MOLECULAR DE SITIOS  
ACTIVOS DE INHIBIDORES DE OXIDASA DE XANTINA CON ACTIVIDAD  
ANTIINFLAMATORIA" JOURNAL OF MOLECULAR GRAPHICS, GUILFORD,  
GB, vol. 3, no. 4, diciembre 1985, páginas 146-150, XP009004653 ISSN: 0263-7855  
D9: MUELLER, CHRISTA E. ET AL: "7-deaza-2-feniladeninas: relaciones  
estructura-actividad de potentes A1 selectivos antagonistas de receptores de adenosina"  
JOURNAL OF MEDICINAL CHEMISTRY (1990), 33(10), 2822-8 CODEN:  
JMCMAR; ISSN: 0022-2623, 1990, XP002275842  
D10: RENA U, THOMAS E. ET AL: "Diseño, síntesis, actividad contra el  
citomegalovirus de análogos no fosforilables de toyocamicina, sangivamicina, y  
tiosangivamicina" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (1992),

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2(12), 1755-1760 CODEN: BMCLE8; ISSN: 0960-894X, vol. 2, no. 12, 1992, páginas 1755-1760, XP002275843

D11: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 de abril de 2001, TAYLOR, EDWARD C. ET AL: "Síntesis de pirrolo[2,3-d]pirimidinas. La fracción agilcon (agylcon) de la toyocamicina" XP002275844 obtenido a partir de STN Database no. de acceso 1965:403323

D12: DALY J W ET AL: "7-DEAZA-9-FENILADENINAS UNA NUEVA CLASE DE ANTAGONISTAS DE RECEPTORES DE ADENOSINA" BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB, vol. 37, no. 19, 1988, páginas 3749-3753, XP002928089 ISSN: 0006-2952

D1 divulga el uso de compuestos para el tratamiento del cáncer (col. 5, líneas 45-55). Los compuestos de la presente fórmula (I) son en parte considerados como una selección de los compuestos sugeridos en D1, en tanto que corresponden a la fórmula general divulgada en D1 (por ejemplo, para  $-Q-A-L-R^3$  = metilo). La materia de las reivindicaciones 1-3, 7, 9, 11-14 por lo tanto es obvia a la luz de D1.

Los compuestos reivindicados también son considerados como una selección entre los compuestos anti-tumorales divulgados en D2 (fórmula (I)). La materia de las reivindicaciones 1-3, 5, 7, 9, 11-14 por lo tanto es obvia a la luz de D2.

D3 y D4 divulgan compuestos que desvirtúan novedad para la materia comprendida en las reivindicaciones 1-4 y 7 (D3, compuestos 5j, 5l; D4, compuestos 8a, b).

D5 divulga compuestos para el tratamiento de por ejemplo el cáncer, los cuales difieren de los compuestos reivindicados en la presente por cuanto un grupo Q tal como se requiere en los compuestos presentes no está presente.

El intercambio de halógeno en las 4-halo-pirrolo[2,3-d]pirimidinas por amoniaco para formar los derivados 4-amino está descrito en D6, página 6, reacción (IV) > (I); página 9, líneas 12-18; ejemplos 4, 5. La materia de la reivindicación 15 carece de nivel inventivo a la luz de D6.

D7 divulga compuestos (6, 11) los cuales corresponden a la presente fórmula (I) y los cuales son citados para enfrentar la novedad de las reivindicaciones 1-3, 7 y 9. El compuesto III de D8 es citado para enfrentar la novedad de las reivindicaciones 1-3, 7 y 9. Los compuestos 1,2,4,9,10 de D9 (tabla 1) y los compuestos 9a, 9c de D10 desvirtúan la novedad de la materia en las reivindicaciones 1-4,7,9,14.

Los compuestos de D11 con número de registro 1488-48-8 y 1501-10-6, y los compuestos 2-4,14 y 16 de D12 desvirtúan la novedad de la materia en las reivindicaciones 1-4,7,9, y 14.

Para la evaluación de las reivindicaciones 11-13 de la presente, sobre si son industrialmente aplicables, no existen criterios unificados en los Estados pertenecientes al PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable aquella materia que reivindique el uso de un compuesto en tratamiento médico, pero

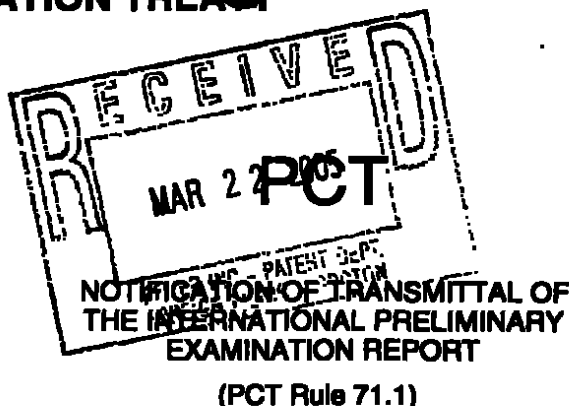
permite, sin embargo, reivindicar sobre un compuesto conocido para primero uso en tratamiento médico y el uso de tal compuesto en la manufactura de un medicamento para un nuevo tratamiento médico.

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# PATENT COOPERATION TREATY

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From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



To:

LUMB, J. Trevor  
PFIZER INC.  
c/o Jackie Lawrence  
Eastern Point Road,  
Mailstop 8260-1615  
Groton, Connecticut 06340  
ETATS-UNIS D'AMERIQUE

Date of mailing  
(day/month/year) 17.03.2005

Applicant's or agent's file reference  
PC25088A

## IMPORTANT NOTIFICATION

International application No.  
PCT/IB 03/05841

International filing date (day/month/year)  
08.12.2003

Priority date (day/month/year)  
19.12.2002

Applicant  
PFIZER PRODUCTS INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:



European Patent Office  
D-80286 Munich  
Tel. +49 89 2369 - 0 Tlx 523656 epmu d  
Fax: +49 89 2369 - 4485

Authorized Officer

Ullrich, J  
Tel. +49 89 2369-8048



INTERNATIONAL PRELIMINARY EXAMINATION REPORT  
(PCT Article 36 and Rule 70)

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                          |                                                                                                                                                                     |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Applicant's or agent's file reference<br>PC25088A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                          | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA16)                                         |  |
| International application No.<br>PCT/IB 03/05841                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | International filing date (day/month/year)<br>08.12.2003 | Priority date (day/month/year)<br>19.12.2002                                                                                                                        |  |
| International Patent Classification (IPC) or both national classification and IPC<br>C07D487/04                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                          |                                                                                                                                                                     |  |
| Applicant<br>PFIZER PRODUCTS INC. et al.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                          |                                                                                                                                                                     |  |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>                                                                                                                                                                          |                                                          |                                                                                                                                                                     |  |
| <p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p> |                                                          |                                                                                                                                                                     |  |
| Date of submission of the demand<br><br>28.01.2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                          | Date of completion of this report<br><br>17.03.2005                                                                                                                 |  |
| Name and mailing address of the international preliminary examining authority:<br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 23699 - 0 Tx: 523656 epmu d<br>Fax: +49 89 23699 - 4465                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                          | Authorized Officer<br><br>Rudolf, M<br><br>Telephone No. +49 89 23699-8804<br> |  |

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/IB 03/05841**

**I. Basis of the report**

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

**Description, Pages**

1-133 as originally filed

**Claims, Numbers**

1-15 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/IB 03/05841**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 11-13 with respect to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 11-13 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the Standard.
- ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

|                               |             |                |
|-------------------------------|-------------|----------------|
| Novelty (N)                   | Yes: Claims | 5,6,8,10-13,15 |
|                               | No: Claims  | 1-4,7,9,14     |
| Inventive step (IS)           | Yes: Claims | 6,8            |
|                               | No: Claims  | 1-5,7,9,11-15  |
| Industrial applicability (IA) | Yes: Claims | 1-10,14-15     |
|                               | No: Claims  |                |

2. Citations and explanations

**see separate sheet**

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB 03/05841

To section III:

Claims 11-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

To section V:

1. The following documents are cited in the search report:

- D1: US-A-6 051 577 (ALTMANN EVA) 18 April 2000 (2000-04-18)
- D2: WO 97/32879 A (CIBA GEIGY AG ; ALTMANN EVA (CH); MISSBACH MARTIN (CH); WIDLER LEO (CH) 12 September 1997 (1997-09-12)
- D3: THOMAS E RENAULT ET AL: "Synthesis of Non-nucleoside Analogs of Toyocamycin, Sangivamycin, and Thiosangivamycin: Influence of Various 7-Substituents on Antiviral Activity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 4, 1996, pages 873-880, XP002139583 ISSN: 0022-2623
- D4: ABDELHAMID A O ET AL: "REACTIONS WITH HETEROCYCLIC ENAMINONITRILES: SYNTHESIS OF PYRROLO2,3-BPYRIDINE, PYRROLO2,3-DPYRIMIDINE AND PYRROLE DERIVATIVES" HETEROCYCLES, XX, XX, vol. 27, no. 8, 1988, pages 1861-1866, XP000973572 ISSN: 0385-5414
- D5: WO 00/17202 A (BASF AG ; MAZDIYASNI HORMOZ (US); DENG BOJUAN B (US); HIRST GAVIN (US)) 30 March 2000 (2000-03-30)
- D6: DE 31 45 287 A (TROPONWERKE GMBH & CO KG) 19 May 1983 (1983-05-19)
- D7: STEINHILBER D ET AL: "NEW CLASS OF 5-LIPOXYGENASE INHIBITORS: CORRELATION BETWEEN INHIBITION OF LTB4 PRODUCTION AND CHEMILUMINESCENCE OF HUMAN POLYMORPHONUCLEAR GRANULOCYTES" PHARMACEUTICAL RESEARCH, NEW YORK, NY, US, vol. 3, no. 5, 1986, pages 271-277, XP009004659 ISSN: 0724-8741
- D8: FOLKERS G ET AL: "ACTIVE SITE MOLECULAR MODELLING OF XANTHINE

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB 03/05841

- OXIDASE INHIBITORS WITH ANTIINFLAMMATORY ACTIVITY" JOURNAL OF MOLECULAR GRAPHICS, GUILDFORD, GB, vol. 3, no. 4, December 1985 (1985-12), pages 146-150, XP009004653 ISSN: 0263-7855
- D9: MUELLER, CHRISTA E. ET AL: "7-Deaza-2-phenyladenines: structure-activity relationships of potent A1 selective adenosine receptor antagonists" JOURNAL OF MEDICINAL CHEMISTRY ( 1990 ), 33(10), 2822-8 CODEN: JMCMAR; ISSN: 0022-2623, 1990, XP002275842
- D10: RENAU, THOMAS E. ET AL: "Design, synthesis, activity against human cytomegalovirus of non-phosphorylatable analogs of toyocamycin, sangivamycin, and thiosangivamycin" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS ( 1992 ), 2(12), 1755-60 CODEN: BMCLE8; ISSN: 0960-894X, vol. 2, no. 12, 1992, pages 1755-1760, XP002275843
- D11: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 April 2001 (2001-04-22), TAYLOR, EDWARD C. ET AL: "Synthesis of pyrrolo[2,3-d]pyrimidines. The aglycon of toyocamycin" XP002275844 retrieved from STN Database accession no. 1965:403323
- D12: DALY J W ET AL: "7-DEAZA-9-PHENYLADENINES A NEW CLASS OF ADENOSINE RECEPTOR ANTAGONISTS" BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB, vol. 37, no. 19, 1988, pages 3749-3753, XP002928089 ISSN: 0006-2952

D1 discloses the use of compounds for the treatment of cancer (col. 5 lines 45-55). The compounds of present formula (I) are in part considered as a selection from the compounds suggested in D1, insofar they correspond to the general formula disclosed in D1 (e.g. for -Q-A-L-R<sup>3</sup> = methyl). The subject matter of claims 1-3,7,9,11-14 therefore is obvious in view of D1.

The presently claimed compounds are also considered as a selection from the antitumor compounds disclosed in D2 (formula (I)). The subject matter of present claims 1-3,5,7,9,11-14 is obvious in view of D2.

D3 and D4 disclose compounds which are novelty-destroying for the subject matter of

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB 03/05841

claims 1-4 and 7 (D3, compounds 5j, 5l; D4, compounds 8a,b).

D5 discloses compounds for the treatment of e.g. cancer, which differ from the presently claimed compounds in that a group Q as required in the present compounds is not present.

The exchange of halogen in 4-halo-pyrrolo[2,3-d]pyrimidines by ammonia to form the 4-amino derivatives is described in D6, page 6, reaction (IV) -> (I); page 9 lines 12-18; examples 4, 5. The subject matter of claim 15 lacks inventive step in view of D6.

D7 discloses compounds (6, 11) which correspond to present formula (I) and which are cited against the novelty of claims 1-3,7, and 9. Compound III of D8 is cited against the novelty of claims 1-3,7, and 9. Compounds 1,2,4,9,10 of D9 (table 1) and compounds 9a,9c of D10 are novelty-destroying for the subject matter of claims 1-4,7,9,14.

The compounds of D11 with registry numbers 1488-48-8 and 1501-10-6, and the compounds 2-4,14 and 16 of D12 are novelty destroying for the subject matter of claims 1-4,7,9, and 14.

For the assessment of the present claims 11-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

# INTERNATIONAL SEARCH REPORT

326 725  
 1st Application No  
 PCT/IB 03/05841

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07D487/04 A61K31/505 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, BEILSTEIN Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                            | Relevant to claim No. |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | US 6 051 577 A (ALTMANN EVA)<br>18 April 2000 (2000-04-18)<br>Col. 1, formula (I)<br>column 5, line 45 -column 5, line 52                                                                     | 1-3,7,9,<br>11-14     |
| X          | WO 97/32879 A (CIBA GEIGY AG ; ALTMANN EVA<br>(CH); MISSBACH MARTIN (CH); WIDLER LEO<br>(CH) 12 September 1997 (1997-09-12)<br>page 1, formula (I)<br>page 8, line 20 -page 9, line 14<br>-/- | 1-3,5,7,<br>9,11-14   |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "A" document member of the same patent family

Date of the actual completion of the international search

1 April 2004

Date of mailing of the international search report

03/05/2004

Name and mailing address of the ISA  
 European Patent Office, P.O. Box 5518 Patentlinien 2  
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Authorized officer

Rudolf, M

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/05841

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                      | Relevant to claim No. |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | THOMAS E RENU ET AL: "Synthesis of Non-nucleoside Analogs of Toyocamycin, Sangivamycin, and Thiosangivamycin: Influence of Various 7-Substituents on Antiviral Activity"<br>JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 39, no. 4, 1996, pages 873-880, XP002139583<br>ISSN: 0022-2623<br>table 3, compounds 5j, 5l | 1-4,7                 |
| X          | ABDELHAMID A O ET AL: "REACTIONS WITH HETEROCYCLIC ENAMINONITRILES: SYNTHESIS OF PYRROLO2,3-BPYRIDINE, PYRROLO2,3-DPYRIMIDINE AND PYRROLE DERIVATIVES"<br>HETEROCYCLES, XX, XX, vol. 27, no. 8, 1988, pages 1861-1866, XP000973572<br>ISSN: 0385-5414<br>compounds 8a, 8b                                                                               | 1-4,7                 |
| A          | WO 00/17202 A (BASF AG ; MAZDIYASNI HORMOZ (US); DENG BOJUAN B (US); HIRST GAVIN (US)) 30 March 2000 (2000-03-30)<br>Page 14, formula (I)<br>page 31, line 18 -page 31, line 22; claims 34,35                                                                                                                                                           | 1-14                  |
| X          | DE 31 45 287 A (TROPONWERKE GMBH & CO KG) 19 May 1983 (1983-05-19)<br>page 6, reaction scheme 1<br>page 9, line 12-18                                                                                                                                                                                                                                   | 15                    |
| X          | STEINHILBER D ET AL: "NEW CLASS OF 5-LIPOXYGENASE INHIBITORS: CORRELATION BETWEEN INHIBITION OF LTB4 PRODUCTION AND CHEMILUMINESCENCE OF HUMAN POLYMORPHONUCLEAR GRANULOCYTES"<br>PHARMACEUTICAL RESEARCH, NEW YORK, NY, US, vol. 3, no. 5, 1986, pages 271-277, XP009004659<br>ISSN: 0724-8741<br>Table II, compounds 6, 11                            | 1-3,7,9               |
| X          | FOLKERS G ET AL: "ACTIVE SITE MOLECULAR MODELLING OF XANTHINE OXIDASE INHIBITORS WITH ANTIINFLAMMATORY ACTIVITY"<br>JOURNAL OF MOLECULAR GRAPHICS, GUILDFORD, GB, vol. 3, no. 4, December 1985 (1985-12), pages 146-150, XP009004653<br>ISSN: 0263-7855<br>compound III                                                                                 | 1-3,7,9, 14           |
|            | -/-                                                                                                                                                                                                                                                                                                                                                     |                       |

## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                         | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X          | MUELLER, CHRISTA E. ET AL:<br>"7-Deaza-2-phenyladenines:<br>structure-activity relationships of potent<br>A1 selective adenosine receptor<br>antagonists"<br>JOURNAL OF MEDICINAL CHEMISTRY ( 1990 ),<br>33(10), 2822-8 CODEN: JMCMAR; ISSN:<br>0022-2623,<br>1990, XP002275842<br>Table 1, compounds 1,2,4,9,10                                                                                                                                                           | 1-4,7,9,<br>14        |
| X          | RENAU, THOMAS E. ET AL: "Design,<br>synthesis, activity against human<br>cytomegalovirus of non-phosphorylatable<br>analogs of toyocamycin, sangivamycin, and<br>thiosangivamycin"<br>BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (<br>1992 ), 2(12), 1755-60 CODEN: BMCLE8;<br>ISSN: 0960-894X,<br>vol. 2, no. 12, 1992, pages 1755-1760,<br>XP002275843<br>Table I, compounds 9a, 9c                                                                                        | 1-4,7,9,<br>14        |
| X          | DATABASE CHEMABS 'Online!<br>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br>OHIO, US; 22 Apr11 2001 (2001-04-22)<br>TAYLOR, EDWARD C. ET AL: "Synthesis of<br>pyrrolo'2,3-d!pyrimidines. The aglycon of<br>toyocamycin"<br>retrieved from STN<br>Database accession no. 1965:403323<br>XP002275844<br>Compounds with RN=1488.48-8, 1501-10-6<br>abstract<br>& JOURNAL OF THE AMERICAN CHEMICAL SOCIETY<br>( 1965 ), 87(9), 1995-2003 CODEN:<br>JACSAT; ISSN: 0002-7863,<br>1965, | 1-4,7,9               |
| X          | DALY J W ET AL: "7-DEAZA-9-PHENYLADENINES<br>A NEW CLASS OF ADENOSINE RECEPTOR<br>ANTAGONISTS"<br>BIOCHEMICAL PHARMACOLOGY, PERGAMON,<br>OXFORD, GB,<br>vol. 37, no. 19, 1988, pages 3749-3753,<br>XP002928089<br>ISSN: 0006-2952<br>Table 1, compounds 2-4,14,16                                                                                                                                                                                                          | 1-4,7,9,<br>14        |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International

Application No

PCT/IB 03/05841

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---|---------------------|----------------------------|---------------------|
| US 6051577                                | A | 18-04-2000          | AT 244719 T                | 15-07-2003          |
|                                           |   |                     | AU 716383 B2               | 24-02-2000          |
|                                           |   |                     | AU 2153497 A               | 10-10-1997          |
|                                           |   |                     | BR 9709443 A               | 10-08-1999          |
|                                           |   |                     | CA 2249739 A1              | 25-09-1997          |
|                                           |   |                     | CN 1216544 A ,B            | 12-05-1999          |
|                                           |   |                     | DE 59710417 D1             | 14-08-2003          |
|                                           |   |                     | DK 888353 T3               | 27-10-2003          |
|                                           |   |                     | WO 9734895 A1              | 25-09-1997          |
|                                           |   |                     | EP 0888353 A1              | 07-01-1999          |
|                                           |   |                     | JP 2000506537 T            | 30-05-2000          |
|                                           |   |                     | NO 984199 A                | 05-11-1998          |
|                                           |   |                     | NZ 331804 A                | 28-04-2000          |
|                                           |   |                     | PT 888353 T                | 28-11-2003          |
| WO 9732879                                | A | 12-09-1997          | AU 1794697 A               | 22-09-1997          |
|                                           |   |                     | WO 9732879 A1              | 12-09-1997          |
| WO 0017202                                | A | 30-03-2000          | AU 752474 B2               | 19-09-2002          |
|                                           |   |                     | AU 6047599 A               | 10-04-2000          |
|                                           |   |                     | BG 105355 A                | 30-11-2001          |
|                                           |   |                     | BR 9913888 A               | 08-01-2002          |
|                                           |   |                     | CA 2344262 A1              | 30-03-2000          |
|                                           |   |                     | CN 1326457 T               | 12-12-2001          |
|                                           |   |                     | CZ 20010959 A3             | 12-12-2001          |
|                                           |   |                     | EP 1114052 A1              | 11-07-2001          |
|                                           |   |                     | HU 0200355 A2              | 29-06-2002          |
|                                           |   |                     | ID 28362 A                 | 17-05-2001          |
|                                           |   |                     | JP 2002527359 T            | 27-08-2002          |
|                                           |   |                     | NO 20011357 A              | 14-05-2001          |
|                                           |   |                     | NZ 510587 A                | 28-11-2003          |
|                                           |   |                     | PL 347138 A1               | 25-03-2002          |
|                                           |   |                     | SK 3852001 A3              | 04-03-2003          |
|                                           |   |                     | TR 200101395 T2            | 21-11-2001          |
|                                           |   |                     | WO 0017202 A1              | 30-03-2000          |
|                                           |   |                     | US 2003187001 A1           | 02-10-2003          |
|                                           |   |                     | ZA 200102201 A             | 15-03-2002          |
| DE 3145287                                | A | 19-05-1983          | DE 3145287 A1              | 19-05-1983          |

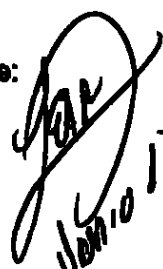
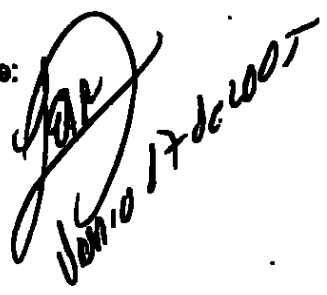
8278  
328

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL  
TRAMITE

|                                                                                         | USUARIO        | RADICADOR |
|-----------------------------------------------------------------------------------------|----------------|-----------|
| PATENTE DE INVENCION ✓                                                                  | ( )            | (✓)       |
| MODELO DE UTILIDAD                                                                      | ( )            | ( )       |
| - Indicación de que se solicita la concesión de una patente.                            | ( )            | (✓)       |
| - Datos de identificación del solicitante o de la persona que se presenta la solicitud. | ( )            | (✓)       |
| - Descripción de la invención.                                                          | ( )            | ( )       |
| - Dibujos de ser estos pertinentes.                                                     | ( )            | (✓)       |
| - Comprobante de Pago de las tasas establecidas.                                        | ( )            | ( )       |
| COMPLETA ( )                                                                            | INCOMPLETA ( ) | ( )       |

|                                                                                                              |                |     |
|--------------------------------------------------------------------------------------------------------------|----------------|-----|
| DISEÑO INDUSTRIAL ( )                                                                                        |                |     |
| - Indicación de que se solicita el registro de Diseño Industrial                                             | ( )            | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta la solicitud.                         | ( )            | ( ) |
| - Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. | ( )            | ( ) |
| - Comprobante de pago de las tasas establecidas                                                              | ( )            | ( ) |
| COMPLETA ( )                                                                                                 | INCOMPLETA ( ) | ( ) |

|                                                                                    |                |     |
|------------------------------------------------------------------------------------|----------------|-----|
| ESQUEMA DE TRAZADO ( )                                                             |                |     |
| - Indicación de que solicita el registro de un Esquema de trazado.                 | ( )            | ( ) |
| - Datos de identificación del solchante o de la persona que presenta La solicitud. | ( )            | ( ) |
| - Representación gráfica del esquema de trazado                                    | ( )            | ( ) |
| - Comprobante de pago de las tasas establecidas.                                   | ( )            | ( ) |
| COMPLETA ( )                                                                       | INCOMPLETA ( ) | ( ) |

Firma Responsable:   
Fecha: 

328  
329

**REPUBLICA DE COLOMBIA**  
**SUPERINTENDENCIA DE INDUSTRIA Y COMERCI**

Bogotá,  
2020

Doctor(a)  
OLARTE GARCIA CARLOS REINALDO  
Apoderado(a) y/o Representante de  
PFIZER PRODUCTS INC

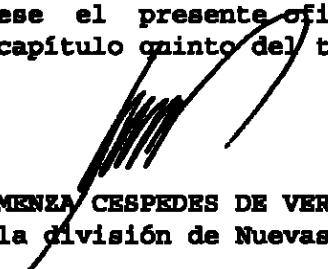
|            |                            |               |
|------------|----------------------------|---------------|
| REFERENCIA | Radicación No.             | 5 59487       |
|            | Solicitud internacional    | IB2003/005841 |
|            | Fecha inicio fase nacional | 19/07/2005    |
|            | Trámite                    | 11            |
|            | Evento                     | 379           |
|            | Actuación                  | 430           |
|            | Oficio No.                 | 7128          |

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

  
ALIX CARMENZA CESPEDES DE VERGEL  
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 19 AGO. 2005  
adpal

10-229  
330

SEÑORES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

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

Ref.: Expediente N°. 05-059.487

Solicitud de Patente de Invención Titulada: "DERIVADOS DE PIRROLOPIRIMIDINA"

Solicitante: PFIZER PRODUCTS INC.

**RESPUESTA AL OFICIO N°. 7128 NOTIFICADO**  
**POR FIJACION EN LISTA No. 327, DE FECHA 19 DE AGOSTO DE 2005,**  
**(EXAMEN DE FORMA)**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, me permito dar respuesta al auto emanado por ese Despacho, dentro del término legal previsto en el artículo 39 de la Decisión 486, en los siguientes términos:

1. En respuesta a la única observación del Examinador, me permito aportar junto al presente memorial, el documento de cesión debidamente legalizado, junto con su correspondiente traducción, según lo previsto en el Art. 26- k de la Decisión 486.

Atentamente,

  
CARLOS R. OLARTE  
C.C. No. 79.782.747 de Bogotá  
T.P. 74.295

Anexo: Documento de Cesión

**APOSTILLA**

(Convención de la Haya del 5 de Octubre de 1961)

1. País: Distrito de Columbia  
Estados Unidos de América
2. El presente documento público fue firmado por: Albert L. Themes
3. Que actuó en su calidad de Notario Público del Distrito de Columbia
4. Lleva el sello de Albert L. Themes Notario Público del Distrito de Columbia  
Se certificó
5. En Washington D.C.
6. El 1 de julio de 2005
7. Por parte del Secretario del Distrito de Columbia.
8. Bajo el Número 144030
9. Aparece el sello del Distrito de Columbia
10. Firmado por Sherryl H. Newman.

231

327  
32  
J

## **CESION**

Por contraprestación valiosa pagada a nosotros por **PFIZER PRODUCTS INC.**, sociedad constituida en virtud de las leyes del Estado de **Connecticut, Estados Unidos de América.** cuya dirección postal completa es **Eastern Point Road, Groton, Connecticut 06340, Estados Unidos de América,** por el presente vendemos y traspasamos a la citada **PFIZER PRODUCTS INC,** todo nuestro derecho, título e interés en y sobre nuestro invento de una nueva y útil mejora en **DERIVADOS DE PIRROLO PIRIMIDINA,** en cuanto respecta a la República de Colombia, tal como se indica y describe plenamente en la especificación y por el presente autorizamos y solicitamos al Comisionado de Patentes de Colombia expedir dicha patente a nombre de la citada **PFIZER PRODUCTS INC,** de conformidad con esta Cesión.

En fe de lo cual, firmamos de nuestro puño y letra,

(Fdo) Joel Thomas ARCARI -14 de junio de 2005 – Groton CT, USA  
Lugar, fecha y firma - Joel Thomas ARCARI

(Fdo) Jinshan CHEN -14 de junio de 2005 – Groton CT, USA  
Lugar, fecha y firma - Jinshan CHEN

(Fdo) Susan LAGRECA -28 de junio de 2005 – Groton CT, USA  
Lugar, fecha y firma - Susan LAGRECA

(Fdo) Matthew Arnold MARX -19 de mayo de 2005 – San Diego, CA  
Lugar, fecha y firma - Matthew Arnold MARX

(Fdo) Matthew David WESSEL -14 de junio de 2005 – Groton CT, USA  
Lugar, fecha y firma - David Matthew WESSEL

Por el presente certifico que este es el documento original.

(Fdo) Sami Swadek 1/jul/05

✓ 33

Suscrito y jurado ante mí, el 1 de julio de 2005.

(Fdo.) ALBERT L. THEMES, Notario Público de Washington Distrito Capital,  
cuyo cargo vence el 14 de junio de 2009, según consta en su  
correspondiente sello notarial.

(Sello Oficial)



05/8/05  
1/23/05  
3/3/05

# Apostille

(Convention de La Haye du 5 octobre 1961)

1. *District of Columbia*  
*United States of America*

2. This public document has been signed by ALBERT L. THEMES

3. acting in the capacity of NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA

ALBERT L. THEMES, PUBLIC IN AND FOR THE

4. bears the seal/stamp of DISTRICT OF COLUMBIA

## CERTIFIED

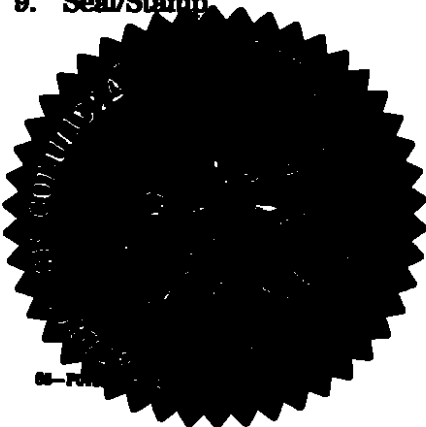
5. at Washington, D.C.

6. the 1 day of JULY 2005

7. by Secretary of the District of Columbia

8. No. 144030

9. Seal/Stamp



10. Signature

Albert L. Themes

## ASSIGNMENT

For valuable consideration paid to me (us) by PFIZER PRODUCTS INC. a corporation organized under the laws of the State of Connecticut, United States of America whose full post office address is Eastern Point Road, Groton, Connecticut 06340, United States of America, I (we) do hereby sell and assign to the said PFIZER PRODUCTS INC., all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in PYRROLOPYRIMIDINE DERIVATIVES so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said PFIZER PRODUCTS INC. in accordance with this assignment.

In witness whereof I (we) have hereunto set my (our) hand(s) this

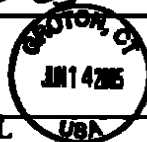
Place, date and signature - Joel Thomas ARCARI

Place, date and signature - Jinshan CHEN

Place, date and signature - Susan LAGRECA

Place, date and signature - Matthew Arnold MARX

Place, date and signature - Matthew David WESSEL



I HEREBY CERTIFY THAT THIS  
IS THE ORIGINAL DOCUMENT

Subscribed and sworn to before me, in my presence, this  
1 day of July 2005, a Notary Public 7.1.05  
In and for the District of DC

Albert L. Themes  
Notary Public  
My commission expires 6/14, 2009.

ALBERT L. THEMES  
NOTARY PUBLIC DISTRICT OF COLUMBIA  
My Commission Expires June 14, 2009

336

**REPUBLICA DE COLOMBIA**  
**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

Folio 335

2020  
Bogotá D.C.,

Doctor(a)  
OLARTE GARCIA CARLOS REINALDO  
Apoderado(a) y/o Representante de  
PFIZER PRODUCTS INC

|            |                            |               |
|------------|----------------------------|---------------|
| REFERENCIA | Radicación No.             | 05 59487      |
|            | Solicitud internacional    | IB2003/005841 |
|            | Fecha inicio fase nacional | 19/07/2005    |
|            | Trámite                    | 11            |
|            | Evento                     | 379           |
|            | Actuación                  | 416           |
|            | Oficio No.                 | 2058          |
|            | Folios                     | 1             |

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase  
Dado en Bogotá DC,

ALIX CARMENZA CESPEDES DE VERGEL  
Jefe de la división de Nuevas Creaciones

adpa10

A  
333

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-058487-00003-0000

Fecha: 2007-05-15 09:53:03 Dep. 2020 NUECREACIONES  
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII  
Act. 538 PETICION Folios: 2

Ref: Expediente No. 05-059.487

Solicitud de patente de invención titulada: "DERIVADOS DE PIRROLOPIRIMIDINA".

Solicitante: PFIZER PRODUCTS INC.

**SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN**  
**EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 575**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$202.000 pesos para cubrir la tasa correspondiente, según la Resolución 36155 del año 2006.

Atentamente,

CARLOS R. OLARTE  
C.C. 79.782.747 de Bogotá  
T.P. 74.295

Anexo: Recibo por \$202.000 pesos

INSTRUMENTO DE FOLIO 1

2  
338

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
  
No. 05-058487- -00003-0000  
Fecha: 2007-05-15 09:53:03 Dep. 2020 NUECREACIONES  
Trib. 11 PATENTEIYII Eje: 379 FASENACIONALI  
Act. 538 PETICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : -07 - 35,763  
: MAYO 8 DE 2007

\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE     | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PGO  | Vr. PAGO     |
|-----------------|--------------|---------------|-------------|----------|------------|--------------|
| OLARTE RAISBECK | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 52331050 | 08/05/2007 | 8,595,000.00 |

\*\*\*\*\* C O N C E P T O \*\*\*\*\*

| CONCEPTO                  | TOTAL CONCEPTO                          |
|---------------------------|-----------------------------------------|
| 1 50005-01-01 SOLICITUDES | 114 PTC CAP-II EXAMEN DE PATENTIBILIDAD |
|                           | 202,000.00                              |
|                           | TOTAL : \$ 202,000.00                   |

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_



**Industria y Comercio**  
SUPERINTENDENCIA

Delegatura de Propiedad Industrial  
División de Nuevas Creaciones

**PCT**  
SOLICITUD  
**PATENTE DE INVENCION**

21. EXPEDIENTE No.

**05-53825**

54. TITULO DERIVADOS DE BENZODIAZEPINA PARA EL TRATAMIENTO DE  
DESORDENES NEUROLÓGICOS

51. CLASIFICACION INTERNACIONAL A61K31/55 // A61P25/00

71. SOLICITANTE GLAXO GROUP LIMITED

DOMICILIO GRAN BRETAÑA

74. APODERADO ALVARO CORREA ORBONIZ  
TP. 20.284

22. BOGOTA, D.C., Junio 2 de 2005



# PETITORIO

**Industria y Comercio**  
**SUPERINTENDENCIA**

INDUSTRIA Y COMERCIO  
Radicación : 0503425 0030220 Folios: 24  
Fecha Recibida: 2005-06-02 17:00:17  
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC  
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

## FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT

ENTRADA EN FASE NACIONAL 20-07-05

1

SOLICITUD DE :

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☐

Capítulo I.

☒ X

Capítulo II.

2

SOLICITANTE

(71)

Nombre: GLAXO GROUP LIMITED

Dirección: Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, Gran Bretaña

Nacionalidad o Domicilio: BRITANICA

Lugar de Constitución: Middlesex, Gran Bretaña

Teléfono:

Fax:

E-Mail

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

3

REPRESENTANTE  
O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No.10-62 Piso 6o.

Teléfono: 634 1500

Fax: 376 2211

E-Mail: patents.bogota@bakernet.com

IDENTIFICACION

C.C.

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Número 79.143.366 de

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4

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7

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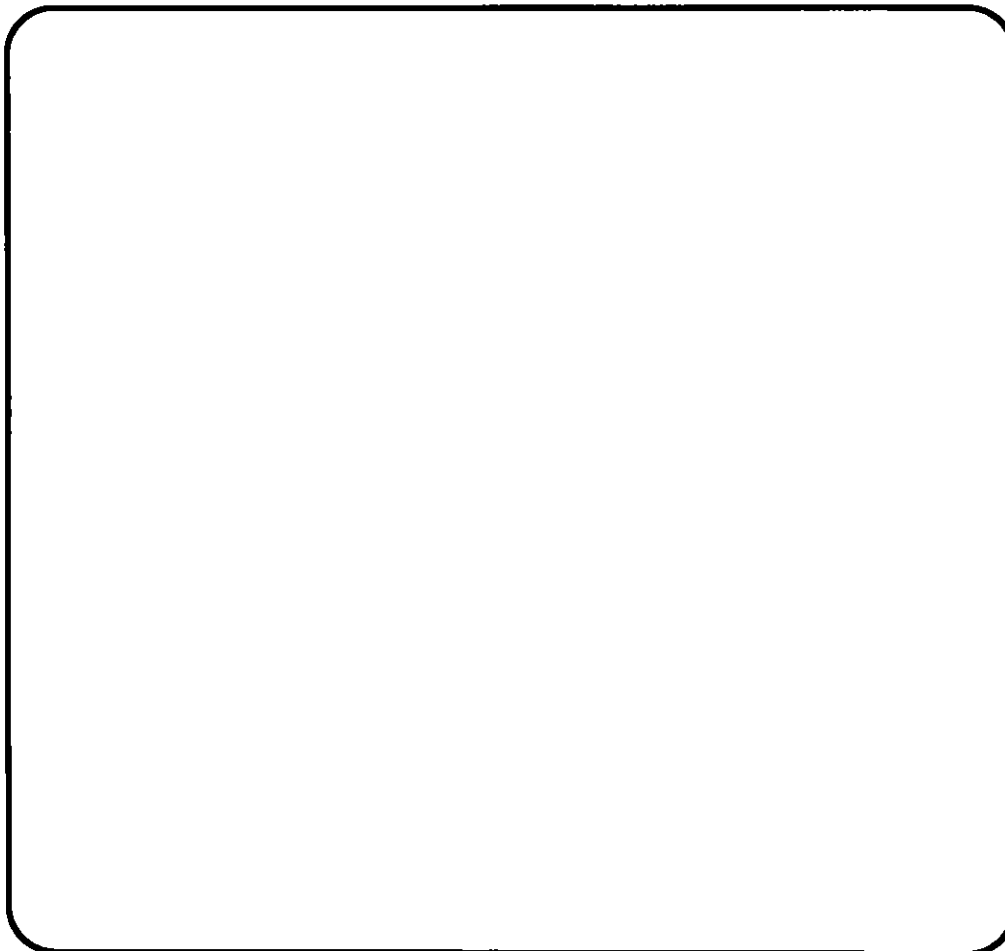
10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, el fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar Internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar Internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
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- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud Internacional.
- ☐ Otros:

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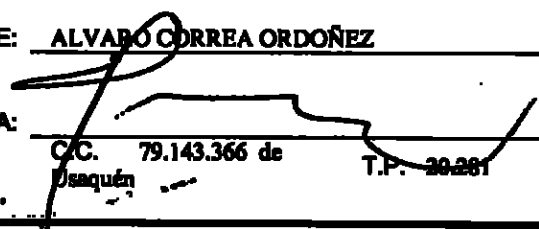
FIGURA CARACTERISTICA



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NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA: 

C.C. 79.143.366 de  
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T.P. 20.281

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\*\*\*\*\* CONCEPTO \*\*\*\*\*

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(54) Title: BENZOXAZEPINE DERIVATIVES FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

(57) Abstract: The present invention relates to benzazepine derivatives of formula (I) wherein: R<sup>1</sup> represents -C<sub>3</sub>, cycloalkyl  
optionally substituted by C<sub>1-3</sub> alkyl; having pharmacological activity, processes for their preparation, to compositions containing  
them and to their use in the treatment of neurological and psychiatric disorders.

WO 2004/056369 A1

## BENZO'DIAZEPINE DERIVATIVES FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

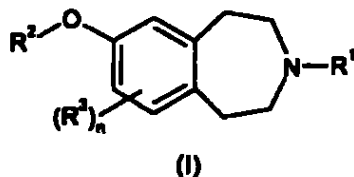
The present invention relates to novel benzazepine derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

JP 2001228289 and WO 00/23437 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives which are claimed to be useful in the treatment of obesity. DE 2207430, US 4,210,749 and FR 2171879 (Pennwalt Corp) and GB 1268243 (Wallace and Tiernan Inc) all describe a series of benzazepine derivatives which are claimed as being antagonists for narcotics (such as morphine or codeine) and also anti-histamines and anticholinergic agents. WO 02/14513 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives with GPR12 activity which are claimed to be useful in the treatment of attention deficit disorder, narcolepsy or anxiety. WO 02/02530 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives as GPR14 antagonists which are claimed to be useful in the treatment of hypertension, atherosclerosis and cardiac infarction. WO 01/03880 (Isis Innovation Ltd) describe a series of benzazepine derivatives which are claimed as effective agents in the preparation of cells for transplantation in addition to the inhibition of diseases such as diabetes. WO 00/21951 (SmithKline Beecham plc) discloses a series of tetrahydrobenzazepine derivatives as modulators of dopamine D3 receptors which are claimed to be useful as antipsychotic agents. WO 01/87834 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives as MCH antagonists which are claimed to be useful in the treatment of obesity. WO 02/15934 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives as urotensin II receptor antagonists which are claimed to be useful in the treatment of neurodegenerative disorders.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. 19, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. 8, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxdan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. 104, 147-155). These data suggest that novel H3 antagonists and/or inverse agonists such as the current series could be useful for the

treatment of cognitive impairments in neurological diseases such as Alzheimer's disease and related neurodegenerative disorders.

- The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

- 10  $R^1$  represents  $-C_{3-7}$  cycloalkyl optionally substituted by  $C_{1-3}$  alkyl;  
 $R^2$  represents hydrogen,  $-C_{1-6}$  alkyl,  $-X-C_{2-6}$  cycloalkyl,  $-X$ -aryl,  $-X$ -heterocyclyl,  $-X$ -heteroaryl,  $-X-C_{2-6}$  cycloalkyl-Y- $C_{3-6}$  cycloalkyl,  $-X-C_{2-6}$  cycloalkyl-Y-aryl,  $-X-C_{2-6}$  cycloalkyl-Y-heteroaryl,  $-X-C_{2-6}$  cycloalkyl-Y-heterocyclyl,  $-X$ -aryl-Y- $C_{2-6}$  cycloalkyl,  $-X$ -aryl-Y-aryl,  $-X$ -aryl-Y-heteroaryl,  $-X$ -aryl-Y-heterocyclyl,  $-X$ -heteroaryl-Y- $C_{2-6}$  cycloalkyl,  $-X$ -heteroaryl-Y-aryl,  $-X$ -heteroaryl-Y-heteroaryl,  $-X$ -heteroaryl-Y-heterocyclyl,  $-X$ -heterocyclyl-Y- $C_{2-6}$  cycloalkyl,  $-X$ -heterocyclyl-Y-aryl,  $-X$ -heterocyclyl-Y-heteroaryl,  $-X$ -heterocyclyl-Y-heterocyclyl;  
 $X$  represents a bond or  $C_{1-3}$  alkyl;  
 $Y$  represents a bond,  $C_{1-6}$  alkyl, CO,  $COC_{2-6}$  alkenyl, O or  $SO_2$ ;  
 20  $R^3$  represents halogen,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, cyano, amino or trifluoromethyl;  
 $n$  is 0, 1 or 2;  
 wherein said alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl groups of  $R^2$  may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano,  
 25 nitro,  $=O$ , trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy,  $C_{1-6}$  alkyl, pentafluoroethyl,  $C_{1-6}$  alkoxy, aryl- $C_{1-6}$  alkoxy,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkoxy- $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl- $C_{1-6}$  alkoxy,  $C_{1-6}$  alkanoyl,  $C_{1-6}$  alkoxy-carbonyl,  $C_{1-6}$  alkylsulfonyl,  $C_{1-6}$  alkylsulfinyl,  $C_{1-6}$  alkylsulfonyloxy,  $C_{1-6}$  alkylsulfonyl- $C_{1-6}$  alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl- $C_{1-6}$  alkyl, aryloxy,  $C_{1-6}$  alkylsulfonamido,  $C_{1-6}$  alkylamino,  $C_{1-6}$  alkylamido,  $-R^4$ ,  $-CO_2R^4$ ,  $-COR^4$ ,  $C_{1-6}$  alkylsulfonamido- $C_{1-6}$  alkyl,  $C_{1-6}$  alkylamido- $C_{1-6}$  alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido- $C_{1-6}$  alkyl, arylcarboxamido- $C_{1-6}$  alkyl, aroyl, aroyl- $C_{1-6}$  alkyl, aryl- $C_{1-6}$  alkanoyl, or a group  $-NR^4R^5$ ,  $-C_{1-6}$  alkyl- $NR^4R^5$ ,  $-C_{2-6}$  cycloalkyl- $NR^4R^5$ ,  $-CONR^4R^5$ ,  $-NR^4COR^5$ ,  $-NR^5SO_2R^5$ ,  $-OCONR^5R^5$ ,  $-NR^5CO_2R^5$ ,  $-NR^4CONR^5R^5$  or  $-SO_2NR^5R^5$  (wherein  $R^4$ ,  $R^5$  and  $R^6$  independently represent hydrogen,  $C_{1-6}$  alkyl,  $-C_{2-6}$  cycloalkyl,  $-C_{1-6}$  alkyl- $C_{2-6}$  cycloalkyl, aryl, heterocyclyl or heteroaryl or  $-NR^6R^6$  may represent a nitrogen containing heterocyclyl group, wherein said  $R^4$ ,  $R^5$  and  $R^6$  groups may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected from the group consisting of halogen, hydroxy,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, cyano, amino,  $=O$  or trifluoromethyl);

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or solvates thereof.

In one particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein:

- 5  $R^2$  represents  $-C_{1-6}$  alkyl,  $-X-C_{2-6}$  cycloalkyl,  $-X$ -aryl,  $-X$ -heterocyclyl,  $-X$ -heteroaryl,  $-X-C_{2-6}$  cycloalkyl-Y- $C_{2-6}$  cycloalkyl,  $-X-C_{2-6}$  cycloalkyl-Y-aryl,  $-X-C_{2-6}$  cycloalkyl-Y-heteroaryl,  $-X-C_{2-6}$  cycloalkyl-Y-heterocyclyl,  $-X$ -aryl-Y- $C_{2-6}$  cycloalkyl,  $-X$ -aryl-Y-aryl,  $-X$ -aryl-Y-heteroaryl,  $-X$ -aryl-Y-heterocyclyl,  $-X$ -heteroaryl-Y- $C_{2-6}$  cycloalkyl,  $-X$ -heteroaryl-Y-aryl,  $-X$ -heteroaryl-Y-heteroaryl,  $-X$ -heteroaryl-Y-heterocyclyl,  $-X$ -heterocyclyl-Y- $C_{2-6}$  cycloalkyl,  $-X$ -heterocyclyl-Y-aryl,  $-X$ -heterocyclyl-Y-heteroaryl,  $-X$ -heterocyclyl-Y-heterocyclyl; and
- 10 Y represents a bond,  $C_{1-6}$  alkyl, CO, O or  $SO_2$ ; and
- $R^4$ ,  $R^5$  and  $R^6$  independently represent hydrogen,  $C_{1-6}$  alkyl,  $-C_{2-6}$  cycloalkyl, aryl, heterocyclyl or heteroaryl or  $-NR^4R^5$  may represent a nitrogen containing heterocyclyl group.

- 15 A specific set of compounds of formula (I) which may be mentioned are those wherein  $R^2$  represents  $-X$ -heterocyclyl,  $-X$ -heterocyclyl-Y- $C_{2-6}$  cycloalkyl,  $-X$ -heterocyclyl-Y-aryl,  $-X$ -heterocyclyl-Y-heteroaryl or  $-X$ -heterocyclyl-Y-heterocyclyl and said heterocyclyl groups are attached to X via a carbon atom.

- 20 Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably  $C_{1-4}$  alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

- 25 References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) or carbocyclic benzofused rings (eg.  $C_{2-6}$  cycloalkyl fused to a phenyl ring, such as dihydroindenyl or tetrahydronaphthalenyl).

- 30 The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered saturated or partially unsaturated aliphatic ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydropyranyl, diazepanyl, azepanyl, imidazolidinyl, isothiazolidinyl, oxazolidinyl, pyrrolidinone and tetrahydro-oxazepinyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, benzodioxolyl, dihydroisoindole, dihydrobenzofuranyl, dihydrobenzothiohydropyranyl and dihydroisoquinolinyl.

- 40 The term "nitrogen containing heterocyclyl" is intended to represent any heterocyclyl group as defined above which contains a nitrogen atom.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl and tetrahydropyranyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinoxalinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, furopyridinyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, R<sup>1</sup> represents unsubstituted -C<sub>3-7</sub> cycloalkyl (eg. cyclobutyl, cyclopentyl or cyclohexyl). Also preferably, R<sup>1</sup> represents -C<sub>2-7</sub> cycloalkyl (eg. cyclopentyl) substituted by a C<sub>1-3</sub> alkyl (eg. methyl) group.

Most preferably, R<sup>1</sup> represents unsubstituted cyclobutyl or cyclopentyl, especially unsubstituted cyclobutyl.

Preferably, R<sup>2</sup> represents hydrogen;  
-C<sub>1-4</sub> alkyl (eg. methyl or propyl) optionally substituted by a -CO<sub>2</sub>R<sup>4</sup> or -CONR<sup>5</sup>R<sup>6</sup> group;  
-X-C<sub>2-6</sub> cycloalkyl-Y-heterocyclyl (eg. -X-cyclohexyl-Y-morpholinyl);  
-X-aryl (eg. -X-phenyl) optionally substituted by one or two halogen (eg. fluorine, iodine or chlorine), C<sub>1-4</sub> alkyl (eg. methyl), C<sub>1-4</sub> alkoxy (eg. methoxy), -CO<sub>2</sub>R<sup>4</sup>, -CONR<sup>5</sup>R<sup>6</sup>, -NR<sup>5</sup>COR<sup>6</sup>, -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup> or cyano groups;  
-X-aryl-Y-heterocyclyl (eg. -X-phenyl-Y-piperazinyl, -X-phenyl-Y-pyrrolidinyl or -X-phenyl-Y-morpholinyl) optionally substituted by one or two =O, halogen (eg. fluorine) or R<sup>4</sup> groups;  
-X-heteroaryl (eg. -X-pyridinyl, -X-pyrazinyl, -X-pyrimidinyl, -X-pyridazinyl, -X-quinolinyl, -X-pyrrolopyridinyl, -X-furopyridinyl, -X-naphthyridinyl, -X-thiazolyl or -X-thienyl) optionally substituted by one or two halogen (eg. bromine or iodine), C<sub>1-4</sub> alkyl (eg. methyl), C<sub>1-4</sub> alkoxy (eg. methoxy or ethoxy), cyano, nitro, -OR<sup>4</sup>, -COR<sup>4</sup>, -CO<sub>2</sub>R<sup>4</sup>, -NR<sup>5</sup>R<sup>6</sup>, -NR<sup>5</sup>COR<sup>6</sup>, -CONR<sup>5</sup>R<sup>6</sup> or =O groups;  
-X-heteroaryl-Y-aryl (eg. -X-pyrazinyl-Y-phenyl) optionally substituted by a C<sub>1-4</sub> alkylsulfonyl (eg. -SO<sub>2</sub>Me) or -NR<sup>5</sup>COR<sup>6</sup> group;  
-X-heteroaryl-Y-heteroaryl (eg. -X-pyridinyl-Y-pyrazolyl, -X-pyridinyl-Y-oxadiazolyl, -X-pyridinyl-Y-oxazolyl or -X-pyridinyl-Y-pyrazinyl) optionally substituted by a C<sub>1-4</sub> alkyl (eg. methyl) group;  
-X-heteroaryl-Y-heterocyclyl (eg. -X-pyridinyl-Y-morpholinyl, -X-pyridinyl-Y-pyrrolidinyl, -X-pyridinyl-Y-piperidinyl, -X-pyridinyl-Y-thiomorpholinyl, -X-pyridinyl-Y-

tetrahydropyranyl, -X-pyridinyl-Y-imidazolidinyl, -X-pyridinyl-Y-tetrahydro-oxazepinyl, -X-pyridinyl-Y-azetidyl, -X-pyridinyl-Y-oxazolidinyl, -X-pyridinyl-Y-isothiazolidinyl, -X-pyrazinyl-Y-morpholinyl, -X-pyrazinyl-Y-piperidinyl, -X-pyrazinyl-Y-pyrrolidinyl, -X-pyrazinyl-Y-thiomorpholinyl, -X-pyrazinyl-Y-oxazolidinyl, -X-pyrazinyl-Y-azetidyl, -X-pyrazinyl-Y-tetrahydropyranyl or -X-pyridazinyl-Y-morpholinyl) optionally substituted by one or two =O, C<sub>1-4</sub> alkyl (eg. methyl), -OR<sup>4</sup> or halogen (eg. chlorine or bromine) groups;

-X-heterocyclyl (eg. -X-piperidinyl or -X-pyrrolidinyl) optionally substituted by a C<sub>1-4</sub> alkylsulfonyl (eg. -SO<sub>2</sub>Me), C<sub>1-4</sub> alkoxy carbonyl (eg. -CO-CH<sub>2</sub>CH<sub>2</sub>OMe), -CO<sub>2</sub>R<sup>4</sup>, -COR<sup>4</sup> or -COR<sup>5</sup>R<sup>6</sup> group;

-X-heterocyclyl-Y-aryl (eg. -X-piperidinyl-Y-phenyl or -X-pyrrolidinyl-Y-phenyl) optionally substituted by a halogen (eg. fluorine), cyano, C<sub>1-4</sub> alkylsulfonyl (eg. -SO<sub>2</sub>Me), R<sup>4</sup> or -CONR<sup>5</sup>R<sup>6</sup> group;

-X-heterocyclyl-Y-heterocyclyl (eg. -X-piperidinyl-Y-tetrahydropyranyl, -X-pyrrolidinyl-Y-tetrahydropyranyl, -X-piperidinyl-Y-dihydrobenzofuranyl, -X-pyrrolidinyl-Y-morpholinyl, -X-piperidinyl-Y-morpholinyl, -X-piperidinyl-Y-thiomorpholinyl, -X-piperidinyl-Y-dihydroisindole, -X-piperidinyl-Y-piperazinyl, -X-piperidinyl-Y-pyrrolidinyl, -X-piperidinyl-Y-piperidinyl or -X-piperidinyl-Y-dihydrobenzothienopyranyl) optionally substituted by one or two =O or R<sup>4</sup> groups;

-X-heterocyclyl-Y-C<sub>3-6</sub> cycloalkyl (eg. -X-piperidinyl-Y-cyclohexyl, -X-piperidinyl-Y-cyclopropyl, -X-piperidinyl-Y-cyclobutyl or -X-piperidinyl-Y-cyclopentyl); or

-X-heterocyclyl-Y-heteroaryl (eg. -X-piperidinyl-Y-isoquinolinyl, -X-piperidinyl-Y-quinolinyl, -X-piperidinyl-Y-isoxazolyl, -X-piperidinyl-Y-benzothiazolyl, -X-piperidinyl-Y-thiophenyl, -X-piperidinyl-Y-furanyl, -X-piperidinyl-Y-pyrazinyl, -X-piperidinyl-Y-pyridyl) optionally substituted by one or two C<sub>1-4</sub> alkyl (eg. methyl), =O, cyano or -CONR<sup>5</sup>R<sup>6</sup> groups.

Preferably, X represents a bond or -CH<sub>2</sub>-, most preferably X represents a bond.

Preferably, Y represents a bond, CO, SO<sub>2</sub> or -CO-CH=CH- most preferably Y represents a bond or CO, especially a bond.

Preferably, R<sup>4</sup> represents hydrogen, C<sub>1-4</sub> alkyl (eg. methyl, ethyl or t-butyl), -C<sub>1-4</sub> alkyl-C<sub>3-6</sub> cycloalkyl (eg. -CH<sub>2</sub>-cyclopropyl), aryl (eg. phenyl optionally substituted by a halogen atom (eg. fluorine), heterocyclyl (eg. morpholinyl) or heteroaryl (eg. pyridinyl or pyrazinyl) optionally substituted by a halogen (eg. fluorine) or C<sub>1-4</sub> alkoxy (eg. methoxy) group.

Preferably, R<sup>5</sup> and R<sup>6</sup> independently represent hydrogen, C<sub>1-4</sub> alkyl (eg. methyl, ethyl, isopropyl or propyl), -C<sub>3-6</sub> cycloalkyl (eg. cyclobutyl or cyclopentyl), -C<sub>1-4</sub> alkyl-C<sub>3-6</sub> cycloalkyl (eg. -CH<sub>2</sub>-cyclopropyl), heterocyclyl (eg. pyrrolidinyl, piperidinyl, morpholinyl or tetrahydropyranyl) or aryl (eg. phenyl) optionally substituted by a halogen (eg. fluorine), cyano or C<sub>1-4</sub> alkoxy (eg. methoxy) group or -NR<sup>5</sup>R<sup>6</sup> represents a nitrogen containing heterocyclyl group (eg. azetidyl, morpholinyl, pyrrolidinyl or piperidinyl) optionally substituted by one or two =O groups.

More preferably, R<sup>5</sup> and R<sup>6</sup> independently represent hydrogen, C<sub>1-6</sub> alkyl (eg. methyl or ethyl), -C<sub>3-6</sub> cycloalkyl (eg. cyclobutyl or cyclopentyl) or -C<sub>1-6</sub> alkyl-C<sub>3-6</sub> cycloalkyl (eg. -CH<sub>2</sub>-cyclopropyl).

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Particularly preferably, R<sup>2</sup> represents

hydrogen;

-C<sub>1-6</sub> alkyl (eg. methyl or propyl) optionally substituted by a -CO<sub>2</sub>R<sup>4</sup> (eg. -CO<sub>2</sub>Et or -CO<sub>2</sub>H) or -CONR<sup>5</sup>R<sup>6</sup> (eg. -CON(Me)<sub>2</sub>, -CON(H)(Me), -CON(H)(cyclopentyl), -

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CON(H)(phenyl), -CO-pyrrolidinyl, -CO-piperidinyl or -CO-morpholinyl) group;

-X-C<sub>3-6</sub> cycloalkyl-Y-heterocyclyl (eg. -cyclohexyl-CO-morpholinyl);

-X-aryl (eg. -phenyl or -CH<sub>2</sub>-phenyl) optionally substituted by one or two halogen (eg. fluorine, iodine or chlorine), C<sub>1-6</sub> alkyl (eg. methyl), C<sub>1-6</sub> alkoxy (eg. methoxy), -CO<sub>2</sub>R<sup>4</sup> (eg. -CO<sub>2</sub>H or -CO<sub>2</sub>Me), -CONR<sup>5</sup>R<sup>6</sup> (eg. -CON(H)(Me), -CON(Et)<sub>2</sub> (optionally substituted

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by a methoxy group), -CON(Me)(Pr) substituted by a cyano group) or -CON(H)(-CH<sub>2</sub>-cyclopropyl), -NR<sup>5</sup>COR<sup>6</sup> (eg. -NHCOMe), -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup> (eg. -SO<sub>2</sub>N(Et)<sub>2</sub>) or cyano groups;

-X-aryl-Y-heterocyclyl (eg. -phenyl-pyrrolidinyl, -phenyl-CO-pyrrolidinyl, -phenyl-CO-morpholinyl, -phenyl-SO<sub>2</sub>-morpholinyl, -CH<sub>2</sub>-phenyl-CO-pyrrolidinyl, -CH<sub>2</sub>-phenyl-CO-

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morpholinyl or -CH<sub>2</sub>-phenyl-CO-piperazinyl) optionally substituted by one or two =O, halogen (eg. fluorine) or R<sup>4</sup> (eg. phenyl (optionally substituted by a fluorine atom) or pyridyl) groups;

-X-heteroaryl (eg. -pyridinyl, -CH<sub>2</sub>-pyridinyl, -pyrazinyl, -pyrimidinyl, -pyridazinyl, -quinolinyl, -CH<sub>2</sub>-quinolinyl, -pyrrolopyridinyl, -furopyridinyl, -naphthyridinyl, -thiazolyl or -

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thienyl) optionally substituted by one or two halogen (eg. bromine or iodine), C<sub>1-6</sub> alkyl (eg. methyl), C<sub>1-6</sub> alkoxy (eg. methoxy or ethoxy), cyano, nitro, -OR<sup>4</sup> (eg. hydroxy), -CO<sub>2</sub>R<sup>4</sup> (eg. CO<sub>2</sub>H or CO<sub>2</sub>Me), -COR<sup>4</sup> (eg. COMe), -NR<sup>5</sup>R<sup>6</sup> (eg. -NH<sub>2</sub> or -N(H)(Me)), -NR<sup>5</sup>COR<sup>6</sup> (eg.

NHCOMe, NHCO-i-Pr, -NHCO-pyrrolidinyl, -NHCO-piperidinyl, -NHCO-morpholinyl or -NHCO-tetrahydropyranyl), -CONR<sup>5</sup>R<sup>6</sup> (eg. -CONH<sub>2</sub>, -CON(Me)<sub>2</sub>, -CON(Me)(Et), -

CON(H)(Me), -CON(H)(i-Pr), -CON(Et)<sub>2</sub> (optionally substituted by a methoxy group), -

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CON(H)(Et) (optionally substituted by a methoxy group), -CON(H)(-CH<sub>2</sub>-cyclopropyl), -CON(H)(cyclobutyl), -CON(H)(cyclopentyl), -CON(H)(cyclopropyl) or -

CON(H)(tetrahydropyranyl) or =O groups;

-X-heteroaryl-Y-aryl (eg. -pyrazinyl-phenyl) optionally substituted by a C<sub>1-6</sub> alkylsulfonyl (eg. -SO<sub>2</sub>Me) or -NR<sup>5</sup>COR<sup>6</sup> (eg. -NHCOMe) group;

35  
-X-heteroaryl-Y-heteroaryl (eg. -pyridinyl-pyrazolyl, -pyridinyl-oxadiazolyl, -pyridinyl-oxazolyl or -pyridinyl-pyrazinyl) optionally substituted by a C<sub>1-6</sub> alkyl (eg. methyl) group;

-X-heteroaryl-Y-heterocyclyl (eg. -pyridinyl-CO-morpholinyl, -pyridinyl-CO-pyrrolidinyl, -pyridinyl-CO-piperidinyl, -pyridinyl-CO-thiomorpholinyl, -pyridinyl-

imidazolidinyl, -pyridinyl-CO-tetrahydro-oxazepinyl, -pyridinyl-CO-azetidyl, -pyridinyl-

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oxazolidinyl, -pyridinyl-isothiazolidinyl, -pyrazinyl-morpholinyl, -pyrazinyl-CO-morpholinyl, -pyrazinyl-CO-piperidinyl, -pyrazinyl-CO-pyrrolidinyl, -pyrazinyl-thiomorpholinyl, -pyrazinyl-

oxazolidinyl, -pyrazinyl-CO-azetidyl, -pyrazinyl-piperidinyl, -pyrazinyl-pyrrolidinyl, -

pyridinyl-pyrrolidinyl, -pyridinyl-piperidinyl, -pyridinyl-SO<sub>2</sub>-morpholinyl or -pyridazinyl-CO-morpholinyl) optionally substituted by one or two =O, C<sub>1-4</sub> alkyl (eg. methyl), -OR<sup>4</sup> (eg. hydroxy) or halogen (eg. chlorine or bromine) groups;

5 -X-heterocyclyl (eg. -piperidinyl, -CH<sub>2</sub>-piperidinyl, -pyrrolidinyl or -CH<sub>2</sub>-pyrrolidinyl) optionally substituted by a C<sub>1-4</sub> alkylsulfonyl (eg. -SO<sub>2</sub>Me), C<sub>1-4</sub> alkoxy carbonyl (eg. -CO-CH<sub>2</sub>CH<sub>2</sub>OMe), -CO<sub>2</sub>R<sup>4</sup> (eg. -CO<sub>2</sub>-t-Bu) -COR<sup>4</sup> (eg. -COCH<sub>2</sub>cyclopropyl) or -COR<sup>5</sup>R<sup>6</sup> (eg. -CON(i-Pr)<sub>2</sub>, -CON(Et)<sub>2</sub>, -CON(i-Pr)(Et) (substituted by a methoxy group), -CON(H)(i-Pr) or -CON(H)(4-fluorophenyl) group;

10 -X-heterocyclyl-Y-aryl (eg. -piperidinyl-CO-phenyl, -pyrrolidinyl-CO-phenyl, -piperidinyl-CO-CH=CH-phenyl, -piperidinyl-SO<sub>2</sub>-phenyl, -pyrrolidinyl-SO<sub>2</sub>-phenyl, -CH<sub>2</sub>-piperidinyl-CO-phenyl, -CH<sub>2</sub>-pyrrolidinyl-CO-phenyl, -CH<sub>2</sub>-piperidinyl-SO<sub>2</sub>-phenyl or -CH<sub>2</sub>-pyrrolidinyl-SO<sub>2</sub>-phenyl) optionally substituted by a halogen (eg. fluorine), cyano, C<sub>1-4</sub> alkylsulfonyl (eg. -SO<sub>2</sub>Me), R<sup>4</sup> (eg. phenyl or morpholinyl) or -CONR<sup>5</sup>R<sup>6</sup> (eg. -CO-pyrrolidinyl substituted by an =O group) group;

15 -X-heterocyclyl-Y-heterocyclyl (eg. -piperidinyl-CO-tetrahydropyranyl, -CH<sub>2</sub>-piperidinyl-CO-tetrahydropyranyl, -pyrrolidinyl-CO-tetrahydropyranyl, -CH<sub>2</sub>-pyrrolidinyl-CO-tetrahydropyranyl, -piperidinyl-CO-dihydrobenzofuranyl, -pyrrolidinyl-CO-morpholinyl, -CH<sub>2</sub>-pyrrolidinyl-CO-morpholinyl, -piperidinyl-CO-morpholinyl, -CH<sub>2</sub>-piperidinyl-CO-morpholinyl, -piperidinyl-CO-thiomorpholinyl, -piperidinyl-CO-dihydroisindole, -piperidinyl-CO-piperazinyl, -piperidinyl-CO-pyrrolidinyl, -piperidinyl-CO-piperidinyl or -piperidinyl-CO-dihydrobenzothiolepyranyl) optionally substituted by one or two =O or R<sup>4</sup> (eg. pyrazinyl) groups;

-X-heterocyclyl-Y-C<sub>3-8</sub> cycloalkyl (eg. -piperidinyl-CO-cyclohexyl, -piperidinyl-CO-cyclopropyl, -piperidinyl-CO-cyclobutyl or -piperidinyl-CO-cyclopentyl); or

25 -X-heterocyclyl-Y-heteroaryl (eg. -piperidinyl-CO-isoquinolinyl, -piperidinyl-CO-quinolinyl, -piperidinyl-CO-isoxazolyl, -piperidinyl-SO<sub>2</sub>-isoxazolyl, -piperidinyl-CO-benzothiazolyl, -piperidinyl-CO-thiophenyl, -piperidinyl-CO-furanyl, -piperidinyl-CO-pyrazinyl, -piperidinyl-pyrazinyl, -piperidinyl-CO-pyridinyl or -piperidinyl-pyridinyl) optionally substituted by one or two C<sub>1-4</sub> alkyl (eg. methyl), =O, cyano or -CONR<sup>5</sup>R<sup>6</sup> (eg. -CON(H)(Me), -CON(H)(-CH<sub>2</sub>cyclopropyl), -CO-azetidyl or -CO-morpholinyl) groups.

More preferably, R<sup>2</sup> represents

-X-aryl (eg. phenyl) optionally substituted by a CONR<sup>5</sup>R<sup>6</sup> group;

35 -X-aryl-Y-heterocyclyl (eg. -X-phenyl-Y-morpholinyl or -X-phenyl-Y-pyrrolidinyl);

-X-heteroaryl (eg. pyrazinyl or pyridinyl) optionally substituted by a CONR<sup>5</sup>R<sup>6</sup> group;

-X-heteroaryl-Y-heterocyclyl (eg. -X-pyridinyl-Y-morpholinyl, -X-pyridinyl-Y-pyrrolidinyl, -X-pyridinyl-Y-piperidinyl, -X-pyridinyl-Y-thiomorpholinyl, -X-pyrazinyl-Y-morpholinyl, -X-pyrazinyl-Y-piperidinyl or -X-pyrazinyl-Y-pyrrolidinyl) optionally substituted by one or two =O groups; or

40 -X-heterocyclyl-Y-heterocyclyl (eg. -X-piperidinyl-Y-tetrahydropyranyl, -X-piperidinyl-Y-morpholinyl or -X-pyrrolidinyl-Y-morpholinyl).

Yet more preferably,  $R^2$  represents

- X-aryl (eg. -phenyl or -CH<sub>2</sub>-phenyl) optionally substituted by one or two halogen (eg. fluorine, iodine or chlorine), C<sub>1-6</sub> alkyl (eg. methyl), C<sub>1-6</sub> alkoxy (eg. methoxy), -CO<sub>2</sub>R<sup>4</sup> (eg. -CO<sub>2</sub>H or -CO<sub>2</sub>Me), -CONR<sup>5</sup>R<sup>6</sup> (eg. -CON(H)(Me), -CON(Et)<sub>2</sub> (optionally substituted by a methoxy group), -CON(Me)(Et) substituted by a cyano group) or -CON(H)(-CH<sub>2</sub>-cyclopropyl), -NR<sup>5</sup>COR<sup>6</sup> (eg. -NHCOMe), -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup> (eg. -SO<sub>2</sub>N(Et)<sub>2</sub>) or cyano groups;
- X-aryl-Y-heterocyclyl (eg. -phenyl-pyrrolidinyl, -phenyl-CO-pyrrolidinyl, -phenyl-CO-morpholinyl, -phenyl-SO<sub>2</sub>-morpholinyl, -CH<sub>2</sub>-phenyl-CO-pyrrolidinyl, -CH<sub>2</sub>-phenyl-CO-morpholinyl or -CH<sub>2</sub>-phenyl-CO-piperazinyl) optionally substituted by one or two =O, halogen (eg. fluorine) or R<sup>4</sup> (eg. phenyl (optionally substituted by a fluorine atom) or pyridyl) groups;
- X-heteroaryl (eg. -pyridinyl, -CH<sub>2</sub>-pyridinyl, -pyrazinyl, -pyrimidinyl, -pyridazinyl, -quinolinyl, -CH<sub>2</sub>-quinolinyl, -pyrrolopyridinyl, -furopyridinyl, -naphthyridinyl, -thiazolyl or -thienyl) optionally substituted by one or two halogen (eg. bromine or iodine), C<sub>1-6</sub> alkyl (eg. methyl), C<sub>1-6</sub> alkoxy (eg. methoxy or ethoxy), cyano, nitro, -OR<sup>4</sup> (eg. hydroxy), -CO<sub>2</sub>R<sup>4</sup> (eg. CO<sub>2</sub>H or CO<sub>2</sub>Me), -COR<sup>4</sup> (eg. COMe), -NR<sup>5</sup>R<sup>6</sup> (eg. -NH<sub>2</sub> or -N(H)(Me)), -NR<sup>5</sup>COR<sup>6</sup> (eg. NHCOMe, NHCO-iPr, -NHCO-pyrrolidinyl, -NHCO-piperidinyl, -NHCO-morpholinyl or -NHCO-tetrahydropyranyl), -CONR<sup>5</sup>R<sup>6</sup> (eg. -CONH<sub>2</sub>, -CON(Me)<sub>2</sub>, -CON(Me)(Et), -CON(H)(Me), -CON(H)(iPr), -CON(Et)<sub>2</sub> (optionally substituted by a methoxy group), -CON(H)(Et) (optionally substituted by a methoxy group), -CON(H)(-CH<sub>2</sub>-cyclopropyl), -CON(H)(cyclobutyl), -CON(H)(cyclopentyl), -CON(H)(cyclopropyl) or -CON(H)(tetrahydropyranyl)) or =O groups;
- X-heteroaryl-Y-heterocyclyl (eg. -pyridinyl-CO-morpholinyl, -pyridinyl-CO-pyrrolidinyl, -pyridinyl-CO-piperidinyl, -pyridinyl-CO-thiomorpholinyl, -pyridinyl-imidazolidinyl, -pyridinyl-CO-tetrahydro-oxazepinyl, -pyridinyl-CO-azetidyl, -pyridinyl-oxazolidinyl, -pyridinyl-isothiazolidinyl, -pyrazinyl-morpholinyl, -pyrazinyl-CO-morpholinyl, -pyrazinyl-CO-piperidinyl, -pyrazinyl-CO-pyrrolidinyl, -pyrazinyl-thiomorpholinyl, -pyrazinyl-oxazolidinyl, -pyrazinyl-CO-azetidyl, -pyrazinyl-piperidinyl, -pyrazinyl-pyrrolidinyl, -pyridinyl-pyrrolidinyl, -pyridinyl-piperidinyl, -pyridinyl-SO<sub>2</sub>-morpholinyl or -pyridazinyl-CO-morpholinyl) optionally substituted by one or two =O, C<sub>1-6</sub> alkyl (eg. methyl), -OR<sup>4</sup> (eg. hydroxy) or halogen (eg. chlorine or bromine) groups; or
- X-heterocyclyl-Y-heterocyclyl (eg. -piperidinyl-CO-tetrahydropyranyl, -CH<sub>2</sub>-piperidinyl-CO-tetrahydropyranyl, -pyrrolidinyl-CO-tetrahydropyranyl, -CH<sub>2</sub>-pyrrolidinyl-CO-tetrahydropyranyl, -piperidinyl-CO-dihydrobenzofuranyl, -pyrrolidinyl-CO-morpholinyl, -CH<sub>2</sub>-pyrrolidinyl-CO-morpholinyl, -piperidinyl-CO-morpholinyl, -CH<sub>2</sub>-piperidinyl-CO-morpholinyl, -piperidinyl-CO-thiomorpholinyl, -piperidinyl-CO-dihydroisindole, -piperidinyl-CO-piperazinyl, -piperidinyl-CO-pyrrolidinyl, -piperidinyl-CO-piperidinyl or -piperidinyl-CO-dihydrobenzothiohydropyranyl) optionally substituted by one or two =O or R<sup>4</sup> (eg. pyrazinyl) groups.

Most preferably,  $R^2$  represents

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-X-aryl (eg. -phenyl) optionally substituted by one or two halogen (eg. fluorine), C<sub>1-6</sub> alkoxy (eg. methoxy), -CONR<sup>5</sup>R<sup>6</sup> (eg. -CON(H)(Me)), -NR<sup>5</sup>COR<sup>6</sup> (eg. -NHCOMe) or cyano groups;

- 5 -X-aryl-Y-heterocyclyl (eg. -phenyl-pyrrolidinyl) optionally substituted by one or two =O or halogen (eg. fluorine) groups;  
 unsubstituted -X-heterocyclyl-Y-heterocyclyl (eg. -piperidinyl-CO-morpholinyl);  
 -X-heteroaryl (eg. -2-pyridinyl or -2-pyrazinyl) optionally substituted by a -CONR<sup>5</sup>R<sup>6</sup> (eg. CON(H)(Me)) group; or  
 10 -X-heteroaryl-Y-heterocyclyl (eg. -2-pyridinyl-N-pyrrolidinyl) wherein said heterocyclyl group is optionally substituted by an =O group (eg. -2-pyridinyl-N-pyrrolidinone).

Especially preferably, R<sup>2</sup> represents -X-heteroaryl (eg. -2-pyridinyl) substituted by a -CONR<sup>5</sup>R<sup>6</sup> group (eg. 4-methylaminocarbonylpyridin-2-yl).

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Preferably, n represents 0 or 1, more preferably 0.

When n represents 1, R<sup>3</sup> is preferably a halogen (eg. iodine) atom or a cyano group.

- 20 Preferred compounds according to the invention include examples E1-E288 as shown below, or a pharmaceutically acceptable salt thereof.

More preferred compounds according to the invention include:

- 25 5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrazine-2-carboxylic acid methyl amide; and  
 1-(6-((3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy)-3-pyridinyl)-2-pyrrolidinone  
 or a pharmaceutically acceptable salt thereof.

- 30 An especially preferred compound according to the invention is 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-methyl-nicotinamide  
 or a pharmaceutically acceptable salt thereof.

- 35 Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of compounds of formula (I) therefore form an aspect of the invention.

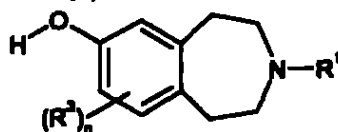
- 40 Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these

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compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

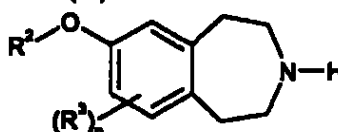
(a) reacting a compound of formula (II)



(II)

10 wherein  $R^1$ ,  $R^3$  and  $n$  are as defined above, with a compound of formula  $R^2-L^1$ , wherein  $R^2$  is as defined above for  $R^2$  or a group convertible thereto and  $L^1$  represents a suitable leaving group such as a halogen atom (eg. bromine or iodine) or an optionally activated hydroxyl group;

15 (b) reacting a compound of formula (III)



(III)

20 wherein  $R^2$ ,  $R^3$  and  $n$  are as defined above, with a compound of formula  $R^1-L^2$ , wherein  $R^1$  is as defined above for  $R^1$  or a group convertible thereto and  $L^2$  represents a suitable leaving group such as a halogen atom (eg. bromine, iodine or tosylate); or

(c) reacting a compound of formula (III) as defined above, with a ketone of formula  $R^1=O$ , wherein  $R^1$  is as defined above for  $R^1$  or a group convertible thereto; or

25 (d) deprotecting a compound of formula (I) which is protected; and

(e) interconversion to other compounds of formula (I).

30 When the leaving group  $L^1$  is attached to an  $sp^3$  hybridised carbon, for example,  $R^2-L^1$  is an alkyl halide, process (a) typically comprises the use of a suitable base, such as potassium carbonate in an appropriate solvent such as 2-butanone optionally in the presence of a catalyst such as potassium iodide at an appropriate temperature such as reflux.

35 When the leaving group  $L^1$  is attached to an  $sp^2$  hybridised carbon, for example,  $R^2-L^1$  is an aryl halide, process (a) typically comprises the use of a copper(I) salt, such as copper (I) iodide. In the presence of a base such as sodium hydride, in an appropriate solvent such as pyridine, at an appropriate temperature such as reflux.

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When the leaving group  $L^1$  is attached to an activated  $sp^2$  hybridised carbon for example,  $R^2-L^1$  is a heteroaryl halide such as a 2-chloropyridine or 2-chloropyrazine, process (a) typically comprises the use of a suitable base, such as sodium hydride in an appropriate solvent such as dimethylformamide or dimethyl sulfoxide, at an appropriate temperature. Alternatively, potassium tert-butoxide in tert-butanol at an appropriate temperature may also be employed.

When the leaving group  $L^1$  is attached to an activated  $sp^2$  hybridised carbon, for example  $R^2-L^1$  is an aryl halide such as 3,4-difluorobenzonitrile, process (a) typically comprises the use of a suitable base, potassium carbonate, in a suitable solvent, such as dimethyl sulfoxide, at a suitable temperature.

When  $L^1$  is a hydroxyl group attached to an  $sp^3$  hybridised carbon, for example,  $R^2-L^1$  is an alcohol, process (a) typically comprises the use of a phosphine such as triphenylphosphine in a suitable solvent such as tetrahydrofuran, followed by addition of an azodicarboxylate such as diethylazodicarboxylate at a suitable temperature such as room temperature.

Process (b) typically comprises the use of a suitable base, such as potassium carbonate in an appropriate solvent such as 2-butanone optionally in the presence of a catalyst such as potassium iodide at an appropriate temperature such as reflux.

Process (c) typically comprises the use of reductive conditions (such as treatment with a borohydride e.g. sodium triacetoxyborohydride), optionally in the presence of an acid, such as acetic acid, in an appropriate solvent such as dichloromethane at a suitable temperature such as room temperature.

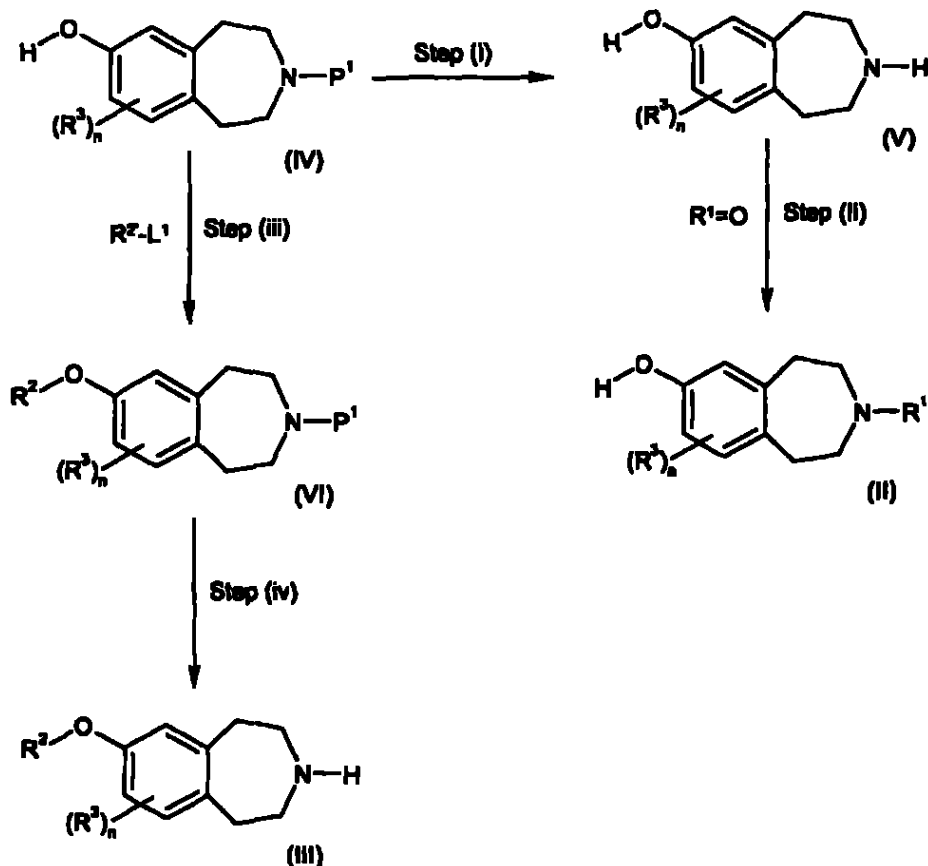
In process (d), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-COCF<sub>3</sub>) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (e) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis, amide bond formation or transition metal mediated coupling

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- reactions. Examples of transition metal mediated coupling reactions useful as interconversion procedures include the following: Palladium catalysed coupling reactions between organic electrophiles, such as aryl halides, and organometallic reagents, for example boronic acids (Suzuki cross-coupling reactions); Palladium catalysed amination and amidation reactions between organic electrophiles, such as aryl halides, and nucleophiles, such as amines and amides; Copper catalysed amidation reactions between organic electrophiles (such as aryl halides) and nucleophiles such as amides; and Copper mediated coupling reactions between phenols and boronic acids.

- 10 Compounds of formula (II) and (III) may be prepared in accordance with the following scheme



- 15 wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $n$  and  $L^1$  are as defined above and  $P^1$  represents a suitable protecting group such as Boc.

- 20 Step (i) typically comprises a deprotection reaction, for example, when  $P^1$  represents Boc the deprotection reaction comprises reaction of a compound of formula (IV) with an acid, for example hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane.

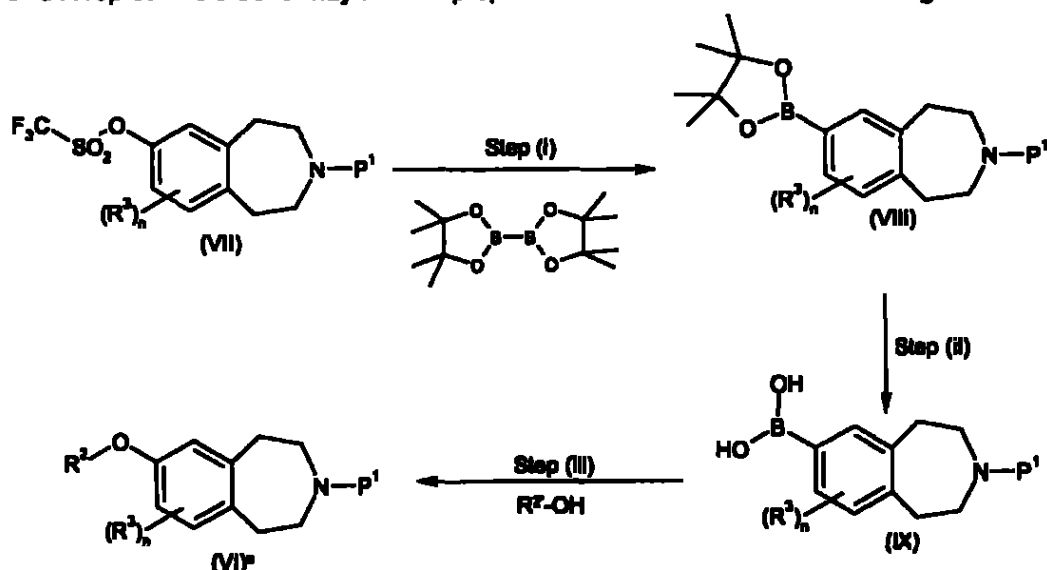
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Step (ii) may be performed under reducing conditions in an analogous manner to that described for process (c).

- 5 Step (iii) may be performed in an analogous manner to that described for process (a).

Step (iv) typically comprises a deprotection reaction to provide a compound of formula (III) and can be performed as described in step (i).

- 10 Compounds of formula (VI) wherein  $R^2$  represents -X-aryl, -X-heteroaryl, -X-aryl-Y-C<sub>3-6</sub> cycloalkyl, -X-aryl-Y-aryl, -X-aryl-Y-heteroaryl, -X-aryl-Y-heterocyclyl, -X-heteroaryl-Y-C<sub>3-6</sub> cycloalkyl, -X-heteroaryl-Y-aryl, -X-heteroaryl-Y-heteroaryl or -X-heteroaryl-Y-heterocyclyl and X represents a bond may also be prepared in accordance with the following scheme



- 15 wherein  $R^2$ ,  $R^3$ ,  $R^3$  and  $n$  are as defined above and  $P^1$  represents a suitable protecting group such as Boc.

- 20 Step (i) may be performed under palladium catalysed cross-coupling conditions, for example using bis(diphenylphosphino)ferrocenedichloropalladium (II) complex and 1,1'-bis(diphenylphosphino)ferrocene as the catalyst system, in combination with a suitable base, such as potassium acetate, in a suitable solvent, for example dioxane, at a suitable temperature, for example reflux.

- 25 Step (ii) may be performed under oxidising conditions, for example using sodium periodate in the presence of ammonium acetate, in a suitable solvent system, such as acetone and water, at a suitable temperature, for example room temperature.

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Step (iii) may be performed in the presence of a copper salt, for example copper acetate, in combination with a suitable base, such as triethylamine, together with molecular sieves, in a suitable solvent, for example dichloromethane, at a suitable temperature, for example room temperature.

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Compounds of formula (IV) may be prepared in an analogous manner to those described in Description 3 of WO 02/40471.

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Compounds of formula (VII) may be prepared as outlined in Bioorg.Med.Chem.Lett.; 10; 22; 2000; 2553-2556.

15

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, neuropathic pain, inflammatory pain, migraine, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia (particularly cognitive deficit of schizophrenia), attention deficit hyperactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

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Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

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The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

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In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

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When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula

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(I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

5 The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

10 Compounds of formula (I) may be used in combination with other therapeutic agents, for example histamine H1 antagonists or medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as 5-HT<sub>2</sub> antagonists, M1 muscarinic agonists, M2 muscarinic antagonists or acetylcholinesterase inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or  
15 simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

20 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such  
25 combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state  
30 the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral,  
35 parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

40 Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants

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and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

5 Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

10 For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for  
15 Injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the  
20 vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

25 The composition may contain from 0.1% to 99% by weight, preferably from 10 to 80% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably  
30 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

35 **Description 1**

**7-Benzoyloxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid tert-butyl ester (D1)**

40 7-Hydroxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid tert-butyl ester (PCT Int. Appl. (2002), WO 02/40471) (780mg, 3mmol), potassium carbonate (1.24g, 9mmol) and catalytic potassium iodide were suspended in 2-butanone (20ml). Benzyl bromide (538µL, 4.5mmol) was added and the mixture heated at reflux for 24 hours. The solids were filtered

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and then washed with acetone. The filtrate was concentrated *in vacuo* and the crude oil purified by column chromatography, eluting with a mixture of ethyl acetate and hexane (1:4) to afford the title compound (D1) (1.06g, 100%), <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.44 (5H, m), 7.03 (1H, d, J 8.1Hz), 6.77 (1H, s), 6.74 (1H, dd, J 8.1 & 2.4 Hz), 3.49 (4H, m), 2.84 (4H, m), 1.48 (9H, s).

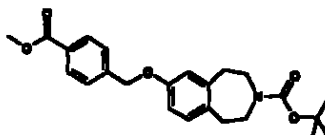
#### Description 2

##### 7-Benzyloxy-1,2,4,5-tetrahydro-benzo[d]azepine (D2)

7-Benzyloxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D1) (1.06g, 3mmol) was dissolved in dichloromethane (15ml) and treated with trifluoroacetic acid (15ml). The solution was stirred at room temperature for 2 hours, concentrated *in vacuo* and then twice co-evaporating with dichloromethane. The residue was dissolved in methanol and applied to a SCX ion exchange column (Varian bond-elute, 10g) and washed with methanol and then a mixture of 0.880 ammonia/ methanol. The combined basic fractions were reduced *in vacuo* and the residue purified by column chromatography, eluting with a mixture of 0.880 ammonia:ethanol: dichloromethane (1:9:90) to afford the title compound (D2) (702mg, 93%), MS (ES+) *m/e* 254 [M+H]<sup>+</sup>.

#### Description 3

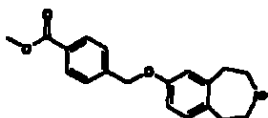
##### 7-(4-Methoxycarbonyl-benzyloxy)-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D3)



7-Hydroxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (WO 02/40471) (5.27 g, 20.0 mmol), potassium carbonate (8.30 g, 60.0 mmol) and catalytic potassium iodide were suspended in butanone (100 ml). Methyl 4-(bromomethyl) benzoate (5.5 g, 24.0 mmol) dissolved in butanone (50 ml) was added dropwise after which the reaction mixture was stirred at reflux for 24 hours. The reaction mixture was cooled, the solids were filtered and then washed with acetone. The filtrate was concentrated *in vacuo* and the crude mixture was purified by column chromatography eluting with a mixture of ethyl acetate:hexane (1:4) to afford the title compound (D3). MS (ES+) *m/e* 344 [(M+H) - CO<sub>2</sub>tBu]<sup>+</sup>.

#### Description 4

##### 4-(2,3,4,5-Tetrahydro-1H-benzo[d]azepin-7-yloxy-methyl)-benzoic acid methyl ester (D4)

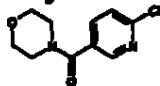


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7-(4-Methoxycarbonyl-benzyloxy)-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (D3) (8.35 g) was dissolved in dichloromethane (30 ml) and treated with trifluoroacetic acid (30 ml). The solution was stirred at room temperature for 2 hours, concentrated *in vacuo* and then twice co-evaporated with dichloromethane. The residue  
5 was dissolved in dichloromethane and washed with 10% aqueous sodium hydroxide, water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford the title compound (D4).

**Description 5**

10 1-(6-Chloro-pyridin-3-yl)-1-morpholin-4-yl-methanone (D5)



Morpholine (0.2 ml, 2.2 mmol) was added to stirred solution of 6-chloronicotinoyl chloride (250 mg, 1.4 mmol) in dichloromethane (10 ml). After 2 hours the reaction was allowed to cool and the crude mixture was applied to a SCX ion exchange cartridge (Varian bond-  
15 elute, 10 g) and washed with methanol. The methanolic fractions were concentrated *in vacuo* to afford the title compound (D5).

**Descriptions 6-31**

20 Descriptions 6-31 (D6-D31) were prepared and used without further characterisation using the method described for Description 5 (D5) from the appropriate aryl halide and amine indicated in the table:

| Description                                                 | Aryl Halide                     | Amine               |
|-------------------------------------------------------------|---------------------------------|---------------------|
| 1-(6-Chloro-pyridin-3-yl)-1-pyrrolidin-1-yl-methanone (D6)  | 6-Chloronicotinoyl chloride     | Pyrrolidine         |
| 6-Chloro-nicotinamide (D7)                                  | 6-Chloronicotinoyl chloride     | Ammonia             |
| 6-Chloro-N,N-dimethyl-nicotinamide (D8)                     | 6-Chloronicotinoyl chloride     | Dimethylamine       |
| 6-Chloro-N-ethyl-N-methyl-nicotinamide (D9)                 | 6-Chloronicotinoyl chloride     | N-Ethylmethyl-amine |
| 6-Chloro-N-methyl-nicotinamide (D10)                        | 6-Chloronicotinoyl chloride     | Methylamine         |
| 6-Chloro-N-cyclopentyl-nicotinamide (D11)                   | 6-Chloronicotinoyl chloride     | Cyclopentylamine    |
| 1-(6-Chloro-pyridin-3-yl)-1-piperidin-1-yl-methanone (D12)  | 6-Chloronicotinoyl chloride     | Piperidine          |
| 1-(2-Chloro-pyridin-4-yl)-1-piperidin-1-yl-methanone (D13)  | 2-Chloro-isonicotinoyl chloride | Piperidine          |
| 1-(2-Chloro-pyridin-4-yl)-1-pyrrolidin-1-yl-methanone (D14) | 2-Chloro-isonicotinoyl chloride | Pyrrolidine         |

|                                                                           |                                       |                             |
|---------------------------------------------------------------------------|---------------------------------------|-----------------------------|
| 1-(2-Chloro-pyridin-4-yl)-1-morpholin-4-yl-methanone (D15)                | 2-Chloro-isonicotinoyl chloride       | Morpholine                  |
| 1-(6-Chloro-pyridin-2-yl)-1-piperidin-1-yl-methanone (D16)                | 6-Chloro-pyridine-2-carbonyl chloride | Piperidine                  |
| 1-(6-Chloro-pyridin-2-yl)-1-(1,1-dioxothiomorpholin-4-yl)-methanone (D17) | 6-Chloro-pyridine-2-carbonyl chloride | Thiomorpholine 1,1-dioxide  |
| 1-(6-Chloro-pyridin-2-yl)-1-pyrrolidin-1-yl-methanone (D18)               | 6-Chloro-pyridine-2-carbonyl chloride | Pyrrolidine                 |
| 1-(6-Chloro-pyridin-2-yl)-1-morpholin-4-yl-methanone (D19)                | 6-Chloro-pyridine-2-carbonyl chloride | Morpholine                  |
| 1-(2-Chloro-pyridin-3-yl)-1-morpholin-4-yl-methanone (D20)                | 2-Chloro-nicotinoyl chloride          | Morpholine                  |
| 1-(2-Chloro-pyridin-3-yl)-1-piperidin-1-yl-methanone (D21)                | 2-Chloro-nicotinoyl chloride          | Piperidine                  |
| 1-(4-Iodo-phenyl)-1-morpholin-4-yl-methanone (D22)                        | 4-Iodo-benzoyl chloride               | Morpholine                  |
| 4-Iodo-N-cyclopropylmethyl-benzamide (D23)                                | 4-Iodo-benzoyl chloride               | Cyclopropylmethyl-amine     |
| 1-(4-Iodo-phenyl)-1-pyrrolidin-1-yl-methanone (D24)                       | 4-Iodo-benzoyl chloride               | Pyrrolidine                 |
| 4-Iodo-N-cyclobutyl-benzamide (D25)                                       | 4-Iodo-benzoyl chloride               | Cyclobutylamine             |
| 4-Iodo-N,N-diethyl-benzamide (D26)                                        | 4-Iodo-benzoyl chloride               | Diethylamine                |
| 4-Iodo-N-(2-cyano-ethyl)-N-methyl-benzamide (D27)                         | 4-Iodo-benzoyl chloride               | 3-Methylamino-propionitrile |
| 1-(3-Iodo-phenyl)-1-morpholin-4-yl-methanone (D28)                        | 3-Iodo-benzoyl chloride               | Morpholine                  |
| 3-Iodo-N-cyclopropylmethyl-benzamide (D29)                                | 3-Iodo-benzoyl chloride               | Cyclopropylmethyl-amine     |
| 4-(4-Iodo-benzenesulfonyl)-morpholine (D30)                               | 4-Iodo-benzenesulfonyl chloride       | Morpholine                  |
| 4-Iodo-N,N-diethyl-benzenesulfonamide (D31)                               | 4-Iodo-benzenesulfonyl chloride       | Diethylamine                |

## Description 32

## 5-Bromo-2-(1-piperidinyl)pyrimidine (D32)



- 5 Piperidine (5.1 ml, 51.6 mmol) was added to a stirred solution of 5-bromo-2-chloropyrimidine (5 g, 25.8 mmol) and triethylamine (9.0 ml, 64.5 mmol) in toluene (30 ml). After stirring at

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room temperature for 24 hours the reaction mixture was diluted with ethyl acetate and washed with 2*N* hydrochloric acid, brine and dried (magnesium sulfate). The organic layer was filtered, concentrated *in vacuo* and the resulting residue was purified by column chromatography eluting with ethyl acetate to afford the title compound (D32).

**Descriptions 33-35**

Descriptions 33-35 (D33-D35) were prepared using an analogous method to that described for Description 32 (D32) substituting piperidine for the appropriate amine indicated in the table:

| Description                                               | Amine                      |
|-----------------------------------------------------------|----------------------------|
| 5-Bromo-2-(1-pyrrolidiny)pyrimidine (D33)                 | Pyrrolidine                |
| 4-(5-Bromo-2-pyrimidinyl)thiomorpholine 1,1-dioxide (D34) | Thiomorpholine 1,1-dioxide |
| 5-Bromo- <i>N</i> -methyl-2-pyrimidinamine (D35)          | Methylamine                |

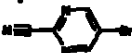
**Descriptions 36-37**

Descriptions 36-37 (D36-D37) were prepared using an analogous method to that described for Description 5 (D5), substituting morpholine for the appropriate amine indicated in the table:

| Description                                                         | Amine                  |
|---------------------------------------------------------------------|------------------------|
| 6-Chloro- <i>N</i> -(cyclopropylmethyl)-3-pyridinecarboxamide (D36) | Cyclopropylmethylamine |
| 5-(1-Azetidinylcarbonyl)-2-chloropyridine (D37)                     | Azetidine              |

**Description 38**

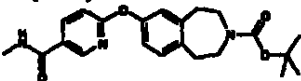
**5-Bromo-2-pyrimidinecarbonitrile (D38)**



Sodium cyanide (2.30 g, 48.6 mmol) was dissolved in dimethylformamide (60 ml) and treated with 5-bromo-2-chloropyrimidine (8.0 g, 31.1 mmol). The resulting mixture was stirred at room temperature for 18 hours, diluted with water and extracted with dichloromethane. The dichloromethane extracts were combined, washed with water, dried (magnesium sulphate), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with a mixture of ethyl acetate: hexane (1:4) to afford the title compound (D38).

**Description 39**

**1,1-Dimethylethyl 7-((5-((methylamino)carbonyl)-2-pyridinyloxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D39)**

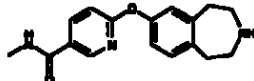


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7-Hydroxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (PCT Int. Appl. (2002), WO 02/40471) (8.7 g, 33 mmol) was dissolved in *tert*-butanol and treated with potassium-*tert*-butoxide (4 g, 36 mmol). After stirring for 30 minutes at room temperature, 6-chloro-*N*-methyl-nicotinamide (D10) (5.1 g, 30 mmol) was added and the reaction mixture was stirred at reflux for 20 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Ice/water was added to the crude residue resulting in a precipitate which was collected by filtration. The solid precipitate was dissolved in ethyl acetate, washed with brine and dried (magnesium sulfate). The organic layer was filtered, concentrated *in vacuo* and the resulting residue was purified by column chromatography eluting with a mixture of ethyl acetate:hexane (1:1) to afford the title compound (D39). NMR(CDCl<sub>3</sub>) 8.52 (1H, d, J = 2.4), 8.12 (1H, dd, J = 8.8), 7.16 (1H, m), 6.85 - 6.81 (3H, m), 6.02 (1H, br), 3.57 (4H, br), 3.02 (3H, d, J = 2.4), 2.89 (4H, br), 1.49 (9H, s).

#### Description 40

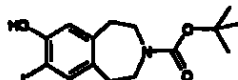
**N-Methyl-6-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yloxy)-3-pyridinecarboxamide (D40)**



1,1-Dimethylethyl 7-({5-[(methylamino)carbonyl]-2-pyridinyl}oxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D39) (3.98 g, 10 mmol) was dissolved in dioxane (40 ml) and treated with a solution of 4M hydrogen chloride in dioxane (35 ml). The reaction mixture was allowed to stir at room temperature for 6 hours and then concentrated *in vacuo* to afford the title compound (D40); MS (ES<sup>+</sup>) *m/e* 298 [M+H]<sup>+</sup>.

#### Description 41

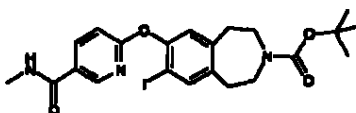
**1,1-Dimethylethyl 7-hydroxy-8-iodo-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D41)**



A solution of 7-hydroxy-1,2,4,5-tetrahydro-3*H*-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (PCT Int. Appl. (2002), WO 02/40471) (5.2 g, 20 mmol) in 33% methylamine in ethanol (30ml) was stirred at 0°C. A solution of sodium iodide (4.6 g, 30 mmol) and iodine (5.2 g, 20 mmol) in water (30 ml) was added below the surface of the reaction mixture. After stirring at 0°C for 1 hour the mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate and water. The organic layer was separated, washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford the title compound (D41); (7.0 g, 80%), <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) 10.0 (1H, br s), 7.41 (1H, s), 6.65 (1H, s), 3.40 (4H, m), 2.70 (4H, m), 1.40 (9H, s).

#### Description 42

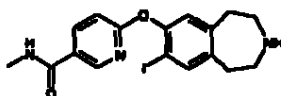
**1,1-Dimethylethyl 7-iodo-8-({5-[(methylamino)carbonyl]-2-pyridinyl}oxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D42)**

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Sodium hydride (60% disp. in mineral oil, 240 mg, 6 mmol) was added to a stirred solution of 1,1-dimethylethyl 7-hydroxy-8-iodo-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (D41) (1.84 g, 5 mmol) in dimethyl sulfoxide (10 ml). After 10 minutes, 6-chloro-N-methyl-nicotinamide (D10) (850 mg, 5 mmol) was added and the reaction mixture was heated to 100 °C for 20 hours. After cooling to room temperature the reaction mixture was diluted with water and dichloromethane. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 ethyl acetate:hexanes) to afford the title product (D42).

#### Description 43

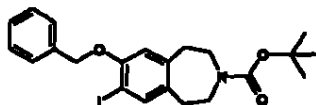
**N-Methyl-6-(8-iodo-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yloxy)-3-pyridinecarboxamide (D43)**



Description 43 (D43) was prepared from 1,1-dimethylethyl 7-iodo-8-((5-((methylamino)carbonyl)-2-pyridinyl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (D42) using an analogous method to that described for Description 2 (D2); MS (ES<sup>+</sup>) *m/z* 424 [M+H]<sup>+</sup>.

#### Description 44

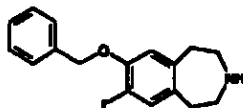
**1,1-Dimethylethyl 7-iodo-8-[(phenylmethyl)oxy]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (D44)**



Sodium hydride (60% disp. in mineral oil, 576 mg, 14.4 mmol) was added to a stirred solution of 1,1-dimethylethyl 7-iodo-8-iodo-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (D41) (4.67 g, 12 mmol) in dimethylformamide (30 ml). After 15 minutes, benzyl bromide (2.04 g, 1.4 ml, 12 mmol) was added and the mixture stirred for 2 hours. The mixture was diluted with water and ethyl acetate, the organic layer was separated, washed with water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a mixture of ethyl acetate:hexanes (1:10) to afford the title product (D44).

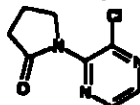
#### Description 45

**7-iodo-8-[(phenylmethyl)oxy]-2,3,4,5-tetrahydro-1H-3-benzazepine (D45)**

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Description D45 (D45) was prepared from 1,1-dimethylethyl 7-iodo-8-[(phenylmethyl)oxy]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (D44) using the analogous method to that described for Description 2 (D2); MS (ES+) m/e 380 [M+H]<sup>+</sup>.

5

**Description 46****1-(3-Chloro-2-pyrazinyl)-2-pyrrolidinone (D46)****Step 1: 3-Chloropyrazine 1-oxide**

- 10 A mixture of chloropyrazine (9.6 g, 83.3 mmol) and hydrogen peroxide solution (30%, 16 ml) in glacial acetic acid (26 ml) was heated at 70 °C for 18 hours. The mixture was allowed to cool to room temperature, poured into water (250 ml) and extracted with dichloromethane (3 x 100 ml). The dichloromethane extracts were combined, washed with saturated sodium bicarbonate solution (2 x 70 ml), water (3 x 100 ml) and brine (100 ml).
- 15 The organic portion was dried under sodium sulfate and evaporated *in vacuo* to give a white solid which was recrystallised from absolute ethanol to give the title compound (0.45 g). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.27-8.28 (1H, d), 8.15 (1H, s), 8.03-8.02 (1H, dd).

**Step 2: 2,3-Dichloropyrazine**

- 20 3-Chloropyrazine 1-oxide (D46, Step 1) (2.2 g, 16.9 mmol) was added slowly to phosphorus oxychloride (10 ml) at 60 °C. When the addition was complete the mixture was heated at reflux for 60 minutes. The mixture was allowed to cool and poured into ice and solid sodium acetate (5 g). This was stirred until the ice had melted and then extracted with dichloromethane. The dichloromethane extracts were combined, washed with saturated sodium bicarbonate solution, water and brine. The organic portion was dried under sodium sulfate and evaporated *in vacuo*. The resulting residue was purified by column chromatography eluting with a mixture of ethyl acetate:hexane (1:20) to afford the title compound (0.86 g). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.32 (2H, s).
- 25

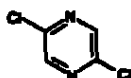
**Step 3: 1-(3-Chloro-2-pyrazinyl)-2-pyrrolidinone**

- 30 Sodium hydride (60 % in mineral oil, 67 mg, 1.62 mmol) was added to a solution of pyrrolidinone (0.12 ml, 1.54 mmol) in dry dimethylformamide (5 ml) under argon at 0 °C. The mixture was allowed to warm to room temperature over 1.5 hours. A solution of 2,3-dichloropyrazine (D46, Step 2) (250 mg, 1.69 mmol) in dry dimethylformamide (2 ml) was added and the mixture stirred at room temperature under argon for 2 hours. The mixture was poured onto water (30 ml) and was extracted with ethyl acetate (x 3). The ethyl acetate
- 35 extracts were combined, washed with brine, dried under magnesium sulfate and evaporated *in vacuo*. The resulting residue was purified by column chromatography eluting with a mixture of ethyl acetate:pentane (1:1) to afford the title compound (0.10 g); MS (ES+) m/e 198 [M+H]<sup>+</sup>.

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## Description 47

## 2,5-Dichloropyrazine (D47)



## 5 Step 1: 5-Chloro-2-pyrazinamine

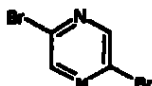
Aminopyrazine (10 g, 10.5 mmol) was dissolved in dry dimethylformamide (80 ml) and was treated with N-chlorosuccinimide (15.36 g, 11.5 mmol) under argon at 0 °C. The mixture was stirred for 30 minutes and then allowed to warm to room temperature. The mixture was poured onto water and extracted with diethyl ether. The diethyl ether layers were combined and evaporated *in vacuo*. The resulting residue was purified by column chromatography eluting with a mixture of ethyl acetate:pentane (1:9) to afford the title compound (1.40 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.02 (1H, s), 7.76 (1H, s), 4.61 (2H, s).

## Step 2: 2,5-Dichloropyrazine

5-Chloro-2-pyrazinamine (D47, Step 1) (2.41 g, 18.6 mmol) was dissolved in concentrated hydrochloric acid (24 ml), cooled in an ice-acetone bath and treated with a solution of sodium nitrite (2.63 g, 38.1 mmol) in water (18 ml) dropwise over a period of 1 hour. The mixture was cooled in an ice-water bath and left to stir for 1 hour. The mixture was allowed to warm to room temperature over 1 hour, neutralised by addition of sodium hydroxide solution (2M) and extracted with dichloromethane. The dichloromethane layers were combined, dried under magnesium sulfate and evaporated *in vacuo*. The resulting residue was purified by column chromatography eluting with a mixture of ethyl acetate:pentane (1:9) to afford the title compound (0.33 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.40 (2H, s).

## Description 48

## 25 2,5-Dibromopyrazine (D48)



## Step 1: 5-Bromo-2-pyrazinamine

Aminopyrazine (5.0 g, 52.6 mmol) was dissolved in chloroform (150 ml) and pyridine (5.11 ml, 63.2 mmol) was added. A solution of bromine (3.24 ml, 63.2 mmol) in chloroform (50 ml) was added dropwise over 1 hour. The mixture was allowed to stir for 30 minutes, diluted with water (50 ml) and allowed to stir for 10 minutes. The organic layer was separated, washed with water (50 ml), dried under magnesium sulfate and evaporated *in vacuo*. The resulting residue was purified by column chromatography eluting with a mixture of ethyl acetate:pentane (1:4) to afford the title compound (0.32 g); MS (ES+) m/e 175 [M+H]<sup>+</sup>.

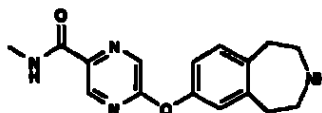
## Step 2: 2,5-Dibromopyrazine

5-Bromo-2-pyrazinamine (D48, Step 1) (317 mg, 1.82 mmol) was added to a cooled (ice-acetone bath) solution of hydrobromic acid (48 % aqueous) (2 ml). After stirring for 5 minutes, bromine (0.28 ml, 5.46 mmol) was added followed by a solution of sodium nitrite

(314 mg, 4.55 mmol) in water dropwise over 15 minutes. The mixture was stirred for 30 minutes and allowed to warm to room temperature over 30 minutes. A solution of sodium hydroxide (2.6 g) in water (7 ml) was added and the mixture stirred for 1 hour. The mixture was extracted with dichloromethane. The dichloromethane layers were combined and evaporated *in vacuo* to afford the title compound (60 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.49 (2H, s).

**Description 49**

**N-Methyl-5-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yloxy)-2-pyrazinecarboxamide (D49)**



**Step 1: 1,1-Dimethylethyl 7-((5-((methyloxy)carbonyl)-2-pyrazinyl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate**

Sodium hydride (60% dispersion in mineral oil) (6.4 g, 0.16 mol) was added portionwise to a solution of 7-hydroxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid *tert*-butyl ester (PCT Int. Appl. (2002), WO 02/40471) (40 g, 0.15 mol) in dry dimethylformamide (200 ml) cooled to 5 °C over 15 minutes. After 15 minutes, the mixture was allowed to warm to room temperature and stirred for 60 minutes. The mixture was cooled in an ice-water bath and methyl 5-chloro-2-pyrazinecarboxylate (31.2 g, 0.18 mol) was added portionwise. The mixture was allowed to warm to room temperature and stirred for 18 hours. The mixture was poured onto water (500 ml) and ice (500 ml) and stirred until the ice had melted. The resulting solid was collected by filtration, washed with water and dissolved in ethyl acetate (1500 ml). The ethyl acetate layer was washed with brine (200 ml), dried under sodium sulfate and evaporated *in vacuo*. The crude product was purified by column chromatography eluting with a mixture of ethyl acetate:hexane (1:2) to afford the title compound (35.07 g).

**Step 2: 5-((3-(((1,1-Dimethylethyl)oxy)carbonyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy)-2-pyrazinecarboxylic acid**

2M Sodium hydroxide solution (110 ml) was added to a solution of 1,1-dimethylethyl 7-((5-((methyloxy)carbonyl)-2-pyrazinyl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (D49, Step 1) (29.38 g, 73.6 mmol) in acetone (480 ml) and the resulting mixture was stirred at room temperature for 25 minutes. The mixture was acidified with 2M hydrochloric acid and then poured into water (2 L). The resulting white solid was collected by filtration, washed with water and dissolved in ethyl acetate (1 L). This solution was dried under sodium sulfate and evaporated *in vacuo* to give the title compound (27.3 g); MS (ES<sup>+</sup>) *m/e* 384 [M-H]<sup>+</sup>.

**Step 3: 1,1-Dimethylethyl 7-((5-((methylamino)carbonyl)-2-pyrazinyl)oxy)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate**

1,1'-Carbonyldimidazole (16.6 g, 102 mmol) was added to a solution of 5-((3-(((1,1-dimethylethyl)oxy)carbonyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy)-2-pyrazinecarboxylic acid (D49, Step 2) (37.5 g, 97 mmol) in dry dichloromethane (400 ml)

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and the resulting mixture was stirred at room temperature for 18 hours. Methylamine (2M solution in tetrahydrofuran) (100 ml) was added and the mixture stirred for 2 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography eluting with a mixture of ethyl acetate:chloroform (1:1) to afford the title compound (25.8 g);

5 MS (ES+) *m/e* 399 [M+H]<sup>+</sup>.

**Step 4: *N*-Methyl-5-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yloxy)-2-pyrazinecarboxamide**

A solution of 1,1-dimethylethyl 7-((5-((methylamino)carbonyl)-2-pyrazinyl)oxy)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D49, Step 3) (44.28 g, 0.11 mol) in  
10 dichloromethane (800 ml) was added dropwise to a stirring solution of 4M hydrogen chloride in dioxane (270 ml, 1.1 mol). The resulting mixture was stirred at room temperature for 60 minutes. A further quantity of 4M hydrogen chloride in dioxane (30 ml, 0.12 mol) was added and the mixture stirred for 60 minutes. The resulting white solid was collected by filtration and washed with dichloromethane. The solid was dissolved in water (2 L) and  
15 basified by addition of saturated sodium carbonate solution. The water layer was extracted with dichloromethane and the extracts filtered through celite. The celite was washed with methanol and the combined dichloromethane and methanol washings were evaporated *in vacuo* to give the title compound (25.1 g); MS (ES+) *m/e* 299 [M+H]<sup>+</sup>.

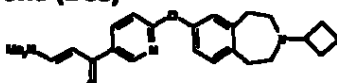
## 20 Descriptions 50-52

Descriptions 50-52 (D50-D52) were prepared and used without further characterisation using the method described for Description 5 (D5) from the appropriate aryl halide and amine indicated in the table:

| Description                                                           | Aryl Halide            | Amine                     |
|-----------------------------------------------------------------------|------------------------|---------------------------|
| <i>N</i> -Ethyl-4-iodo- <i>N</i> -(2-(methyloxy)ethyl)benzamide (D50) | 4-iodobenzoyl chloride | 2-Methoxyethyl ethylamine |
| 4-iodo- <i>N</i> -methylbenzamide (D51)                               | 4-iodobenzoyl chloride | Methylamine               |
| 1-((3-iodophenyl)carbonyl)pyrrolidine (D52)                           | 3-iodobenzoyl chloride | Pyrrolidine               |

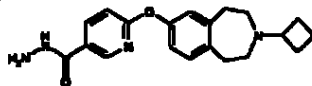
## 25 Description 53

(2*E*)-1-(6-((3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy)-3-pyridinyl)-3-(dimethylamino)-2-propen-1-one (D53)

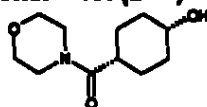


A mixture of 1-(6-((3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)oxy)-3-pyridinyl)ethanone (E214) (186 mg, 0.55 mmol), dimethylformamide dimethyl acetyl (0.25 ml) and xylene (4 ml) was heated at reflux for 8 hours. The residue was diluted with toluene and concentrated *in vacuo* to afford the title compound (D53); MS (ES+) *m/e* 392 [M+H]<sup>+</sup>.

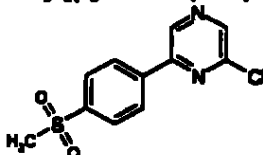
31

**Description 54****6-[(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinecarbohydrazide (D54)**

- 5 A mixture of thionyl chloride (2 ml) and 6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinecarboxylic acid (E198b) (200 mg, 0.58 mmol) was stirred at reflux for 1 hour. The reaction mixture was concentrated *in vacuo* to afford a crude residue. The residue was dissolved in tetrahydrofuran (5 ml), cooled to 0 °C and hydrazine hydrate (1.5 ml) in tetrahydrofuran (1.5 ml) was added dropwise. The reaction mixture was allowed
- 10 to warm to room temperature and stirred for 1 hour. The reaction mixture was then diluted with ethyl acetate and washed with a saturated solution of sodium carbonate, water, brine and dried (magnesium sulfate). The organic layer was filtered and concentrated *in vacuo* to afford the title compound (D54); MS (ES+) *m/e* 381 [M+H]<sup>+</sup>.

**Description 55****cis-4-(4-Morpholinylcarbonyl)cyclohexanol (D55)**

- A solution of *cis*-4-hydroxycyclohexanecarboxylic acid (720 mg, 0.5 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.33 g, 6 mmol) and 1-hydroxy-7-azabenzotriazole (816 mg, 6 mmol) in dichloromethane (6 ml) was treated with morpholine 1.3 ml, 15 mmol). After stirring at room temperature for 18 hours, the crude reaction was applied to a SCX ion exchange cartridge (Varian bond-elute, 5 g) and washed with methanol and then a mixture of .880 ammonia:methanol (1:9). The combined basic fractions were concentrated *in vacuo*, and the resulting residue was purified by column chromatography eluting with a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (D55); MS (ES+) *m/e* 214 [M+H]<sup>+</sup>.
- 20
- 25

**Description 56****2-Chloro-6-[4-(methylsulfonyl)phenyl]pyrazine (D56)**

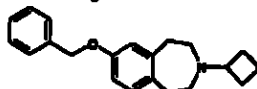
- 30 2,6-Dichloropyrazine (2.98g, 20.0mmol), [4-(methylsulfonyl)phenyl]boronic acid (2g, 10.0mmol), tetrakis(triphenylphosphine)palladium (1.15g, 1.0mmol), potassium phosphate (10.2g, 48mmol) and dimethylformamide (90ml) were heated to 80° c for 16hours. The solvent was removed *in vacuo* and the product was dissolved in chloroform and filtered
- 35 through celite. The filtrate was washed with water then separated. The residue was purified

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by column chromatography eluting with a mixture of ethylacetate:hexane (4:6) to afford the title compound. MS (ES+) m/e 270 [M+H]<sup>+</sup>.

#### Example 1

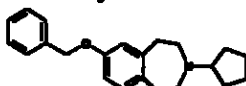
##### 5 7-Benzyloxy-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E1)



7-Benzyloxy-1,2,4,5-tetrahydro-benzo[d]azepine (D2) (25.3 g, 100 mmol) was dissolved in 2.5% acetic acid in dichloromethane (400 ml) at 0 °C and treated dropwise with cyclobutanone (11.2 ml, 150 mmol). The mixture was stirred for 30 minutes and then  
10 sodium triacetoxymethylborohydride (31.8 g, 150 mmol) was added portion wise. The reaction mixture was stirred at room temperature for 4 hours, basified with saturated sodium carbonate solution and extracted with dichloromethane. The combined extracts were washed with water, brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was triturated with hexane and filtered to afford the title product (E1).  
15 MS (ES+) m/e 308 [M+H]<sup>+</sup>.

#### Example 2

##### 7-Benzyloxy-3-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E2)



20 Title compound (E2) was prepared from 7-benzyloxy-1,2,4,5-tetrahydro-benzo[d]azepine (D2) and cyclopentanone using the method described for Example 1; MS (ES+) m/e 322 [M+H]<sup>+</sup>.

#### Example 3

##### 25 3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3)



7-Benzyloxy-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E1) (9.22 g, 30 mmol) was dissolved in ethanol (150 ml) and tetrahydrofuran (50 ml). Palladium (1.5 g, 10% on charcoal paste) was added and the reaction mixture was stirred at room temperature under  
30 hydrogen (1 atmosphere) for 5 hours. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo*. The crude residue was triturated with diethyl ether and filtered to afford the title product (E3); MS (ES+) m/e 218 [M+H]<sup>+</sup>.

#### Example 4

##### 35 3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E4)



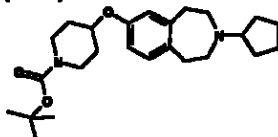
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Title compound (E4) was prepared from 7-benzyloxy-3-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E2) using the method described for Example 3 (E3); <sup>1</sup>H NMR (DMSO, d6) 9.08 (1H, brs), 6.70 (1H, d), 6.53-6.47 (2H, m), 3.31-2.50 (9H, m) 1.88-1.43 (8H, m).

5

**Example 5a**

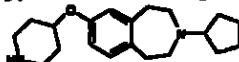
**4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-carboxylic acid-tert-butyl ester (E5a)**



- 10 3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E4) (1.1 g, 4.8 mmol), 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (1.15 g, 5.7 mmol), di-tert-butyl azodicarboxylate (1.31 g, 5.7 mmol) and triphenylphosphine (1.5 g, 5.7 mmol) were stirred at room temperature for 18 hours in tetrahydrofuran (20 ml). The mixture was acidified with acetic acid and applied to a SCX ion exchange cartridge (Varian bond-elute, 10 g) and
- 15 washed with methanol and then a mixture of .880 ammonia:methanol (1:9). The combined basic fractions were concentrated *in vacuo* and the resulting residue was purified by column chromatography eluting with a mixture of .880 ammonia:methanol:dichloromethane (1:9:90) to afford the title product (E5a); MS (ES+) *m/e* 415 [M+H]<sup>+</sup>.

20 **Example 5**

**3-Cyclopentyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E5)**



- 4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-carboxylic acid-tert-butyl ester (E5a) (593 mg, 1.43 mmol) was dissolved in dichloromethane (5 ml)
- 25 and treated with trifluoroacetic acid (3 ml). The solution was stirred at room temperature for 1 hour, concentrated *in vacuo* and applied to a SCX ion exchange cartridge (Varian bond-elute, 5 g) and washed with methanol and then a mixture of .880 ammonia: methanol (1:9). The combined basic fractions were concentrated *in vacuo* and the resulting residue was purified by column chromatography eluting with a mixture of .880 ammonia: methanol:
- 30 dichloromethane (1: 9: 90) to afford the title product (E5). MS (ES+) *m/e* 315 [M+H]<sup>+</sup>.

**Examples 6-12**

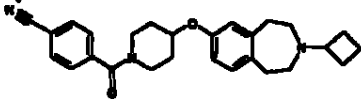
- Examples 6-12 (E6-12) were prepared from either 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3) or 3-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E4)
- 35 and the appropriate alcohol indicated in the table using an analogous method to that described for Example 5a (E5a) followed by the method described for the preparation of Example 5 (E5).

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| Example                                                                                            | Starting Material | Alcohol                                                                             | LC/MS (M+H <sup>+</sup> ) |
|----------------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------------------------------|---------------------------|
| 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)                      | E3                | 4-Hydroxy-piperidine-1-carboxylic acid <i>tert</i> -butyl ester                     | 301                       |
| 3-Cyclobutyl-7-(piperidin-4-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E7)                  | E3                | 4-Hydroxymethyl-piperidine-1-carboxylic acid <i>tert</i> -butyl ester               | 315                       |
| 3-Cyclobutyl-7-(( <i>R</i> )-1-pyrrolidin-2-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E8)  | E3                | ( <i>R</i> )-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester | 301                       |
| 3-Cyclobutyl-7-(( <i>R</i> )-pyrrolidin-3-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E9)        | E3                | ( <i>R</i> )-3-Hydroxy-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester       | 287                       |
| 3-Cyclobutyl-7-(( <i>S</i> )-pyrrolidin-3-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E10)       | E3                | ( <i>S</i> )-3-Hydroxy-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester       | 287                       |
| 3-Cyclobutyl-7-(( <i>S</i> )-1-pyrrolidin-2-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E11) | E3                | ( <i>S</i> )-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester | 301                       |
| 3-Cyclopentyl-7-(piperidin-4-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E12)                | E4                | 4-Hydroxymethyl-piperidine-1-carboxylic acid <i>tert</i> -butyl ester               | 329                       |

Example 13

4-{1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-methanoyl}-benzonitrile (E13)



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4-Cyanobenzoic acid (147 mg, 1 mmol), 1-hydroxy benzotriazole hydrate (154 mg, 1 mmol) and N-cyclohexylcarbodiimide N'-methyl polystyrene (1.8 mmol/g, 555 mg, 1 mmol) were stirred at room temperature in dichloromethane (5 ml) for 15 minutes. 3-cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6) (150 mg, 0.5 mmol) was added and stirring continued for 16 hours. The reaction mixture was applied to a SCX ion exchange cartridge (Varian bond-elute, 5 g) and washed with methanol and then a mixture

34  
35

of .880 ammonia:methanol (1:9). The combined basic fractions were concentrated *in vacuo* and the resulting residue was purified by column chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title product (E13). MS (ES+) *m/e* 430 [M+H]<sup>+</sup>.

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#### Examples 14-42

Examples 14-42 (E14-E42) were prepared using an analogous method to that described for Example 13 (E13) from the appropriate amine and acid as indicated in the table:

| Example                                                                                                                              | Amine                                                                                  | Acid                                 | LC/MS<br>(M+H <sup>+</sup> ) |
|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------|------------------------------|
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-(tetrahydro-pyran-4-yl)-methanone (E14)  | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E6) | Tetrahydro-pyran-4-carboxylic acid   | 413                          |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-cyclohexyl-methanone (E15)               | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E6) | Cyclohexane carboxylic acid          | 411                          |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-isoquinolin-1-yl-methanone (E16)         | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E6) | Isoquinoline-1-carboxylic acid       | 456                          |
| 4-[(E)-3-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepin-7-yloxy)-piperidin-1-yl]-3-oxopropenyl]-benzonitrile (E17)   | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E6) | (E)-3-(4-Cyano-phenyl)-acrylic acid  | 456                          |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-isoquinolin-6-yl-methanone (E18)         | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E6) | Isoquinoline-6-carboxylic acid       | 456                          |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-(5-methyl-isoxazol-3-yl)-methanone (E19) | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E6) | 5-Methyl-isoxazole-3-carboxylic acid | 410                          |

|                                                                                                                                             |                                                                                      |                                                            |     |
|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------|-----|
| 1-Benzothiazol-6-yl-1-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-methanone (E20)                        | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)        | Benzothiazole-6-carboxylic acid                            | 482 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-pyridin-4-yl-methanone (E21)                             | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)        | Isonicotinic acid                                          | 406 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-[4-(1-pyrrolidin-1-yl-methanoyl)-phenyl]-methanone (E22) | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)        | 4-(1-Pyrrolidin-1-yl-methanoyl)-benzoic acid (WO 03/04468) | 502 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-thiophen-3-yl-methanone (E23)                            | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)        | Thiophene-3-carboxylic acid                                | 411 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-furan-3-yl-methanone (E24)                               | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)        | Furan-3-carboxylic acid                                    | 395 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-piperidin-1-yl]-1-tetrahydro-pyran-4-yl-methanone (E25)              | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E7)        | Tetrahydro-pyran-4-carboxylic acid                         | 427 |
| 1-[(R)-2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-pyrrolidin-1-yl]-1-(tetrahydro-pyran-4-yl)-methanone (E26)       | 3-Cyclobutyl-7-[(R)-1-pyrrolidin-2-yloxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E8) | Tetrahydro-pyran-4-carboxylic acid                         | 413 |
| 1-[(R)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrrolidin-1-yl]-1-(tetrahydro-pyran-4-yl)-methanone (E27)             | 3-Cyclobutyl-7-[(R)-pyrrolidin-3-yloxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E9)   | Tetrahydro-pyran-4-carboxylic acid                         | 399 |

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37

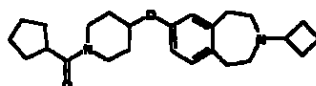
|                                                                                                                                  |                                                                                           |                                          |     |
|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------------------------------|-----|
| 1-[(S)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrrolidin-1-yl]-1-(tetrahydro-pyran-4-yl)-methanone (E28)  | 3-Cyclobutyl-7-((S)-pyrrolidin-3-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E10)       | Tetrahydro-pyran-4-carboxylic acid       | 399 |
| 1-[(S)-2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrrolidin-1-yl]-1-(tetrahydro-pyran-4-yl)-methanone (E29)  | 3-Cyclobutyl-7-((S)-1-pyrrolidin-2-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E11) | Tetrahydro-pyran-4-carboxylic acid       | 413 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-(methanesulfonyl-phenyl)-methanone (E30)      | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)             | 4-Methanesulfonyl-benzoic acid           | 483 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-pyrazin-2-yl-methanone (E31)                  | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)             | 2-Pyrazine carboxylic acid               | 407 |
| 5-[1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-methanoyl]-1H-pyridone (E32)                 | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)             | 6-Hydroxy nicotinic acid                 | 422 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-(2,3-dihydro-benzofuran-5-yl)-methanone (E33) | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)             | 2,3-Dihydro-benzofuran-5-carboxylic acid | 447 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-3-methoxypropan-1-one (E34)                     | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)             | 3-Methoxy-propionic acid                 | 387 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-(2,3-dihydro-benzofuran-7-yl)-methanone (E35)   | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)             | 2,3-Dihydro-benzofuran-7-carboxylic acid | 447 |

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|                                                                                                                                                     |                                                                                 |                                                              |     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------|-----|
| 4-{1-[4-(3-Cyclopentyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)methyl]piperidin-1-yl]-methanoyl}-benzonitrile (E36)      | 3-Cyclopentyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E12) | 4-Cyano-benzoic acid                                         | 458 |
| 1-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)methyl]-piperidin-1-yl]-1-[4-(1-pyrrolidin-1-yl-methanoyl)-phenyl]-methanone (E37) | 3-Cyclopentyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E12) | 4-(1-Pyrrolidin-1-yl-methanoyl)-benzoic acid (WO 03/04468A1) | 530 |
| 4-{1-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-methanoyl}-benzonitrile (E38)                                  | 3-Cyclopentyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E5)  | 4-Cyano-benzoic acid                                         | 444 |
| 1-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-pyridin-4-yl-methanone (E39)                                    | 3-Cyclopentyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E5)  | Isonicotinic acid                                            | 420 |
| 1-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-quinolin-6-yl-methanone (E40)                                   | 3-Cyclopentyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E5)  | Quinoline-6-carboxylic acid                                  | 470 |
| 1-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-[4-(1-pyrrolidin-1-yl-methanoyl)-phenyl]methanone (E41)         | 3-Cyclopentyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E5)  | 4-(1-Pyrrolidin-1-yl-methanoyl)-benzoic acid (WO 03/04468A1) | 516 |
| 1-Biphenyl-4-yl-1-[4-(3-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-methanone (E42)                                   | 3-Cyclopentyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E5)  | 4-Biphenyl carboxylic acid                                   | 495 |

**Example 43**

**1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-cyclopentyl-methanone (E43)**

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3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6) (150 mg, 0.5 mmol) was stirred in dichloromethane (5 ml) with diethylaminomethyl polystyrene (3.2 mmol/g, 625 mg, 2 mmol). Cyclopentane carbonyl chloride (80  $\mu$ l, 0.6 mmol) was added and the mixture stirred at room temperature for 16 hours. The resin was filtered, washed with dichloromethane and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title product (E43); MS (ES+) *m/e* 397 [M+H]<sup>+</sup>.

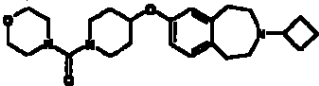
#### Examples 44-51

Examples 44-51 (E44-E51) were prepared using an analogous method to that described for Example 43 (E43) from the appropriate amine and carbonyl chloride as indicated in the table:

| Example                                                                                                                      | Amine                                                                                    | Carbonyl chloride        | LC/MS (M+H <sup>+</sup> ) |
|------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------|---------------------------|
| 4-{1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-piperidin-1-yl]-methanoyl}-benzonitrile (E44)      | 3-Cyclobutyl-7-(piperidin-4-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E7)        | 4-Cyano benzoyl chloride | 444                       |
| 4-{1-[(R)-2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-pyrrolidin-1-yl]-methanoyl}-benzonitrile (E45) | 3-Cyclobutyl-7-[(R)-1-pyrrolidin-2-ylmethoxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E8) | 4-Cyano benzoyl chloride | 430                       |
| 4-{1-[(R)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrrolidin-1-yl]-methanoyl}-benzonitrile (E46)       | 3-Cyclobutyl-7-[(R)-pyrrolidin-3-yloxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E9)       | 4-Cyano-benzoyl chloride | 416                       |
| 4-{1-[(S)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrrolidin-1-yl]-methanoyl}-benzonitrile (E47)       | 3-Cyclobutyl-7-[(S)-pyrrolidin-3-yloxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E10)      | 4-Cyano-benzoyl chloride | 416                       |
| 4-{1-[(S)-2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-                                                            | 3-Cyclobutyl-7-[(S)-1-pyrrolidin-2-                                                      | 4-Cyano-benzoyl chloride | 430                       |

|                                                                                                                 |                                                                               |                                |     |
|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------------|-----|
| yloxy)-pyrrolidin-1-yl]-methanoyl)-benzonitrile (E48)                                                           | ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E11)                        |                                |     |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-2,2-dimethylpropan-1-one (E49) | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6) | 2,2-Dimethylpropionyl chloride | 385 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-cyclopropyl-methanone (E50)  | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6) | Cyclopropane carbonyl chloride | 389 |
| 1-Cyclobutyl-1-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-yl]-methanone (E51)  | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6) | Cyclobutane carbonyl chloride  | 383 |

**Example 52**  
**4-{1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-morpholin-4-yl-methanone (E52)**



5 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6) (150 mg, 0.5 mmol) was stirred in dichloromethane (5 ml) with diethylaminomethyl polystyrene (3.2 mmol/g, 625 mg, 2 mmol). Morpholine carbamoyl chloride (70  $\mu$ L, 0.6 mmol) was added and the mixture stirred at room temperature for 16 hours. The resin was filtered, washed with dichloromethane and the filtrate concentrated *in vacuo*. The residue was purified by  
10 column chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title product (E52). MS (ES+) *m/e* 414 [M+H]<sup>+</sup>.

15 **Examples 53-60**  
Examples 53-60 (E53-E60) were prepared using an analogous method to that described for Example 52 (E52) from the appropriate amine and carbonyl chloride indicated in the table:

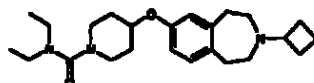
| Example                     | Amine           | Carbonyl Chloride | LC/MS (M+H <sup>+</sup> ) |
|-----------------------------|-----------------|-------------------|---------------------------|
| 1-[4-(3-Cyclobutyl-2,3,4,5- | 3-Cyclobutyl-7- | Morpholine-       | 428                       |

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41

|                                                                                                                              |                                                                                           |                                 |     |
|------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------|-----|
| tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-piperidin-1-yl]-1-morpholin-4-yl-methanone (E53)                                 | (piperidin-4-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E7)                        | 4-carbonyl chloride             |     |
| 1-[(R)-2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-pyrrolidin-1-yl]-1-morpholin-4-yl-methanone (E54) | 3-Cyclobutyl-7-[(R)-1-pyrrolidin-2-ylmethoxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E8)  | Morpholine-4-carbonyl chloride  | 414 |
| 1-[(R)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrrolidin-1-yl]-1-morpholin-4-yl-methanone (E55)       | 3-Cyclobutyl-7-[(R)-pyrrolidin-3-yloxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E9)        | Morpholine-4-carbonyl chloride  | 400 |
| 1-[(S)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrrolidin-1-yl]-1-morpholin-4-yl-methanone (E56)       | 3-Cyclobutyl-7-[(S)-pyrrolidin-3-yloxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E10)       | Morpholine-4-carbonyl chloride  | 400 |
| 4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-carboxylic acid diisopropylamide (E57)            | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)             | Diisopropyl-carbonyl chloride   | 428 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-pyrrolidin-1-yl-methanone (E58)             | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)             | Pyrrolidine-1-carbonyl chloride | 398 |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidin-1-yl]-1-piperidin-1-yl-methanone (E59)            | 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)             | Piperidine-1-carbonyl chloride  | 412 |
| 1-[(S)-2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-pyrrolidin-1-yl]-1-morpholin-4-yl-methanone (E60) | 3-Cyclobutyl-7-[(S)-1-pyrrolidin-2-ylmethoxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E11) | Morpholine-4-carbonyl chloride  | 414 |

**Example 61**

**4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-carboxylic acid diethylamide (E61)**



5

3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6) (1.5 g, 5 mmol) dissolved in toluene (40 ml) was added slowly to a 20% phosgene in toluene solution (12.5 ml, 25 mmol) at 0 °C. The mixture was stirred at room temperature for 3 hours and concentrated *in vacuo* to afford a crude residue (1.91 g). The crude product (300

42

mg, 0.75 mmol) was then added to a stirred slurry of diethylamine (207  $\mu$ L, 2 mmol) and diethylaminomethyl polystyrene (3.2 mmol/g, 1.41 g, 4.5 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 16 hours, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title product (E61). MS (ES+) *m/e* 400 [M+H]<sup>+</sup>.

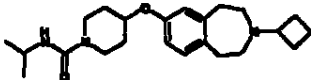
Examples 62-65

Examples 62-65 (E62-E65) were prepared using an analogous method to that described for Example 61 (E61) from 3-cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E6) and the appropriate amine indicated in the table:

| Example                                                                                                                                                          | Amine                                            | LC/MS (M+H <sup>+</sup> ) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|---------------------------|
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[ <i>d</i> ]azepin-7-yloxy)-piperidin-1-yl]-1-(1,3-dihydro-isolindol-2-yl)-methanone (E62)                | 2,3-Dihydro-1 <i>H</i> -isoindole                | 446                       |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[ <i>d</i> ]azepin-7-yloxy)-piperidin-1-yl]-1-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone (E63) | 3,4,5,6-Tetrahydro-2 <i>H</i> -[1,2']bipyrazinyl | 491                       |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[ <i>d</i> ]azepin-7-yloxy)-piperidine-1-carboxylic acid isopropyl-(2-methoxy-ethyl) amide (E64)          | Isopropyl-(2-methoxy-ethyl-amine                 | 444                       |
| 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[ <i>d</i> ]azepin-7-yloxy)-piperidin-1-yl]-1-(1,1-dioxo-thiomorpholin-4-yl)-methanone (E65)              | Thiomorpholine 1,1-dioxide                       | 462                       |

Example 66

4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-piperidine-1-carboxylic acid isopropylamide (E66)



A solution of 3-cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E6) (150 mg, 0.5 mmol) and isopropyl isocyanate (60  $\mu$ L, 0.6 mmol) in dichloromethane (5 ml) was stirred at room temperature for 16 hours. The solution was concentrated *in vacuo* and the residue was purified by column chromatography eluting with dichloromethane then a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title product (E66). MS (ES+) *m/e* 386 [M+H]<sup>+</sup>.