

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
DIRECCION DE NUEVAS CREACIONES**

2020  
Bogotá, D.C.,

Abogado:  
**ALICIA LLOREDA RICAURTE**

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



**No. 07-053254- -00003-0000**

Fecha: 2010-12-22 14:17:54 Dep. 2020 DIR.NUEVASCR  
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI  
Act. 519 TRASLADOINFORME Folios: 1

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|---------|----------------|------------|
| ASUNTO: | Radicación No. | 07 053 254 |
|         | Trámite        | 011        |
|         | Evento         | 378        |
|         | Actuación      | 430        |
|         | Oficio         |            |
|         | Folios         |            |

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Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

**Documentos estudiados:**

|                   |                                                                     |
|-------------------|---------------------------------------------------------------------|
| Descripción:      | Folios 46 a 107 como se radicó inicialmente.                        |
| Reivindicaciones: | Folios 127 a 133 como fue modificado en fase nacional<br>26.09.2007 |
| Prioridad:        | SE 0402972-4 (06.12.2006); SE 0501093-9 (13.05.2005)                |

**Objeto de la Invención**

Título de la invención: "NOVEDOSOS DERIVADOS DE PIRROLO[3,2-D]PIRIMIDINA-4-ONA Y SU USO EN TERAPIA"

Problema Técnico Planteado: "Necesidad de compuestos con actividad inhibidora sobre la enzima MPO"

Solución: "Proveer derivados de pirrolo [3,2-d] pirimidin-4-ona"

IPC: C07D 487/04; A61K 31/519; A61P 9/10

El capítulo reivindicatorio modificado se ha presentado así:

Reivindicación 1 a 14: Un compuesto de acuerdo a la fórmula I; Reivindicación 15: Un compuesto de acuerdo a la fórmula I, para su uso como medicamento; Reivindicación 16: Una composición farmacéutica que contiene el compuesto de fórmula I; Reivindicación 17 a 21: Uso del compuesto de fórmula I; Reivindicación 22: Un proceso para la preparación de un compuesto de fórmula I.

**Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)**

Las reivindicaciones 17 a 21 se refieren a un uso por lo cual deberían ser retiradas del capítulo reivindicatorio modificado.

**Análisis de la Solicitud de Patente**

**Reivindicaciones (Art 30 D 486, Art 22 PCT)**

Claridad y soporte en la descripción:

La reivindicación 1 presenta definiciones poco concisas para cada uno de los radicales allí revelados, p.ej.: R1 representa H, ó i) un anillo saturado..., ó ii) un sistema de anillo aromático (f.109), en donde se observa que i) y ii) tienen una variación altísima en el número de los miembros que conforman los anillos y a su vez, estos anillos pueden estar opcionalmente sustituidos por un número indeterminado de sustituyentes de diferentes tamaños y funciones. Lo anterior ocasiona que bajo la luz de la reivindicación 1 haya un número indeterminado de compuestos, con una altísima variabilidad entre ellos por lo cual podrían no conservar la misma actividad biológica.

Se observa en la Descripción una serie de ejemplos de síntesis de compuestos que conservan la estructura tioxo-1,2,3,5-tetrahidropirrolo[3,2-d]pirimidin-4-ona (f.77 a 106) y la actividad biológica está demostrada por ensayos de inhibición de MPO determinada para los compuestos de los ejemplos 2, 5 y 11 (f.106-107).

Se concluye que las definiciones para los radicales de la formula I carecen de Concisión, y que el alcance de la reivindicación 1 no encuentra Soporte en la Descripción para la totalidad de los compuestos allí reclamados.

Se sugiere restringir las definiciones de los radicales

La reivindicación 15 no agrega ninguna característica técnica que defina el compuesto de la formula I. Se concluye que esta reivindicación no es clara y sugiere retirarla del capítulo reivindicatorio.

**Determinación del Estado de la Técnica**

El Estado de la Técnica se determinó con base en la fecha de presentación 14/07/03 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

| Item | Documento   | Título                                                                | Fecha de Publicación |
|------|-------------|-----------------------------------------------------------------------|----------------------|
| D1   | WO03/089430 | Thioxanthine derivatives as myeloperoxidase inhibitors                | 30.10.2003           |
| D2   | WO99/40091  | Bicyclic pyrimidine derivatives as neuropeptide Y receptor antagonist | 12.08.1999           |

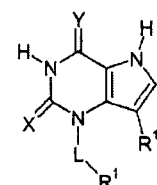
D1 revela el uso de compuestos derivados de tioxantinas para el tratamiento de enfermedades en las cuales la inhibición de la enzima mieloperoxidasa (MPO) es benéfica (portada, f.137; p.1, f.138).

D2 revela compuestos derivados de pirimidinas y piridinas bicíclicas en las cuales que pueden ser usadas para el tratamiento de la enfermedad de Alzheimer (portada, f.144) También presenta derivados pirimidinas fusionadas que pueden ser usadas para inhibir la proteínas tirosina quinasa (p.12, f.146).

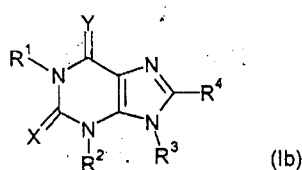
### Análisis de Patentabilidad (Art 14 D486)

#### Nivel Inventivo (Art18 D486)

La reivindicación 1 dice: "Un compuesto de fórmula (I) En donde: Por lo menos uno de X y Y representa S y el otro representa O ó S; L representa un enlace directo o alquileo C1-7, dicho alquileo incorporando opcionalmente un heteroátomo seleccionado de O, S(O)<sub>n</sub> y NR<sub>6</sub>...", lo demás con en el folio 127.



D1 revela compuestos de acuerdo a la formula Ib, en donde uno de X y Y representan S, y el otro representa O o S; R1, H; R2, alquilo C1-6 opcionalmente sustituidos por i) anillos de 3 a 7 miembros saturados o parcialmente saturados opcionalmente incorporan 2 heteroátomos seleccionados de O, N o S e incorporando opcionalmente un carbonilo; donde dicho anillo esta sustituido por uno o más sustituyentes seleccionados de halógeno, hidroxilo, alcoxi C1-6, y alquilo C1-6, donde dicho alquilo esta sustituido además por hidroxilo o alcoxi C1-6; ii) alcoxi C1-6; iii) un anillo aromático seleccionado de fenilo, furilo, tienilo, y dicho anillo aromático sustituido por halógeno, alquilo C1-6 o alcoxi C1-6 y R4, H.

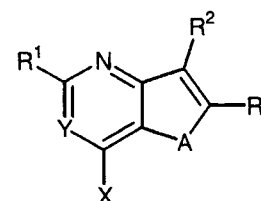


La solicitud se diferencia en el núcleo central heterocíclico: D1 posee un N adicional en la estructura cíclica fusionada.

El efecto técnico que logra la diferencia es proveer compuestos para el tratamiento de las enfermedades relacionadas con trastornos de la actividad de la enzima MPO.

El problema objetivo de la invención es la necesidad de compuestos novedosos para el tratamiento de enfermedades relacionadas con la enzima MPO.

D2 revela compuestos de acuerdo a la formula de la derecha, en donde A es N-H (p.15, f.149, ln 5); Y es N (p.27, ln.30). También presenta compuestos en los ejemplos que poseen el mismo núcleo estructural reclamado por la presente solicitud (p.217, ej. 124, f.151).



El experto en la materia habría sido sugerido por D2 a excluir el átomo N de la estructura bicíclica fusionada revelada por D1. Por otro lado la actividad biológica de los compuestos de la presente invención es la misma que se reclamó en la anterioridad D1. g

Se concluye que los compuestos presentados por la presente reivindicación 1 pueden carecer de nivel inventivo.

### Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

|    | Documento   | Reivindicaciones afectadas | Requisito que afecta |
|----|-------------|----------------------------|----------------------|
| D1 | WO03/089430 | 1-16 y 22                  | Nivel Inventivo      |
| D2 | WO99/40091  | 1-16 y 22                  | Nivel Inventivo      |

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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

  
**JOSÉ LUIS SALAZAR LÓPEZ**  
 Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha

|                                  |                                     |
|----------------------------------|-------------------------------------|
| CONCEPTO TECNICO<br>NUMERO: 4076 | EXAMINADOR TÉCNICO<br>Código:202092 |
|----------------------------------|-------------------------------------|

137  
D1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
30 October 2003 (30.10.2003)

PCT

(10) International Publication Number  
**WO 03/089430 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 473/20**,  
473/22, A61K 31/52, 31/522, A61P 25/28, 35/00

SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,  
UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number: PCT/SE03/00617

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date: 15 April 2003 (15.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0201193-0 19 April 2002 (19.04.2002) SE  
0202239-0 17 July 2002 (17.07.2002) SE

**Declarations under Rule 4.17:**

as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)  
— of inventorship (Rule 4.17(iv)) for US only

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(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

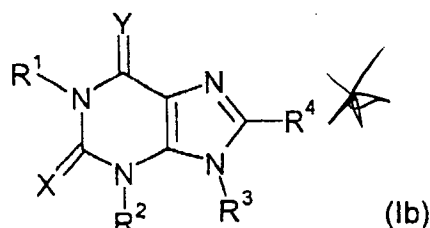
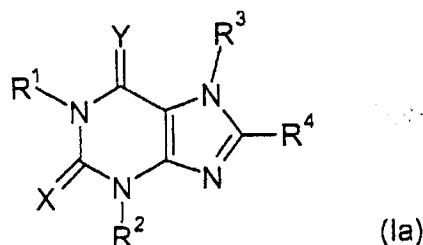
**Published:**

with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,

(54) Title: THIOXANTHINE DERIVATIVES AS MYELOPEROXIDASE INHIBITORS



(57) Abstract: There is disclosed the use of a compound of formula (Ia) or (Ib) wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and Y are as defined in the specification, and pharmaceutically acceptable salts thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of the enzyme myeloperoxidase (MPO) is beneficial. Certain novel compounds of formula (Ia) or (Ib) and pharmaceutically acceptable salts thereof are disclosed, together with processes for their preparation. The compounds of formulae (Ia) and (Ib) are MPO inhibitors and are thereby particularly useful in the treatment or prophylaxis of neuroinflammatory disorders.

WO 03/089430 A1

## THIOXANTHINE DERIVATIVES AS MYELOPEROXIDASE INHIBITORS

Field of the Invention

The present invention relates to the use of thioxanthine derivatives as inhibitors of the enzyme myeloperoxidase (MPO). Certain novel thioxanthine derivatives are also disclosed together with processes for their preparation, compositions containing them and their use in therapy.

Background of the Invention

Myeloperoxidase (MPO) is a heme-containing enzyme found predominantly in polymorphonuclear leukocytes (PMNs). MPO is one member of a diverse protein family of mammalian peroxidases that also includes eosinophil peroxidase, thyroid peroxidase, salivary peroxidase, lactoperoxidase, prostaglandin H synthase, and others. The mature enzyme is a dimer of identical halves. Each half molecule contains a covalently bound heme that exhibits unusual spectral properties responsible for the characteristic green colour of MPO. Cleavage of the disulphide bridge linking the two halves of MPO yields the hemi-enzyme that exhibits spectral and catalytic properties indistinguishable from those of the intact enzyme. The enzyme uses hydrogen peroxide to oxidize chloride to hypochlorous acid. Other halides and pseudohalides (like thiocyanate) are also physiological substrates to MPO.

PMNs are of particular importance for combating infections. These cells contain MPO, with well documented microbicidal action. PMNs act non-specifically by phagocytosis to engulf microorganisms, incorporate them into vacuoles, termed phagosomes, which fuse with granules containing myeloperoxidase to form phagolysosomes. In phagolysosomes the enzymatic activity of the myeloperoxidase leads to the formation of hypochlorous acid, a potent bactericidal compound. Hypochlorous acid is oxidizing in itself, and reacts most avidly with thiols and thioethers, but also converts amines into chloramines, and chlorinates aromatic amino acids. Macrophages are large phagocytic cells which, like PMNs, are capable of phagocytosing microorganisms. Macrophages can generate

hydrogen peroxide and upon activation also produce myeloperoxidase. MPO and hydrogen peroxide can also be released to the outside of the cells where the reaction with chloride can induce damage to adjacent tissue.

- 5 Linkage of myeloperoxidase activity to disease has been implicated in neurological diseases with a neuroinflammatory response including multiple sclerosis, Alzheimer's disease, Parkinson's disease and stroke as well as other inflammatory diseases or conditions like asthma, chronic obstructive pulmonary disease, cystic fibrosis, atherosclerosis, inflammatory bowel disease, renal glomerular damage and rheumatoid
- 10 arthritis. Lung cancer has also been suggested to be associated with high MPO levels.

WO 01/85146 discloses various compounds that are MPO inhibitors and are thereby useful in the treatment of chronic obstructive pulmonary disease (COPD). 3-n-Propyl-2-thioxanthine is disclosed in Drug Development Research, 1999, 47, 45-53. 3-Isobutyl-6-thioxanthine is disclosed in J. Chem. Soc., 1962, 1863. 2-Thioxanthine is commercially

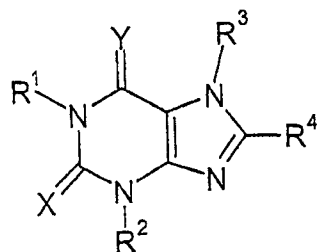
15 available.

The present invention relates to a group of thioxanthine derivatives that surprisingly display useful properties as inhibitors of the enzyme MPO.

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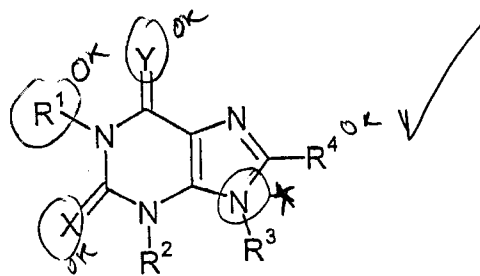
### Disclosure of the invention

According to the present invention, there is provided the use of a compound of formula (Ia) or (Ib)



(Ia)

or



(Ib)

25

wherein:

one of X and Y represents S, and the other represents O or S;

R<sup>1</sup> represents hydrogen or C1 to 6 alkyl;

R<sup>2</sup> represents hydrogen or C1 to 6 alkyl, said alkyl group being optionally substituted by:

i) a saturated or partially unsaturated 3- to 7-membered ring optionally incorporating one or two heteroatoms selected independently from O, N and S, and optionally incorporating a carbonyl group; said ring being optionally substituted by one or more substituents selected from halogen, hydroxy, C1 to 6 alkoxy and C1 to 6 alkyl; said alkyl being optionally further substituted by hydroxy or C1 to 6 alkoxy; or

ii) C1 to 6 alkoxy; or

iii) an aromatic ring selected from phenyl, furyl or thienyl; said aromatic ring being optionally further substituted by halogen, C1 to 6 alkyl or C1 to 6 alkoxy;

R<sup>3</sup> and R<sup>4</sup> independently represent hydrogen or C1 to 6 alkyl;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of the enzyme MPO is beneficial.

The compounds of formula (Ia) or (Ib) may exist in enantiomeric forms. Therefore, all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention.

It will be appreciated that when R<sup>3</sup> in formulae (Ia) and (Ib) represents hydrogen, the two alternative representations (Ia) and (Ib) are tautomeric forms of the same compound. All such tautomers and mixtures of tautomers are included within the scope of the present invention.

A more particular aspect of the invention provides the use of a compound of formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of neuroinflammatory disorders.

Example 21Enantiomers of 3-(2-Tetrahydrofuryl-methyl)-2-thioxanthine

5 A solution of racemic 3-(2-tetrahydrofuryl-methyl)-2-thioxanthine (3 mg/mL) was separated by chiral HPLC on a Chiralpak AD-RH column (4.6 x 150 mm; 5 $\mu$ m). The mobile phase was methanol: acetic acid: triethylamine (100: 0.1: 0.1) and the flow rate 1 mL/min. The injection volume was 20 $\mu$ L.

**Enantiomer 1**

10 e.e. 93.6%; MS (ES)  $m/z$  253 (M+1).

**Enantiomer 2**

e.e. 97.3%; MS (ES)  $m/z$  253 (M+1).

Example 22

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3-n-Butyl-2-thioxanthine

The title compound was prepared using the procedure described for Example 6.

20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  13.82 (s, 1H), 12.40 (s, 1H), 8.15 (s, 1H), 4.45 (m, 2H), 1.73 (m, 2H), 1.34 (sextet, 2H,  $J=7.5$ ), 0.92 (t, 3H,  $J=7.5$ ).

$^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  173.31, 152.62, 149.30, 141.47, 110.84, 47.37, 28.61, 19.48, 13.72.

MS (ES)  $m/z$  225 (M+1).

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Screens

Methods for the determination of MPO inhibitory activity are disclosed in co-pending patent application WO 02/090575. The pharmacological activity of compounds according to the invention was tested in the following screen:

Assay buffer: 20 mM sodium/potassium phosphate buffer pH 6.5 containing 10 mM taurine and 100 mM NaCl.

Developing reagent: 2 mM 3,3',5,5'-tetramethylbenzidine (TMB), 200  $\mu$ M KI, 200 mM acetate buffer pH 5.4 with 20 % DMF.

To 10  $\mu$ l of diluted compounds in assay buffer, 40  $\mu$ l of human MPO (final concentration 2.5 nM) was added for 10 minutes at room temperature. Then 50  $\mu$ l of H<sub>2</sub>O<sub>2</sub> (final concentration 100  $\mu$ M), or assay buffer alone as a control, were added for 10 minutes at room temperature. The reaction was stopped by adding 10  $\mu$ l 0.2 mg/ml of catalase (final concentration 18  $\mu$ g/ml) for 5 minutes before 100  $\mu$ l of TMB developing reagent was added (2 mM TMB in 200 mM acetate buffer pH 5.4 containing 20% dimethylformamide (DMF) and 200  $\mu$ M KI). Plates were mixed and the amount of oxidised 3,3',5,5'-tetramethylbenzidine formed was then measured after about 5 minutes using absorbance spectroscopy at about 650 nM. IC<sub>50</sub> values were then determined using standard procedures.

When tested in the above screen, the compounds of Examples 1 to 22 gave IC<sub>50</sub> values of less than 60  $\mu$ M, indicating that they are expected to show useful therapeutic activity. Representative results are shown in the following Table:

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| Compound   | Inhibition of MPO (IC <sub>50</sub> $\mu$ M) |
|------------|----------------------------------------------|
| Example 6  | 0.87                                         |
| Example 10 | 0.53                                         |
| Example 14 | 0.51                                         |
| Example 15 | 0.44                                         |
| Example 16 | 2.94                                         |
| Example 17 | 7.57                                         |
| Example 18 | 0.49                                         |
| Example 20 | 0.96                                         |

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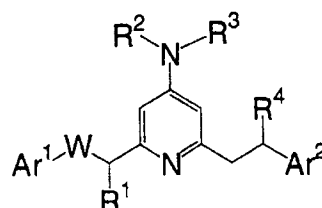


D2  
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

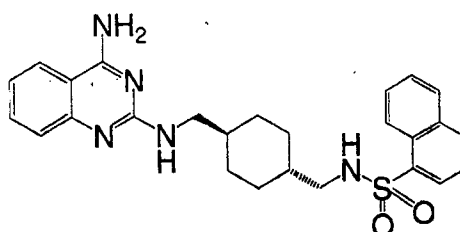
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| (51) International Patent Classification <sup>6</sup> :<br><b>C07D 471/04, A61K 31/44, 31/505,<br/>31/52, C07D 487/04</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  | <b>A1</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | (11) International Publication Number: <b>WO 99/40091</b><br>(43) International Publication Date: 12 August 1999 (12.08.99) |
| (21) International Application Number: <b>PCT/US99/02500</b><br>(22) International Filing Date: <b>5 February 1999 (05.02.99)</b><br>(30) Priority Data:<br>60/073,927 6 February 1998 (06.02.98) US<br>60/073,981 6 February 1998 (06.02.98) US<br>60/093,482 20 July 1998 (20.07.98) US<br>60/093,577 20 July 1998 (20.07.98) US<br>09/246,775 4 February 1999 (04.02.99) US<br>(71) Applicant: <b>AMGEN INC. [US/US]; One Amgen Center Drive,<br/>Thousand Oaks, CA 91320-1799 (US).</b><br>(72) Inventors: <b>NORMAN, Mark, H.; 3038 Shadow Hill Circle,<br/>Thousand Oaks, CA 91360 (US). CHEN, Ning; 2888<br/>Capella Way, Thousand Oaks, CA 91362 (US). HAN,<br/>Nianhe; 2217 Rutland Place, Thousand Oaks, CA 91362<br/>(US). LIU, Longbin; 753 Rushing Creek Place, Thousand<br/>Oaks, CA 91320 (US). HURT, Clarence, R.; 269 Camino<br/>Toluca, Camarillo, CA 93010 (US). FOTSCH, Christopher,<br/>H.; 533 Timberwood Avenue, Thousand Oaks, CA 91360<br/>(US). JENKINS, Tracy, J.; 391 Country Club Drive, #16,<br/>Simi Valley, CA 93065 (US). MORENO, Ofir, A.; 148 Poli<br/>Street, Ventura, CA 93001 (US).</b> |  | (74) Agents: <b>ODRE, Steven, M. et al.; Amgen, Inc., One Amgen<br/>Center Drive, Thousand Oaks, CA 91320-1799 (US).</b><br>(81) Designated States: <b>AL, AM, AT, AU, AZ, BA, BB, BG, BR,<br/>BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD,<br/>GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP,<br/>KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,<br/>MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG,<br/>SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW,<br/>ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW),<br/>Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),<br/>European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,<br/>GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF,<br/>BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN,<br/>TD, TG).</b> |                                                                                                                             |
| <b>Published</b><br><i>With international search report.<br/>Before the expiration of the time limit for amending the<br/>claims and to be republished in the event of the receipt of<br/>amendments.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                             |
| (54) Title: <b>BICYCLIC PYRIDINE AND PYRIMIDINE DERIVATIVES AS NEUROPEPTIDE Y RECEPTOR ANTAGONISTS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                             |
| (57) Abstract<br><p>There are provided compounds, compositions and methods of use thereof in the modulation of feeding behavior, obesity, diabetes, cancer (tumor), inflammatory disorders, depression, stress related disorders, Alzheimer's disease and other disease conditions.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                             |

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Further, the following compound and related compounds are noted to be useful in NPY5 associated disorders and are disclosed in PCT publications,

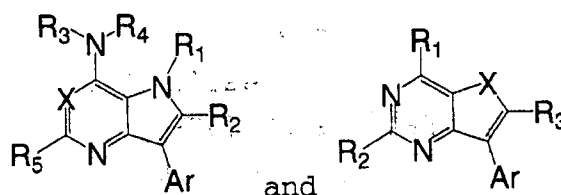
5 WO 97/20823, WO 97/20820, WO 97/20821. and WO 97/20822:



and WO 98/35944 and WO 98/35957 disclose substituted alkylamide NPY5 receptor antagonists.

See, also, L. Criscione, et al., Society for  
10 Neuroscience, 23, Abstract No. 231.2, (1997).

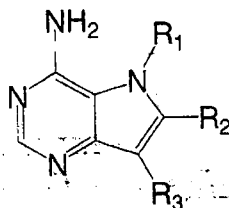
Other published compounds include the following general formulae:



15 (See, respectively, PCT publication, WO 96/35689, published Nov. 14, 1996 - CRF1 receptor agonist or antagonist compounds useful for treating and diagnosis of stress related disorders; and PCT publication,  
20 WO 97/29110, published Aug. 14, 1997 - CRF receptor antagonist compounds useful for treating disorders relating to hypersecretion of CRF); and,

factor (EGF) and of c-erbB2 kinase. These receptor-specific enzyme activities play a key role in signal transmission in a large number of mammalian cells, including human cells, especially epithelial cells, cells of the immune system and cells of the central and peripheral nervous system. In various cell types, EGF-induced activation of receptor-associated protein tyrosine kinase (EGF-R-PTK) is a prerequisite for cell division and thus for the proliferation of the cell population. Inhibition of protein kinases, such as EGF-receptor-specific tyrosine kinase, inhibits the proliferation of the cells. The compounds were also reported to inhibit other protein tyrosine kinases that are involved in signal transmission mediated by trophic factors, for example abl kinase (such as v-abl kinase), kinases from the family of the src kinases (such as c-src kinase), lck, fyn, other kinases of the EGF family (such as c-erbB2 kinase (HER-2), c-erbB3 kinase, c-erbB4 kinase), members of the family of the PDGF receptor protein tyrosine kinases (such as PDGF receptor kinase, CSF-1 receptor kinase, Kit receptor kinase, VEGF receptor kinase and FGF receptor kinase), the receptor kinase of the insulin-like growth factor (IGF-1 kinase), and serine/threonine kinases (such as protein kinase C or cdc kinases), all of which play a part in growth regulation and transformation in mammalian cells, including human cells.

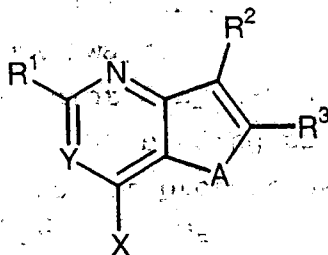
WO 97/49706 (incorporated herein by reference in its entirety) discloses that compounds of the general formula



wherein  $R_1$ ,  $R_2$ , and  $R_3$  are as defined therein, are protein tyrosine kinase inhibitors.

### Summary of the Invention

5        There is a need to provide therapeutic and prophylactic methods for the modulation of feeding behavior, obesity, diabetes, cancer (tumor), inflammatory disorders, depression, stress related disorders, Alzheimer's disease and other disease  
10    conditions. Additionally, there is a need to provide therapeutic and prophylactic methods for the modulation of other disease states which result from the same or related biological pathways, including the biological pathways which are mediated by NPY and/or NPY  
15    receptors; CRF and/or CRH binding protein; protein tyrosine kinases and/or of protein serine/threonine kinases; MCP-1 and/or its receptor; and the like. The present invention provides compounds which can be used to modulate such activities. In particular, the present  
20    invention provides novel compounds and methods for modulating feeding behavior, obesity or diabetic conditions, as well as other disease states associated with the same pathways effecting the noted disease states, especially those modulated by NPY or NPY  
25    receptors and related pathways. Compounds useful in the various aspects of the invention are represented by the formula



wherein A, X, Y,  $R^1$ ,  $R^2$  and  $R^3$  are defined below.

30        Additionally, there are provided formulations which comprise a compound of this invention in

combination with a pharmaceutically acceptable carrier,  
diluent or excipient therefor. These formulations may  
be used in the noted methods. Further, there are  
provided processes for preparing the compounds of this  
5 invention.

#### Brief Description of the Drawings

Fig. 1 outlines a general reaction scheme for the  
synthesis of pyrrolo[3,2-d]pyrimidines of the  
10 invention.

Fig. 2 outlines a general reaction scheme for the  
synthesis of pyrrolo[3,2-d]pyridines and pyrrolo[3,2-d]  
pyrimidines.

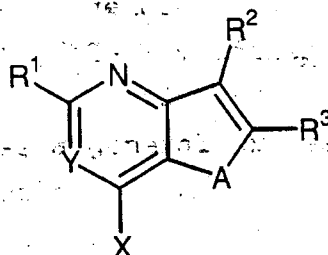
Fig. 3 provides a general process for the  
15 synthesis of thiopheno-, furano-, and pyrrolo-[3,2-d]-  
pyrimidines and -pyridines of the invention.

Fig. 4 provides a general process for the  
synthesis of 5-hydrocyclopenta[2,1-d]pyrimidines of the  
invention.

20 In the drawings, L represents a leaving group  
familiar to one skilled in the art and E represents  
-CO<sub>2</sub>CH<sub>3</sub>, -C(O)X or -CN, wherein X is a halogen.

#### Detailed Description of the Invention

25 In accordance with the present invention, there is  
provided compounds of the formula:



or a pharmaceutically acceptable salt, ester, solvate  
or N-oxide thereof, wherein Y is N or C(R<sup>6</sup>);

15

A is O, S, S(O), S(O)<sub>2</sub>, N-H, N-R<sup>4</sup> or CR<sup>4</sup>R<sup>7</sup>; preferably, A is O, S, S(O)<sub>2</sub>, N-H, N-R<sup>4</sup> or CHR<sup>4</sup>; more preferably, A is O, S, N-H or N-R<sup>4</sup>; more preferably, A is O, S or N-H; most preferably, A is N-H;

5

R<sup>1</sup> is a hydrogen, -OH, halo, -CF<sub>3</sub>, -OCF<sub>3</sub>, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, -Z(aryl), -NH<sub>2</sub>, -NH((C<sub>1</sub>-C<sub>8</sub>)alkyl), -N((C<sub>1</sub>-C<sub>8</sub>)alkyl)<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl or -Z(Q) radical; preferably, R<sup>6</sup> is a hydrogen, -OH, halo, -CF<sub>3</sub>, -OCF<sub>3</sub>,

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(C<sub>1</sub>-C<sub>8</sub>)alkoxy, aryl, -NH<sub>2</sub>, -NH((C<sub>1</sub>-C<sub>8</sub>)alkyl), -N((C<sub>1</sub>-C<sub>8</sub>)alkyl)<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl or -Z(Q) radical; more preferably, R<sup>6</sup> is a hydrogen, -OH, halo, -CF<sub>3</sub>, -OCF<sub>3</sub>, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, aryl, -NH<sub>2</sub>, -NH((C<sub>1</sub>-C<sub>8</sub>)alkyl), -N((C<sub>1</sub>-C<sub>8</sub>)alkyl)<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)alkyl,

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(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl or -Z(Q) radical; more preferably, R<sup>6</sup> is a hydrogen, -OH, halo, -CF<sub>3</sub>, -OCF<sub>3</sub>, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, -NH<sub>2</sub>, -NH((C<sub>1</sub>-C<sub>4</sub>)alkyl), -N((C<sub>1</sub>-C<sub>4</sub>)alkyl)<sub>2</sub>, (C<sub>1</sub>-C<sub>4</sub>)alkyl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl radical; more preferably, R<sup>6</sup> is a hydrogen, -OH, chloro, fluoro, -CF<sub>3</sub>, -OCF<sub>3</sub>,

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(C<sub>1</sub>-C<sub>2</sub>)alkoxy, -NH<sub>2</sub>, -NH((C<sub>1</sub>-C<sub>2</sub>)alkyl), -N((C<sub>1</sub>-C<sub>2</sub>)alkyl)<sub>2</sub> or (C<sub>1</sub>-C<sub>4</sub>)alkyl radical; more preferably, R<sup>6</sup> is a hydrogen, -OH, chloro, fluoro, -CF<sub>3</sub>, -OCF<sub>3</sub>, (C<sub>1</sub>-C<sub>2</sub>)alkoxy or (C<sub>1</sub>-C<sub>2</sub>)alkyl radical; most preferably, R<sup>6</sup> is a hydrogen radical;

25

R<sup>1</sup> is a hydrogen, halo, -OH, -NO<sub>2</sub>, -NHOH, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, -Z((C<sub>1</sub>-C<sub>8</sub>)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C<sub>3</sub>-C<sub>10</sub>)cycloalkyl), -Z(NR<sup>5</sup>SO<sub>2</sub>R<sup>5</sup>), -Z(CON(R<sup>5</sup>)<sub>2</sub>), -Z(CO<sub>2</sub>R<sup>5</sup>), -Z(N(R<sup>5</sup>)<sub>2</sub>), -Z(NR<sup>5</sup>CON(R<sup>5</sup>)<sub>2</sub>), -Z(NR<sup>5</sup>(CO)R<sup>5</sup>), -Z(NR<sup>5</sup>CO<sub>2</sub>R<sup>5</sup>), -Z(COR<sup>5</sup>), -Z(S(O)<sub>p</sub>R<sup>5</sup>) or -Z(Q) radical; preferably, R<sup>1</sup> is a hydrogen, halo, -OH, -NO<sub>2</sub>, -NHOH, -CF<sub>3</sub>, -OCF<sub>3</sub>, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, -Z((C<sub>1</sub>-C<sub>8</sub>)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl),

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-Z((C<sub>3</sub>-C<sub>10</sub>)cycloalkyl), -Z(NR<sup>5</sup>SO<sub>2</sub>R<sup>5</sup>), -Z(CON(R<sup>5</sup>)<sub>2</sub>), -Z(CO<sub>2</sub>R<sup>5</sup>), -Z(N(R<sup>5</sup>)<sub>2</sub>), -Z(NR<sup>5</sup>CON(R<sup>5</sup>)<sub>2</sub>), -Z(NR<sup>5</sup>(CO)R<sup>5</sup>),

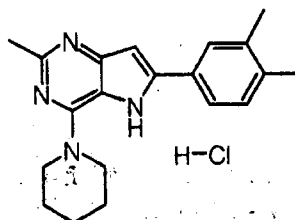
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- Z(NR<sup>5</sup>CO<sub>2</sub>R<sup>5</sup>), -Z(COR<sup>5</sup>), -Z(S(O)<sub>p</sub>R<sup>5</sup>) or -Z(Q) radical; more preferably, R<sup>1</sup> is a hydrogen, halo, -OH, -NO<sub>2</sub>, -NHOH, -CF<sub>3</sub>, -OCF<sub>3</sub>, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, -Z((C<sub>1</sub>-C<sub>8</sub>)alkoxy), -Z(aryloxy), -Z(aryl),
- 5 -Z(heteroaryl), -Z((C<sub>3</sub>-C<sub>10</sub>)cycloalkyl), -Z(NR<sup>5</sup>SO<sub>2</sub>R<sup>5</sup>), -Z(CON(R<sup>5</sup>)<sub>2</sub>), -Z(CO<sub>2</sub>R<sup>5</sup>), -Z(N(R<sup>5</sup>)<sub>2</sub>), -Z(NR<sup>5</sup>CON(R<sup>5</sup>)<sub>2</sub>), -Z(NR<sup>5</sup>(CO)R<sup>5</sup>), -Z(NR<sup>5</sup>CO<sub>2</sub>R<sup>5</sup>), -Z(COR<sup>5</sup>), -Z(S(O)<sub>p</sub>R<sup>5</sup>) or -Z(Q) radical; more preferably, R<sup>1</sup> is a hydrogen, halo, -OH, -NO<sub>2</sub>, -NHOH, -CF<sub>3</sub>, -OCF<sub>3</sub>, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl,
- 10 -Z((C<sub>1</sub>-C<sub>8</sub>)alkoxy), -Z((C<sub>3</sub>-C<sub>6</sub>)cycloalkyl), -Z(NR<sup>10</sup>SO<sub>2</sub>R<sup>5</sup>), -Z(N(R<sup>5</sup>)<sub>2</sub>) or -Z(Q) radical; more preferably, R<sup>1</sup> is a hydrogen, halo, -OH, -NO<sub>2</sub>, -NHOH, -CF<sub>3</sub>, -OCF<sub>3</sub>, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, -(NR<sup>10</sup>)<sub>k</sub>((C<sub>1</sub>-C<sub>2</sub>)alkyl)<sub>k</sub>-cyclopropyl or -(NR<sup>10</sup>)<sub>k</sub>((C<sub>1</sub>-C<sub>2</sub>)alkyl)<sub>k</sub>-N(R<sup>10</sup>)<sub>2</sub> radical;
- 15 more preferably, R<sup>1</sup> is a bromo, chloro, fluoro, -OH, -NO<sub>2</sub>, -NHOH, -CF<sub>3</sub>, -OCF<sub>3</sub>, (C<sub>1</sub>-C<sub>2</sub>)alkyl, (C<sub>1</sub>-C<sub>2</sub>)alkoxy, -(NR<sup>10</sup>)<sub>k</sub>((C<sub>1</sub>-C<sub>2</sub>)alkyl)<sub>k</sub>-cyclopropyl, -NH<sub>2</sub> or -NH((C<sub>1</sub>-C<sub>2</sub>)alkyl) radical; most preferably, R<sup>1</sup> is a -CF<sub>3</sub>, -OCF<sub>3</sub>, methyl, methoxy, cyclopropyl, -NH<sub>2</sub> or -NH-methyl
- 20 radical; alternatively, preferably, R<sup>1</sup> is not an optionally substituted aryl or heteroaryl radical;

- X is a hydrogen, halo, -OH, -NO<sub>2</sub>, -NHOH, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, -Z((C<sub>1</sub>-C<sub>8</sub>)alkoxy), -Z(aryloxy),
- 25 -Z(aryl), -Z(heteroaryl), -Z((C<sub>3</sub>-C<sub>10</sub>)cycloalkyl), -Z(NR<sup>5</sup>SO<sub>2</sub>R<sup>5</sup>), -Z(CON(R<sup>5</sup>)<sub>2</sub>), -Z(CO<sub>2</sub>R<sup>5</sup>), -Z(N(R<sup>5</sup>)<sub>2</sub>), -Z(NR<sup>5</sup>CON(R<sup>5</sup>)<sub>2</sub>), -Z(NR<sup>5</sup>(CO)R<sup>5</sup>), -Z(NR<sup>5</sup>CO<sub>2</sub>R<sup>5</sup>), -Z(COR<sup>5</sup>), -Z(S(O)<sub>p</sub>R<sup>5</sup>) or -Z(Q) radical; preferably, X is a (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl,
- 30 -(NR<sup>5</sup>)<sub>k</sub>((C<sub>1</sub>-C<sub>8</sub>)alkyl)(C<sub>1</sub>-C<sub>8</sub>)alkoxy, -(NR<sup>5</sup>)<sub>k</sub>((C<sub>1</sub>-C<sub>8</sub>)alkyl)aryloxy, -(NR<sup>5</sup>)<sub>k</sub>((C<sub>1</sub>-C<sub>8</sub>)alkyl)S(O)<sub>p</sub>R<sup>5</sup>, -(NR<sup>5</sup>)<sub>k</sub>((C<sub>1</sub>-C<sub>8</sub>)alkyl)S(O)<sub>p</sub>R<sup>5</sup>, -(NR<sup>5</sup>)D(C<sub>1</sub>-C<sub>8</sub>)alkoxy, -(NR<sup>5</sup>)(CH<sub>2</sub>)<sub>m</sub>((C<sub>3</sub>-C<sub>10</sub>)cycloalkyl)<sub>k</sub>(CH<sub>2</sub>)<sub>m</sub>(C<sub>1</sub>-C<sub>8</sub>)alkoxy, -(NR<sup>5</sup>)<sub>k</sub>(CH<sub>2</sub>)<sub>m</sub>((C<sub>3</sub>-C<sub>10</sub>)cycloalkyl)<sub>k</sub>(CH<sub>2</sub>)<sub>m</sub>(C<sub>1</sub>-C<sub>8</sub>)alkoxy,
- 35 -(NR<sup>5</sup>)<sub>k</sub>(CH<sub>2</sub>)<sub>m</sub>((C<sub>3</sub>-C<sub>10</sub>)cycloalkyl)(CH<sub>2</sub>)<sub>m</sub>(C<sub>1</sub>-C<sub>8</sub>)alkoxy, -(NR<sup>5</sup>)(CH<sub>2</sub>)<sub>m</sub>((C<sub>3</sub>-C<sub>10</sub>)cycloalkyl)<sub>k</sub>(CH<sub>2</sub>)<sub>m</sub>aryloxy,

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7.17 mmol), *N,N*-diisopropylethylamine (1.2 mL, 7.17 mmol), piperidine (1.1 mL, 11.5 mmol),  $\text{NEt}_3$  (1.1 mL) and  $\text{SnCl}_4$  (21 mL of a 2 M soln in DMF). In this example the  $\text{SnCl}_4$  solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5  $\text{CHCl}_3/\text{MeOH}$  as eluant to give 742 mg (26%) of trifluoro[4-(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenylthio]methane as a beige colored foam. This compound (741 mg, 1.90 mmol) was dissolved in 10:1 EtOAc/MeOH (60 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.90 mL, 1.90 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL),  $\text{Et}_2\text{O}$  (3 x 15 mL) and dried under vacuum at 60 °C to give 418 mg (13%) of the title compound as white colored needles. Mp: 270-272 °C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ; 400 MHz):  $\delta$  1.65 (br s, 6), 2.51 (s, 3), 4.00 (br s, 4), 6.96 (s, 1), 7.84 (d, 2,  $J = 8.1$ ), 8.06 (d, 2,  $J = 8.2$ ), 12.12 (s, 1), 14.39 (s, 1). MS  $m/z$ : 393 ( $M+1$  for free base). Anal. Calcd for  $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_4\text{S}\cdot\text{HCl}\cdot\text{H}_2\text{O}$ : C, 51.06; H, 4.96; N, 12.54; Cl, 7.93. Found: C, 51.02; H, 4.98; N, 12.46; Cl, 8.02.

**Example 124**

6-(3,4-Dimethylphenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.