

CAVELIER

ABOGADOS

www.cavelier.com
cavelier@cavelier.com

EDIFICIO S
CARRERA 4 N
BOGOTA 8, C

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-039105-00006-0000

Fecha: 2009-12-07 15:47:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYI Eve: 378 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 12

Teléfono: (57-1) 347 3611

9650

814

660

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 444

Referencia : Expediente No. 06039105
Asunto : Solicitud de patente para: **DERIVADOS DE N-TIAZOL-2IL-BENZAMIDA**
Solicitante : H. LUNDBECK A/S
Clase : A61K 031/426, A61P 025/008, A61P 025/016, C07D 277/046
Fecha solicitud: 25 de abril de 2006

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, de acuerdo con la sustitución del poder a mí otorgada por el doctor Emilio Ferrero, me refiero al oficio No. 8758 notificado por fijación en lista del 31 de julio de 2009.

2. Mediante memorial radicado el día 01 de octubre de 2009 solicité plazo de treinta (30) días para atender el oficio No. 8758.

3. Mediante oficio No. 8758 se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

3.1 De la solicitud de patente

3.1.1 Reivindicaciones

El Examinador ha solicitado señalar el verdadero alcance y límite de los radicales que se encuentren debidamente sustentados en el aparte descriptivo de la solicitud, por cuanto observa que el empleo de términos como arilo, heteroarilo, alifático, entre otros, permite

incluir de manera especulativa radicales que no han sido objeto de comprobación técnica.

3.1.2 Reivindicaciones relativas a un uso

Bajo este marco se han objetado las reivindicaciones 1 a 26 y 49 y 50, ya que hacen referencia al empleo de derivados de N-tiazol-2-il-benzamida para la fabricación de un medicamento.

3.2 Análisis de patentabilidad

3.2.1 Nivel inventivo

El Examinador ha citado el documento D1: WO 0026202, considerando que éste afecta el nivel inventivo de la presente solicitud. Según los argumentos expuestos, los compuestos de la presente invención difieren de los compuestos de D1 en los grupos funcionales que sustituyen al anillo de fenilo que se enlaza al anillo de tiazol mediante el puente de carboxamido. Sin embargo, el Examinador considera que dicha diferencia estructural no parece conferir un efecto técnico inesperado.

4. Con el fin de subsanar las objeciones expuestas, se desean presentar las siguientes modificaciones, aclaraciones y argumentos:

4.1 Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar nuevo pliego reivindicatorio conformado por una única reivindicación.

De esta manera, siguiendo las observaciones del Examinador se han eliminado las reivindicaciones 1 a 39 y 41 a 50 con el objeto de presentar una única reivindicación (antigua reivindicación 40) la cual indica claramente los compuestos que se desean proteger.

Por lo tanto se presenta en esta oportunidad un pliego reivindicatorio claro, conciso, debidamente soportado en la descripción y que no incluye reivindicaciones de uso. Por lo tanto, consideramos que las objeciones formuladas a este respecto se deben tener por superadas. Solicitamos atentamente tener en cuenta este nuevo pliego reivindicatorio que cumple con las disposiciones de la Decisión 486.

4.2 Argumentos a favor del nivel inventivo de la solicitud

237
238

El artículo 18 de la Decisión 486 señala lo siguiente:

Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica [subrayado fuera del texto]

Con el fin de evitar la subjetividad en el análisis de la obviedad de la invención frente a las enseñanzas del estado del arte, fue necesario que la Doctrina internacional desarrollara el método problema-solución que delimita claramente el papel del examinador y le da certeza a los solicitantes de patentes sobre la forma cómo se estudiará la patentabilidad de sus invenciones.

A este respecto, se considera entonces que un documento o una combinación de éstos sólo deben ser considerados válidos para la afectación de este requisito, cuando una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras sobre la manera como se resuelve el problema técnico, es decir, sobre la invención tal como se encuentra reivindicada.

Para los anteriores efectos, el método problema solución enseña que el primer paso en el estudio del nivel inventivo de una invención es determinar cuál es el estado del arte más próximo a la invención frente al cual ésta última debe ser comparada.

Dicho estado del arte más próximo es, de acuerdo con el Manual Andino de Patentes, aquel que resuelve el mismo problema técnico que pretende resolver la invención bajo estudio. Lo anterior, por cuanto esta sería la información a la cual normalmente accedería quien pretende resolver dicho problema técnico.

La aplicación de este método para el estudio del nivel inventivo de las solicitudes a su cargo por parte de las oficinas de patentes de los países miembros de la Comunidad Andina resulta obligatoria teniendo en cuenta la jurisprudencia del Tribunal de Justicia de la Comunidad Andina.

CAVELIER

ABOGADOS

Adicionalmente es importante poner de presente que el estudio de nivel inventivo llevado a cabo por el Examinador no puede ser un análisis en retrospectiva, toda vez que su tarea debe estar encaminada a ponerse en el lugar del inventor en el momento en el que él busca la solución al problema técnico y sin utilizar la solución reivindicada como punto de partida de dicho análisis.

En resumen, una anterioridad afectaría el nivel inventivo de una solicitud si una persona medianamente versada en la materia, en el momento de buscar la solución al problema técnico, encontrase en dicha anterioridad un problema técnico comparable y asimismo, encontrara enseñanzas o sugerencias que le llevasen de manera obvia a la solución reivindicada.

En el presente caso se tiene que la invención está relacionada con derivados de N-tiazol-2-il-benzamida que tienen afinidad para el receptor de adenosina 2A (A_{2A}) y que son útiles en el tratamiento de trastornos neurológicos y psiquiátricos donde hay compromiso de un receptor A_{2A} . Tal como se indica en la descripción de la invención, las interacciones entre receptores A_{2A} y D_2 , y en especial, las acciones de antagonistas A_{2A} son de gran interés en el tratamiento de la enfermedad de Parkinson que supone una disminución en los niveles de dopamina. Se tiene que los receptores A_{2A} interactúan tónica y antagónicamente con los receptores D_2 para dopamina con la estimulación. Por lo tanto, los antagonistas A_{2A} pueden tener la capacidad de mejorar el efecto de la dopamina endógena, tanto como los agonistas de la dopamina utilizados clínicamente y de incrementar el periodo de respuesta del fármaco dopaminérgico.

Por su parte, el documento D1 está relacionado con derivados de 2-amino-tiazol, y su empleo como agentes terapéuticos particularmente en el tratamiento del cáncer y desórdenes de proliferación celular. El objeto de este documento está dirigido a reemplazar las drogas citotóxicas tales como fluorouracilo (5-FU), doxorubicina y camptotecinas las cuales resultan en daños del ADN y afectan el ciclo celular. Los compuestos reclamados son agentes antitumor con alta especificidad para generar apoptosis, con eficacia y baja toxicidad. Por lo tanto, las enseñanzas y sugerencias del documento D1 están dirigidas a la inhibición directa de la actividad cdk/ciclina para restringir la proliferación no regulada de una célula tumoral. D1



Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

241

1

SOLICITUD DE:

☐ Corrección de Error Material ☒ Modificación a una solicitud

2

SOLICITANTE

Nombre: H. LUNDBECK A/S
Sociedad constituida y existente bajo las leyes de Dinamarca.

Dirección: 9 Ottiliavej,
2500 Valby-Copenhagen,
Dinamarca

Domicilio: Valby-Copenhagen,
Dinamarca

Teléfono: 546 09 70 **Fax:** 249 40 70
E-mail: clientes@cavelier.com

IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐

Número: _____

3

**REPRESENTANTE
O APODERADO**

Nombre: LUZ CLEMENCIA DE PÁEZ
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐

Cual _____

Número 35.456.344 T. P. 23.555

4

Número de expediente: 06.039.105

5

Descripción de la corrección o modificación solicitada:

Presento nuevo capítulo reivindicatorio compuesto por 1 reivindicación con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.

6

Comprobante de pago No.

Fecha:

7

Anexos

- ☐ Comprobante de pago de la tasa por \$111.000, por concepto de modificaciones.
- ☐ Comprobante de pago por reivindicaciones adicionales después de la decimoquinta reivindicación por
- ☐ Poderes, si fuere el caso
- ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.
- ☒ Copia auténtica de la Sustitución de poder del Doctor EMILIO FERRERO a la Doctora LUZ CLEMENCIA DE PÁEZ.

2

NOTARIA SEXTA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C. **22 OCT 2009**
Ante mí AMPARO QUINTERO ARTURO,
NOTARIA SEXTA DEL CÍRCULO DE
BOGOTÁ, D.C.
Comparado(aron) *Emilio Ferrera*
Williamson y Luz Clemencia
Duárez de Ríos
Quien(es) exhibi(eron) la(s) C.C.
CP 438019 TP 31429
CP 37456344 TP 23553
Y declaro(aron) que la(s) firma(s) que aparece(n)
en el presente documento es(son) la(s) suya(s) y
que el contenido del mismo es cierto.
En constancia se firma esta diligencia.

Luz Clemencia Suárez



COMO NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ
D.C. HAGO CONSTAR QUE LA FOTOCOPIA CORRESPONDE
CON EL ORIGINAL QUE ME TENGO A LA VISTA
BOGOTÁ D.C. REPÚBLICA DE COLOMBIA
30 NOV. 2009
AMPARO QUINTERO ARTURO
NOTARIA

~~243~~
244

REIVINDICACIONES

1. Un compuesto seleccionado del grupo que consiste de:

- 4-Butirilamino-*N*-tiazol-2-il-benzamida, (1)
- rac*-3-metoxi-4-(3-metil-4-oxo-pentanoilamino)-*N*-tiazol-2-il-benzamida, (2)
- rac*-4-(3-metil-pentanoilamino)-*N*-tiazol-2-il-benzamida, (3)
- 4-hexanoilamino-3-metil-*N*-tiazol-2-il-benzamida, (4)
- 4-(2-cicloheptil-acetilamino)-*N*-tiazol-2-il-benzamida, (5)
- rac*-3-metoxi-4-(3-metil-pentanoilamino)-*N*-tiazol-2-il-benzamida, (6)
- 4-(2-cicloheptil-acetilamino)-3-metoxi-*N*-tiazol-2-il-benzamida, (7)
- rac*-4-[2-(2-oxo-ciclopentil)-acetilamino]-*N*-tiazol-2-il-benzamida, (8)
- 4-hexanoilamino-3-metoxi-*N*-tiazol-2-il-benzamida, (9)
- 3-metil-4-(4-fenil-butilamino)-*N*-tiazol-2-il-benzamida, (10)
- 4-(2-ciclohexil-acetilamino)-*N*-tiazol-2-il-benzamida, (11)
- rac*-4-(2-biciclo[2.2.1]hept-2-il-acetilamino)-*N*-tiazol-2-il-benzamida, (12)
- 4-(3,3-dimetil-butilamino)-*N*-(4,5-dimetil-tiazol-2-il)-benzamida, (13)
- 4-(2-adamantan-1-il-acetilamino)-*N*-tiazol-2-il-benzamida, (14)
- 4-(3-benzo[1,3]dioxol-5-il-propionilamino)-3-metil-*N*-tiazol-2-il-benzamida, (15)
- 4-(3-hidroxi-3-metil-butilamino)-3-metoxi-*N*-tiazol-2-il-benzamida, (16)
- 4-(4-fluoro-benzoilamino)-3-metoxi-*N*-tiazol-2-il-benzamida, (17)
- 4-benzoilamino-*N*-tiazol-2-il-benzamida, (18)
- ácido tiofeno-3-carboxílico [4-(tiazol-2-ilcarbamoil)-fenil]-amida, (19)
- N*-tiazol-2-il-4-(2-*o*-tolil-acetilamino)-benzamida, (20)
- N*-tiazol-2-il-4-(2-tiofen-3-il-acetilamino)-benzamida, (21)
- 4-(2-ciclopentil-acetilamino)-3-metil-*N*-tiazol-2-il-benzamida, (22)
- 4-(3,3-dimetil-butilamino)-*N*-tiazol-2-il-benzamida, (23)
- 4-(3,3-dimetil-butilamino)-3-metil-*N*-tiazol-2-il-benzamida, (24)
- 4-(3,3-dimetil-butilamino)-2-metoxi-*N*-tiazol-2-il-benzamida, (25)
- 3-cloro-4-(3-metil-butilamino)-*N*-tiazol-2-il-benzamida, (26)
- 3-bromo-4-(3,3-dimetil-butilamino)-*N*-tiazol-2-il-benzamida, (27)
- 4-(3-metil-butilamino)-*N*-tiazol-2-il-benzamida, (28)
- 3-bromo-4-(3-metil-butilamino)-*N*-tiazol-2-il-benzamida, (29)
- 4-(2-ciclopentil-acetilamino)-*N*-tiazol-2-il-benzamida, (30)
- 3-metil-4-(3-metil-butilamino)-*N*-tiazol-2-il-benzamida, (31)
- 3-cloro-4-(ciclopentanocarbonil-amino)-*N*-tiazol-2-il-benzamida, (32)
- 3-cloro-4-(2-metil-benzoilamino)-*N*-tiazol-2-il-benzamida, (33)
- 3-bromo-4-(ciclopentanocarbonil-amino)-*N*-tiazol-2-il-benzamida, (34)
- 4-(ciclopentanocarbonil-amino)-*N*-tiazol-2-il-benzamida, (35)

244
245

- 4-(ciclopentanocarbonil-amino)-3-metil-*N*-tiazol-2-il-benzamida, (36)
- ácido cicloheptanocarboxílico [2-bromo-4-(tiazol-2-ilcarbamoil)-fenil]-amida, (37)
- 4-isobutirilamino-2-metoxi-*N*-tiazol-2-il-benzamida, (38)
- ácido 8-(3,3-dimetil-butilamino)-2,3-dihidro-benzo[1,4]dioxina-5-carboxílico tiazol-2-ilamida, (39)
- 3-bromo-4-butilamino-*N*-tiazol-2-il-benzamida, (40)
- 2-metoxi-4-(3-metil-butilamino)-*N*-tiazol-2-il-benzamida, (41)
- ácido cicloheptanocarboxílico [4-(tiazol-2-ilcarbamoil)-fenil]-amida, (42)
- rac*-2-metoxi-4-(2-metil-butilamino)-*N*-tiazol-2-il-benzamida, (43)
- 4-(ciclopentanocarbonil-amino)-2-metoxi-*N*-tiazol-2-il-benzamida, (44)
- 3-bromo-4-(2-metil-benzoilamino)-*N*-tiazol-2-il-benzamida, (45)
- 3-cloro-4-(3,3-dimetil-butilamino)-*N*-tiazol-2-il-benzamida, (46)
- 4-(2-ciclopentil-acetilamino)-2-propoxi-*N*-tiazol-2-il-benzamida, (47)
- 4-(3,3-dimetil-butilamino)-2-propoxi-*N*-tiazol-2-il-benzamida, (48)
- 4-(2-ciclopentil-acetilamino)-3-fluoro-*N*-tiazol-2-il-benzamida, (49)
- 4-(3-metil-butilamino)-2-propoxi-*N*-tiazol-2-il-benzamida, (50)
- 3-fluoro-4-(3-metil-butilamino)-*N*-tiazol-2-il-benzamida, (51)
- 4-butilamino-3-fluoro-*N*-tiazol-2-il-benzamida, (52)
- 4-butilamino-2-propoxi-*N*-tiazol-2-il-benzamida, (53)
- 3-fluoro-4-(2-metil-benzoilamino)-*N*-tiazol-2-il-benzamida, (54)
- ácido cicloheptanocarboxílico [2-fluoro-4-(tiazol-2-ilcarbamoil)-fenil]-amida, (55)
- 4-(ciclopentanocarbonil-amino)-3-fluoro-*N*-tiazol-2-il-benzamida, (56)
- 4-(3,3-dimetil-butilamino)-2-(2-metoxi-etoxi)-*N*-tiazol-2-il-benzamida, (57)
- 3-fluoro-4-(3-metil-benzoilamino)-*N*-tiazol-2-il-benzamida, (58)
- rac*-3-fluoro-*N*-tiazol-2-il-4-(3,5,5-trimetil-hexanoilamino)-benzamida, (59)
- 4-(2-ciclopentil-acetilamino)-2-(2-metoxi-etoxi)-*N*-tiazol-2-il-benzamida, (60)
- ácido 4-(2-metil-benzoil)-3,4-dihidro-2H-benzo[1,4]oxazina-7-carboxílico tiazol-2-il-amida, (61)
- 4-(3,3-dimetil-butilamino)-3-fluoro-*N*-tiazol-2-il-benzamida, (62)
- 4-(3,3-dimetil-butilamino)-2-metil-*N*-tiazol-2-il-benzamida, (63)
- 5-cloro-4-(3,3-dimetil-butilamino)-2-metoxi-*N*-tiazol-2-il-benzamida, (64)
- 4-(3,3-dimetil-butilamino)-*N*-(5-metil-tiazol-2-il)-benzamida, (65)
- 5-cloro-2-metoxi-4-(3-metil-butilamino)-*N*-tiazol-2-il-benzamida, (66)
- 4-(2-metil-benzoilamino)-*N*-(5-metil-tiazol-2-il)-benzamida, (67)
- ácido 1-(3,3-dimetil-butil)-1,2,3,4-tetrahidro-quinolina-6-carboxílico tiazol-2-il-amida, (68)
- 5-cloro-2-metoxi-4-(2-metil-benzoilamino)-*N*-tiazol-2-il-benzamida, (69)
- ácido 1-(3-metil-butil)-1,2,3,4-tetrahidro-quinolina-6-carboxílico tiazol-2-ilamida, (70)
- ácido 1-(3,3-dimetil-butil)-2,3-dihidro-1H-indol-5-carboxílico tiazol-2-ilamida, (71)
- 4-[(3,3-dimetil-butil)-metil-amino]-*N*-tiazol-2-il-benzamida, (72)
- 4-[(2-ciclopentil-acetil)-propil-amino]-*N*-tiazol-2-il-benzamida, (73)

245
246

- 2-(2-metoxi-etoxi)-4-(3-metil-butililamino)-*N*-tiazol-2-il-benzamida, (74)
rac-2-propoxi-*N*-tiazol-2-il-4-(3,5,5-trimetil-hexanoilamino)-benzamida, (75)
rac-*N*-tiazol-2-il-4-(3,5,5-trimetil-hexanoilamino)-benzamida, (76)
 4-(3-ciclopentil-propionilamino)-*N*-tiazol-2-il-benzamida, (77)
 4-(2-ciclopentil-acetilamino)-3-metoxi-*N*-tiazol-2-il-benzamida, (78)
 ácido cicloheptanocarboxílico [2-metil-4-(tiazol-2-ilcarbamoil)-fenil]-amida, (79)
 3-metoxi-4-(3-fenil-propionilamino)-*N*-tiazol-2-il-benzamida, (80)
 ácido cicloheptanocarboxílico [2-cloro-4-(tiazol-2-ilcarbamoil)-fenil]-amida, (81)
 4-[2-(3-metoxi-fenil)-acetilamino]-3-metil-*N*-tiazol-2-il-benzamida, (82)
 3-bromo-4-(2-ciclopentil-acetilamino)-*N*-tiazol-2-il-benzamida, (83)
 4-butililamino-3-cloro-*N*-tiazol-2-il-benzamida, (84)
 5-cloro-4-(2-ciclopentil-acetilamino)-2-metoxi-*N*-tiazol-2-il-benzamida, (85)
 5-cloro-4-(ciclopentanocarbonil-amino)-2-metoxi-*N*-tiazol-2-il-benzamida, (86)
 4-(ciclohexanocarbonil-amino)-2-metoxi-*N*-tiazol-2-il-benzamida, (87)
 2-metoxi-4-(4-metoxi-benzoilamino)-*N*-tiazol-2-il-benzamida, (88)
 3-metoxi-4-fenilacetilamino-*N*-tiazol-2-il-benzamida, (89)
 3-metil-*N*-tiazol-2-il-4-(2-tiofen-2-il-acetilamino)-benzamida, (90)
 3-cloro-4-(2-ciclopentil-acetilamino)-*N*-tiazol-2-il-benzamida, (91)
 4-(4-metoxi-benzoilamino)-3-metil-*N*-tiazol-2-il-benzamida, (92)
 4-butililamino-3-metil-*N*-tiazol-2-il-benzamida, (93)
 4-(2-cloro-benzoilamino)-3-metil-*N*-tiazol-2-il-benzamida, (94)
 4-(2,5 di-cloro-benzoilamino)-3-metil-*N*-tiazol-2-il-benzamida, (95)
 4-(2-cloro-benzoilamino)-2-metoxi-*N*-tiazol-2-il-benzamida, (96)
 4-(2-etil-butililamino)-2-metoxi-*N*-tiazol-2-il-benzamida, (97)
 2-metoxi-4-(2-metil-benzoilamino)-*N*-tiazol-2-il-benzamida, (98)
 3-metil-4-(3-fenil-propionilamino)-*N*-tiazol-2-il-benzamida, (99)
 4-(3,3-dimetil-butililamino)-3-metoxi-*N*-tiazol-2-il-benzamida, (100)
rac-3-metil-*N*-tiazol-2-il-4-(3,5,5-trimetil-hexanoilamino)-benzamida, (101)
 ácido *rac*-2,3-dihidro-benzo[1,4]dioxina-2-carboxílico [2-metoxi-4-(tiazol-2-il- (102)
 carbamoil)-fenil]-amida,
 4-(2,2-dimetil-propionilamino)-3-metoxi-*N*-tiazol-2-il-benzamida, (103)
 2-metoxi-4-(4-metil-benzoilamino)-*N*-tiazol-2-il-benzamida, (104)
 ácido tiofeno-2-carboxílico [3-metoxi-4-(tiazol-2-ilcarbamoil)-fenil]-amida, (105)
 4-(3-metoxi-benzoilamino)-*N*-tiazol-2-il-benzamida, (106)
 ácido 8-(2-ciclopentil-acetilamino)-2,3-dihidro-benzo[1,4]dioxina-5-carboxílico tiazol-2- (107)
 ilamida,
 ácido 6-(2-ciclopentil-acetilamino)-bifenil-3-carboxílico tiazol-2-ilamida, (108)
 4-(2-ciclopentil-acetilamino)-3-(2-metoxi-etoxi)-*N*-tiazol-2-il-benzamida (109)
 4-(3,3-dimetil-butililamino)-2-fluoro-*N*-tiazol-2-il-benzamida, (110)

~~246~~
247

- 2-cloro-4-(2-metil-benzoilamino)-*N*-tiazol-2-il-benzamida, (111)
4-(2-fluoro-benzoilamino)-*N*-tiazol-2-il-benzamida, (112)
4-(2-metoxi-benzoilamino)-*N*-tiazol-2-il-benzamida, (113)
ácido benzo[b]tiofeno-2-carboxílico [2-metil-4-(tiazol-2-ilcarbamoil)-fenil]- (114)
amida,
ácido 5-(3,3-dimetil-butililamino)-bifenil-2-carboxílico tiazol-2-ilamida, (115)
N-(5-cloro-tiazol-2-il)-4-(3,3-dimetil-butililamino)-benzamida, (116)
N-(5-cloro-tiazol-2-il)-4-(3-metil-butililamino)-benzamida, (117)
N-(5-cloro-tiazol-2-il)-4-(2-ciclopropil-acetilamino)-benzamida, (118)
4-butililamino-*N*-(5-cloro-tiazol-2-il)-benzamida, (119)
4-benzoilamino-*N*-(5-cloro-tiazol-2-il)-benzamida, (120)
3-fluoro-*N*-tiazol-2-il-4-(4,4,4-trifluoro-3-metil-butililamino)-benzamida, (121)
4-(3,3-dimetil-butililamino)-*N*-tiazol-2-il-3-trifluorometoxi-benzamida, (122)
4-(3,3-dimetil-butililamino)-3-metoximetil-*N*-tiazol-2-il-benzamida, (123)
4-(3,3-dimetil-butililamino)-3-propoxi-*N*-tiazol-2-il-benzamida, (124)
3-cloro-4-(3,3-dimetil-butililamino)-5-metil-*N*-tiazol-2-il-benzamida, (125)
4-(3,3-dimetil-butililamino)-3,5-difluoro-*N*-tiazol-2-il-benzamida, (126)
4-(3,3-dimetil-butililamino)-3,5-dimetil-*N*-tiazol-2-il-benzamida, (127)
4-(3,3-dimetil-butililamino)-*N*-tiazol-2-il-3-trifluorometil-benzamida, (128)
3-cloro-4-(3,3-dimetil-butililamino)-*N*-tiazol-2-il-5-trifluorometil-benzamida, (129)
N-(2,2-dimetil-propil)-*N'*-tiazol-2-il-terephthalamida, (130)
3,5-dicloro-4-(3,3-dimetil-butililamino)-*N*-tiazol-2-il-benzamida, (131)
4-(3-*terc*-butil-ureido)-*N*-tiazol-2-il-benzamida, y (132)
éster de 2,2-dimetil-propilo de ácido [4-(tiazol-2-ilcarbamoil)-fenil]-carbámico. (133)



Publications A-Z

Home | Authors & Reviewer

Journal of Medicinal Chemistry

J. Med. Chem. ACS Med. Chem. Lett.

☒ J. Med. Chem. ☐ All PublicaPersonalize your experience: [Log](#)ACS Mobile is a new app for iPhone and iPod Touch. [Find out more](#)Performing your original search, adenosine receptor and BENZAMIDE, within the ACS Publications collection will retrieve 148 results. [Go to results](#)

Article

Thiazole and Thiadiazole Analogues as a Novel Class of Adenosine Receptor Antagonists

Jacqueline E. van Mulijwijk-Koezen,* Hendrik Timmerman, Roeland C. Vollinga,† Jacobien Frijtag von Drabbe Künzel,‡ Miriam de Groote,‡ Sven Visser, and Adriaan P. IJzerman‡

Department of Pharmacochimistry, Division of Medicinal Chemistry, Leiden/Amsterdam Center for Drug Research, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands, and Gorlaeus Laboratories, Division of Medicinal Chemistry, Leiden/Amsterdam Center for Drug Research, Universiteit Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

J. Med. Chem., 2001, 44 (5), pp 749-762

DOI: 10.1021/jm0003945

Publication Date (Web): January 18, 2001

Copyright © 2001 American Chemical Society

Abstract

Abstract

Full Text HTML

Hi-Res PDF [362 KB]

Supporting Info

Tools

Add to Favorites

Download Citation

Email a Colleague

Permalink

Order Reprints

Rights & Permissions

Citation Alerts

SciFinder Links



Get Reference Detail

Get Substances

Get Reactions

Get Cited

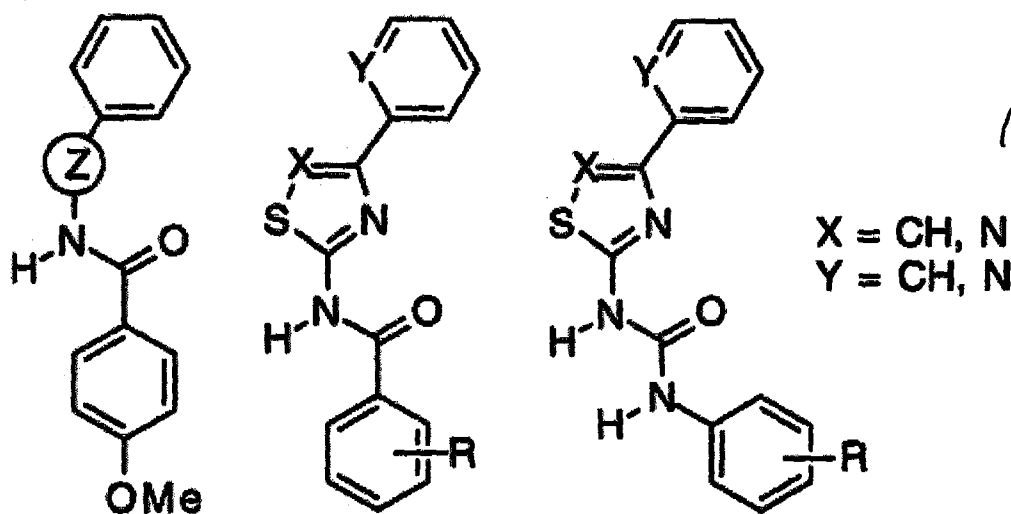
Get Citing

Explore by:

☒ Author of this Article☐ Any Author☐ Research Topic

van Mulijwijk-Koezen, Jacq

[Search](#)



Novel classes of heterocyclic compounds as adenosine antagonists were developed based on a template approach. Structure–affinity relationships revealed insights for extended knowledge of the receptor–ligand interaction. We replaced the bicyclic heterocyclic ring system of earlier described isoquinoline and quinazoline adenosine A_3 receptor ligands by several monocyclic rings and investigated the influence thereof on adenosine receptor affinity. The thiazole or thiadiazole derivatives seemed most promising, so we continued our investigations with these two classes of compounds. The large difference between a pyridine and isoquinoline ring in binding adenosine A_1 and A_3 receptors showed the importance of the second ring of the isoquinoline ligands. We prepared several *N*-[4-(2-pyridyl)thiazol-2-yl]benzamides, and these compounds showed adenosine affinities in the micromolar range. Most surprising in the series of the *N*-[4-(2-pyridyl)thiazol-2-yl]amides were the retained adenosine affinities by introduction of a cyclopentanamide instead of the benzamide. A second series of compounds, the thiadiazolobenzamide series of compounds, revealed potent and selective adenosine receptor antagonists, especially *N*-(3-phenyl-1,2,4-thiadiazol-5-yl)-4-hydroxybenzamide (LUF5437, **8h**) showing a K_i value of 7 nM at the adenosine A_1 receptor and *N*-(3-phenyl-1,2,4-thiadiazol-5-yl)-4-methoxybenzamide (LUF5417, **8e**) with a K_i value of 82 nM at the adenosine A_3 receptor. 4-Hydroxybenzamide **8h** is the most potent adenosine A_1 receptor antagonist of this new class of compounds. Structure–affinity relationships showed the existence of a steric restriction at the *para*-position of the benzamide ring for binding adenosine A_1 and A_3 receptors. The electronic nature of the 4-substituents played an important role in binding the adenosine A_3 receptor. *Cis*- and *trans*-4-substituted cyclohexyl derivatives were made next to the 4-substituted benzamide analogues. We used them to study the proposed specific interaction between the adenosine A_1 receptor and the 4-hydroxy group of this class of thiadiazolo compounds, as well as a suggested special role for the 4-methoxy group in binding the A_3 receptor. Both the adenosine A_1 and A_3 receptor slightly preferred the *trans*-analogues over the *cis*-analogues, while all compounds showed low affinities at the adenosine A_{2A} receptor. Our investigations provided the potent and highly selective adenosine

248
HistoryPublished In Issue
March 01, 2001

Received September 7, 2000

Recommend & Share

CiteULike

Delicious

Digg This

Facebook

Newsvine

250
251

Thiazole and Thiadiazole Analogues as a Novel Class of Adenosine Receptor Antagonists

Jacqueline E. van Muijlwijk-Koezen,* Hendrik Timmerman, Roeland C. Vollinga,[†] Jacobien Frijtag von Drabbe Künzel,[‡] Miriam de Groote,[‡] Sven Visser, and Adriaan P. IJzerman[‡]

Department of Pharmacochemistry, Division of Medicinal Chemistry, Leiden/Amsterdam Center for Drug Research, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands, and Gorlaeus Laboratories, Division of Medicinal Chemistry, Leiden/Amsterdam Center for Drug Research, Universiteit Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Received September 7, 2000

Novel classes of heterocyclic compounds as adenosine antagonists were developed based on a template approach. Structure–affinity relationships revealed insights for extended knowledge of the receptor–ligand interaction. We replaced the bicyclic heterocyclic ring system of earlier described isoquinoline and quinazoline adenosine A₃ receptor ligands by several monocyclic rings and investigated the influence thereof on adenosine receptor affinity. The thiazole or thiadiazole derivatives seemed most promising, so we continued our investigations with these two classes of compounds. The large difference between a pyridine and isoquinoline ring in binding adenosine A₁ and A₃ receptors showed the importance of the second ring of the isoquinoline ligands. We prepared several *N*-[4-(2-pyridyl)thiazol-2-yl]benzamides, and these compounds showed adenosine affinities in the micromolar range. Most surprising in the series of the *N*-[4-(2-pyridyl)thiazol-2-yl]amides were the retained adenosine affinities by introduction of a cyclopentanamide instead of the benzamide. A second series of compounds, the thiadiazolobenzamide series of compounds, revealed potent and selective adenosine receptor antagonists, especially *N*-(3-phenyl-1,2,4-thiadiazol-5-yl)-4-hydroxybenzamide (LUF5437, **8h**) showing a *K_i* value of 7 nM at the adenosine A₁ receptor and *N*-(3-phenyl-1,2,4-thiadiazol-5-yl)-4-methoxybenzamide (LUF5417, **8e**) with a *K_i* value of 82 nM at the adenosine A₃ receptor. 4-Hydroxybenzamide **8h** is the most potent adenosine A₁ receptor antagonist of this new class of compounds. Structure–affinity relationships showed the existence of a steric restriction at the *para*-position of the benzamide ring for binding adenosine A₁ and A₃ receptors. The electronic nature of the 4-substituents played an important role in binding the adenosine A₃ receptor. *Cis*- and *trans*-4-substituted cyclohexyl derivatives were made next to the 4-substituted benzamide analogues. We used them to study the proposed specific interaction between the adenosine A₁ receptor and the 4-hydroxy group of this class of thiadiazolo compounds, as well as a suggested special role for the 4-methoxy group in binding the A₃ receptor. Both the adenosine A₁ and A₃ receptor slightly preferred the *trans*-analogues over the *cis*-analogues, while all compounds showed low affinities at the adenosine A_{2A} receptor. Our investigations provided the potent and highly selective adenosine A₁ antagonist *N*-(3-phenyl-1,2,4-thiadiazol-5-yl)-*trans*-4-hydroxycyclohexanamide (VUF5472, **8m**) showing a *K_i* value of 20 nM. A third series of compounds was formed by urea analogues, *N*-substituted with thiazolo and thiadiazolo heterocycles. The SAR of this class of compounds was not commensurate with the SAR of the previously described quinazoline urea. On the basis of these findings we suggest the existence of a special interaction between adenosine receptors and a region of high electron density positioned between the thia(dia)zole ring and phenyl(pyridyl) ring. Molecular electrostatic potential contour plots showed that for this reason the ligands need either a thiadiazole ring instead of a thiazole or a 2-pyridyl group instead of a phenyl. The derived novel classes of antagonists will be useful for a better understanding of the molecular recognition at the adenosine receptors.

Introduction

Extracellular adenosine regulates several physiological functions by activation of specific cell membrane receptors. The combination of pharmacological studies and molecular cloning revealed the existence of four distinct adenosine receptor subtypes which are identified and classified as A₁, A_{2A}, A_{2B}, and A₃. Whereas the

adenosine A₁ and A₃ receptor subtypes are coupled to the G_i protein, inhibiting adenylate cyclase, A_{2A} and A_{2B} subtypes stimulate this enzyme via G_s.

The xanthine core structure has served as the basis for numerous selective antagonists for adenosine A₁, A_{2A}, and A_{2B} receptors.^{1,2} The development of selective antagonists for the A₃ receptor has relied on chemically rather diverse structural leads. Triazonaphthopyridine,^{3,4} thiazolopyrimidine,³ 1,4-dihydropyridines,^{5–7} pyridines,⁸ pyridinium salts,⁹ pyrans,¹⁰ triazoloquinazolines,^{11,12} flavonoids,¹³ and triazolopyrimidines¹⁴ have

* To whom correspondence should be addressed. Tel: (+31) 20 4447604. Fax: (+31) 20 4447610. E-mail: muijlwyk@chem.vu.nl.

[†] Universiteit Leiden.

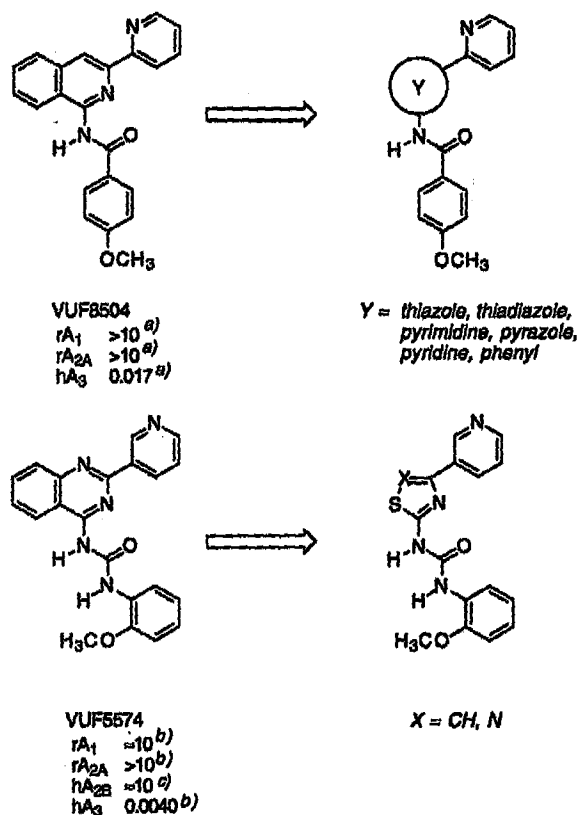


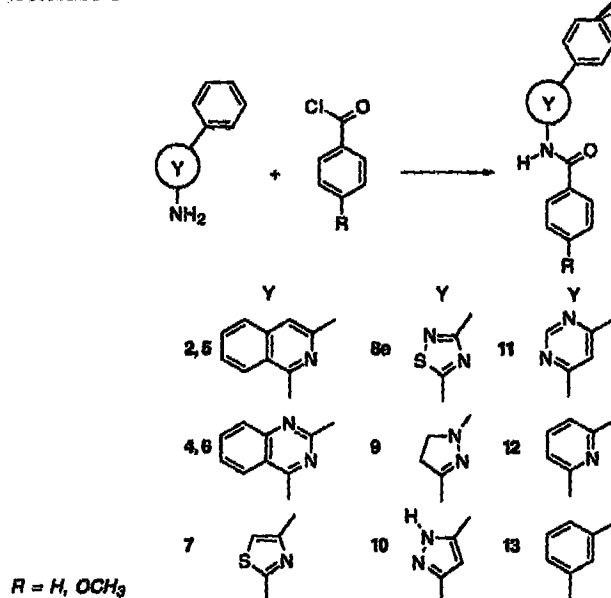
Figure 1. Template approach in the development of novel classes of adenosine analogues, i.e. replacement of the bicyclic ring system by a simple monocyclic heterocycle. Affinities at adenosine receptors are expressed as K_i values in μM . ^aData from ref 16. ^bData from ref 17. ^c45% displacement of specific [³H]DPCPX binding at human A_{2B} receptors, stably expressed in COS-7 cells ($n = 2$).

all been identified as adenosine A_3 receptor antagonists through the screening of chemical libraries.

Recently we reported on a series of isoquinoline and quinazoline analogues as adenosine A_3 receptor antagonists.^{15–17} In these studies we showed that higher adenosine A_1 and A_3 receptor affinities resulted from spacer-coupled aromatic groups on the 1-position of the isoquinoline ring.¹⁵ An amide¹⁶ or urea¹⁷ moiety as spacer between the heterocyclic ring and aromatic group on position 1 provided an increase in adenosine A_3 receptor affinity; in case the aromatic group is phenyl a substitution of this nucleus led to A_3 -selective antagonists (Figure 1). We also found that an aromatic group at position 2 of the quinazoline ring increased adenosine A_3 receptor affinity.¹⁷

In the present study, we describe the development of a new class of heterocyclic compounds as adenosine receptor antagonists, based on a template approach (see also Figure 1). We replaced the bicyclic heterocyclic ring system by several monocyclic rings and investigated its influence on adenosine receptor affinity. Thiazole or thiadiazole derivatives appeared most promising; hence we focused our investigations on these two classes of compounds. We prepared several substituted *N*-thiadiazole- and *N*-thiazolebenzamide derivatives and investigated the influence of benzamide substituents on the adenosine receptor affinities.

Scheme 1



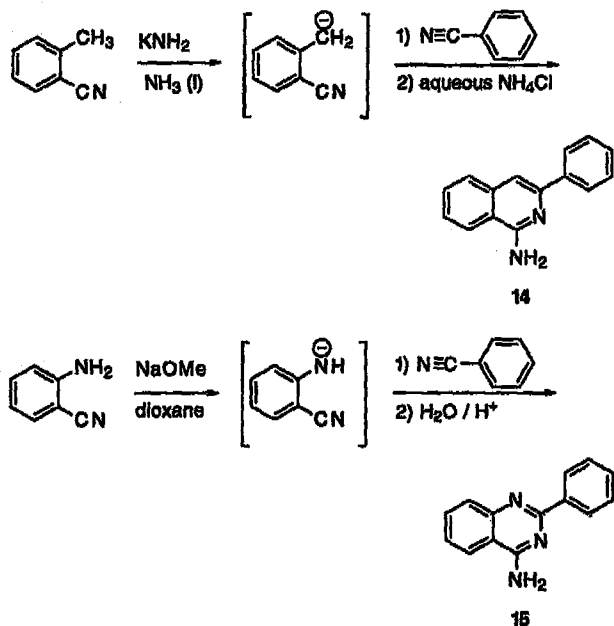
Chemistry

Compounds 2 and 5–13 were prepared from *p*-anisoyl chloride and phenyl-substituted heterocyclic amines, using different circumstances, depending on (1) the deactivating properties of the heterocyclic ring and (2) the reactivity of the resulting amide (Scheme 1). In case of strong deactivation of the amine, such as in the synthesis of isoquinoline derivative 5 or pyrimidine derivative 11, high temperature and excess of acid chloride were needed, whereas the more reactive amines used in the synthesis of 6, 7, or 10 gave good results at low temperature. 2-Amino-4-phenyltriazine and 4-amino-2-phenylpyrimidine were not sufficiently reactive toward acid chlorides, even after deprotonation with a butyllithium reaction could not be achieved, probably due to delocalization of the negative charge. In case of 9 and 12 the benzamides were more reactive than the corresponding primary amines and the *N,N*-dibenzoyl analogues were easily obtained. Adjusting the reaction conditions of method C (Scheme 4) by using an excess of the amine and dilution of the reaction mixture led to the desired compound 12. Hydrolysis of the dibenzoyl analogue with sodium methoxide in dioxane yielded the desired compound 9. The amines 14 and 15 were prepared from the corresponding nitriles as described in previous studies^{16,17} (Scheme 2).

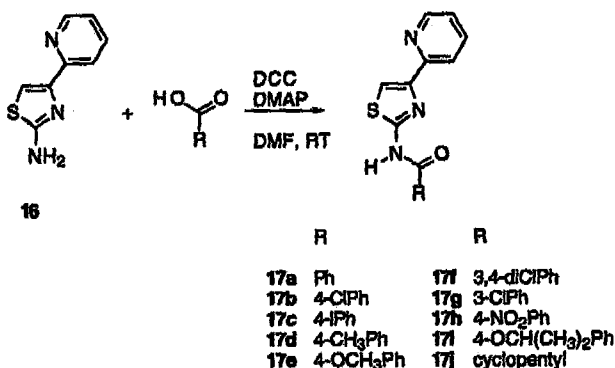
2-Amino-4-(2-pyridyl)thiazole 16 was prepared according to a literature procedure,¹⁸ and the amides 17a–j were synthesized by a reaction of amine 16 with the appropriate carboxylic acids in the presence of dicyclohexylcarbodiimide and DMAP (Scheme 3). Different methods were used for the synthesis of thiadiazole derivatives 8a–l (Scheme 4). In methods A and B carboxylic acids were reacted with 5-amino-3-phenyl-1,2,4-thiadiazole, while in methods C and D the acid chlorides were used.

4-Hydroxybenzamide 8h was prepared by cleavage of the methyl ether of 8e under the influence of sodium cyanide (Scheme 5). The phenol 8h in turn was alkylated by bromoethyl acetate and subsequently hydro-

Scheme 2



Scheme 3



lyzed, yielding the carboxylic acid **8i**. Methyl ethers **8k,l** were cleaved using alumina tribromide in the presence of ethanethiol,^{19,20} yielding hydroxy derivatives **8m,n**. Other cleavage methods were explored, such as the use of BBr₃ at low temperature,²¹ the application of this Lewis acid in the presence of 15-crown-5 and KI,²² or the use of silylated compounds,^{23,24} without success. Compound **18g** was prepared by oxidation of 4-methoxy-3-methylbenzaldehyde²⁵ to the corresponding carboxylic acid (**19**) which was easily converted into the acid chloride (Scheme 6).

Urea analogues **20–22** were prepared by coupling the aminothiazole or aminothiadiazaole derivatives with substituted phenyl isocyanates in dry acetonitrile (Scheme 7).

Results and Discussion

Binding Studies. All synthesized compounds were tested in radioligand binding assays to determine their affinities for the adenosine A₁, A_{2A}, and A₃ receptors. The affinities at adenosine A₁ receptors were determined using membranes from rat brain cortex, with [³H]DPCPX as radioligand.²⁶ The affinities at adenosine A_{2A} receptors were obtained on membranes from rat

striatum with [³H]CGS 21680²⁷ (Tables 1 and 2) or [³H]ZM 241385 (Tables 3–5) as radioligands. The affinity at adenosine A₃ receptors was determined on membranes from HEK 293 cells, stably expressing the human A₃ receptor, using [¹²⁵I]AB-MECA as radioligand.^{28,29} The results are shown in Tables 1–5.

Template Approach. We have demonstrated earlier that A₃ receptor potency and selectivity could be achieved in isoquinoline and quinazoline derivatives through a combination of an aromatic group at the 2-position and an aromatic group coupled by a spacer at the 4-position of the quinazoline ring or at the appropriate 3- and 1-positions of an isoquinoline ring.^{15–17} In the present study we applied a template approach in the development of novel classes of adenosine receptor ligands and replaced the bicyclic ring system by simpler monocyclic heterocycles (Figure 1).

For synthetic reasons we preferred the phenyl instead of the pyridinyl derivatives; earlier investigations had revealed that 2-(2-pyridinyl)-, 2-(4-pyridinyl)-, and 2-phenyl-substituted quinazoline derivatives showed comparable adenosine receptor affinities.¹⁷ To check whether this also held in the benzamide series, we prepared the phenyl-substituted analogues **2** and **4** of VUF8507 (**1**)¹⁶ and *N*-[2-(2-pyridinyl)quinazolin-4-yl]benzamide (**3**),¹⁶ respectively, and tested their adenosine receptor binding (Table 1).

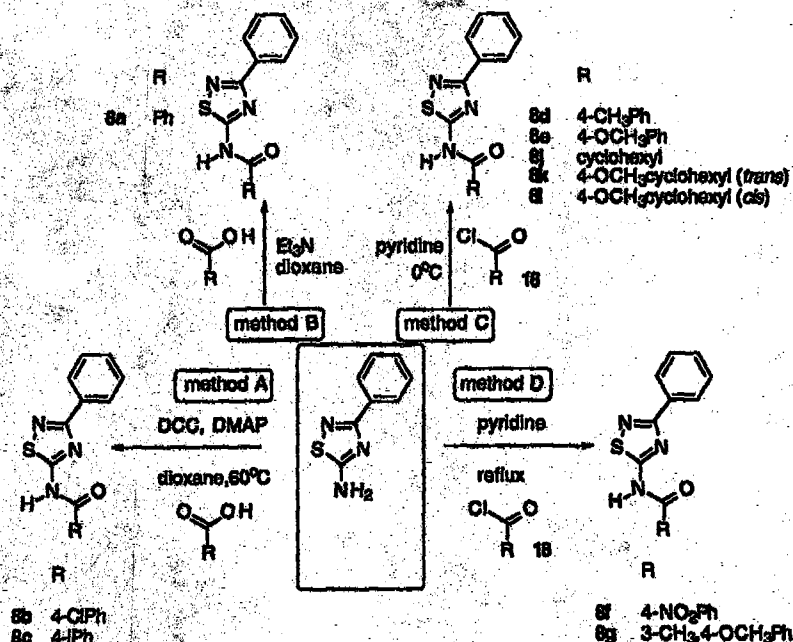
Isoquinoline as well as quinazoline analogues showed comparable adenosine A₁ and A_{2A} receptor binding for 2-pyridinyl and phenyl substituents. However, the affinity at the human adenosine A₃ receptor was the same for quinazolines **3** and **4**, but *N*-(3-phenylisoquinolin-1-yl)benzamide **2** showed a 6-fold decrease in adenosine A₃ receptor affinity compared to pyridinyl analogue **1**. In the molecular modeling section we will deal with this difference.

We altered the central heterocyclic ring to gain more insight into the structural requirements for binding adenosine receptors (compounds **5–13**). We chose several monocyclic ring systems and kept a phenyl ring and an *N*-4-methoxybenzamide (as in earlier studies) as substituents. For comparison, we prepared phenyl-substituted bicyclic heterocycles **5** and **6**. The various compounds and their adenosine receptor affinities are listed in Table 2.

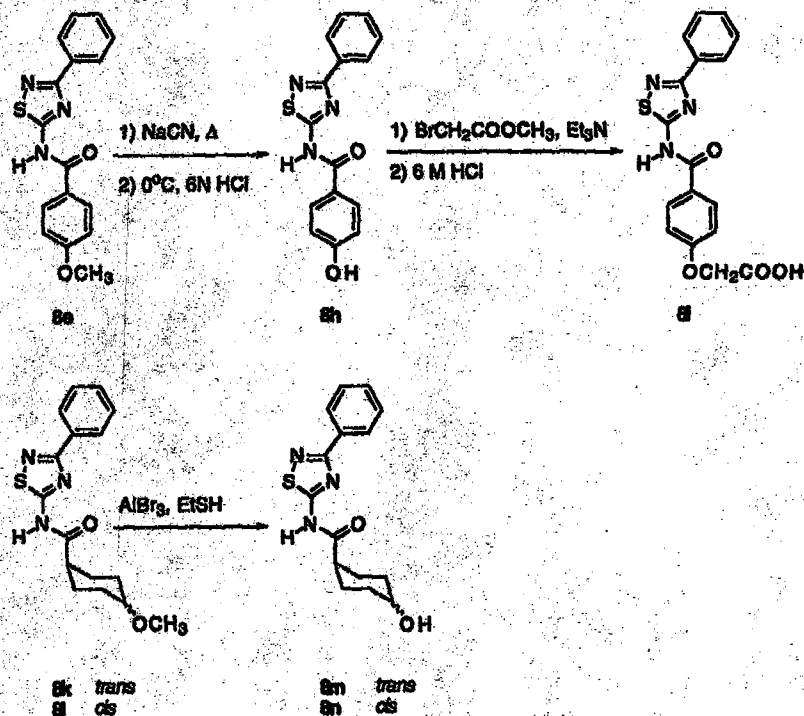
Isoquinoline **5** showed negligible affinity at the adenosine A_{2A} receptor but has a *K_i* value of 3 μM at the adenosine A₁ receptor and a *K_i* value of 79 nM at the adenosine A₃ receptor. The 4-fold lower adenosine A₃ receptor affinity of **5** compared to VUF8504¹⁶ should be determined by the lack of a nitrogen atom in the 3-substituent. Quinazoline **6** is also an adenosine A₃ receptor-selective compound with a *K_i* value of 27 nM, i.e. 66-fold selectivity over A₁ and more than 350-fold over A_{2A}.

Replacement of the bicyclic heterocycle of **5** by a monocyclic thiazole moiety yielded LUF5433 (**7**), which showed remarkable adenosine receptor affinities. This thiazole derivative possessed reasonable affinities at all three receptor subtypes, with *K_i* values of 76 nM at the adenosine A₁ receptor, 2 μM at the adenosine A_{2A} receptor, and 0.7 μM at the adenosine A₃ receptor. With this compound as a lead we developed a new class of adenosine receptor antagonists (next section).

Scheme 4



Scheme 5

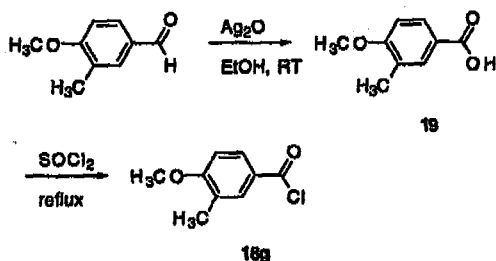


In analogy to compounds 5 and 7, we replaced the quinazoline of 6 by a monocyclic thiadiazole moiety, resulting in LUF5417 (8e). Like thiazole 7, thiadiazole 8e showed affinities at adenosine receptors from the micromolar to the nanomolar range. The 8 times increased adenosine A₃ receptor affinity of 8e, compared to thiazole 7, is remarkable. This can be ascribed to the same effect as was seen in compounds 5 and 6. Again, we will return to this in the molecular modeling section.

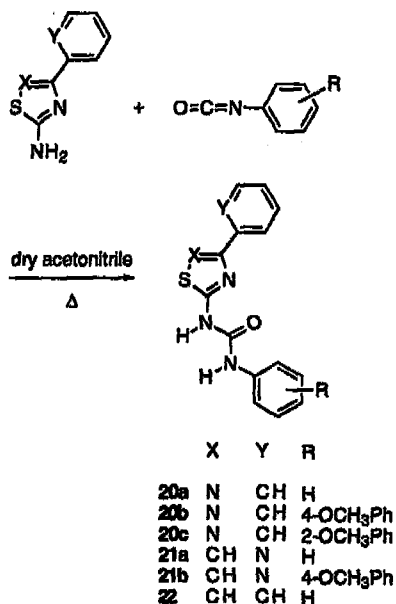
We continued our investigations on monocyclic heterocycles with two other five-membered rings and three

six-membered ring systems. The choice of ring systems depended on synthetic accessibility. Dihydropyrazole 9 and pyrazole analogue 10 showed negligible affinity at all three adenosine subtypes. Different six-membered rings were used in compounds 11–13. Compound 11 contains a pyrimidine ring, 12 a pyridyl ring, and 13 a phenyl ring. The pyrimidine analogue, although lacking a nitrogen between the two substituents, possessed substantial affinities at the adenosine A₁ and A₃ receptors with K_i values of 0.2 and 0.8 μM, respectively. The pyridine analogue 12 was slightly A₃-selective and

Scheme 6



Scheme 7



showed a K_i value of 8.7 μ M. This analogue can hardly be compared with the known class of 3,5-diacyl-2,4-dialkylpyridine analogues as adenosine A₃ receptor antagonists,⁸ because of the large difference in substitution pattern of the compounds. Analogue 13, lacking heteroatoms in the central ring, had a comparably low A₃ receptor affinity as 12, with a K_i value of 10 μ M. Comparison of 5 and 12 showed that the additional ring of 5 largely increased adenosine A₃ receptor affinity. It might be that substituents at positions 3 and 4 of the pyridine ring can fulfill the same role in binding.

Thiazolylbenzamide Analogues. Based on 1 and 7, several substituted *N*-[4-(2-pyridyl)thiazol-2-yl]-benzamides were synthesized to explore the structure-activity relationships (SARs) at the benzamide ring. In Table 3 the affinities of compounds 17a-j at the adenosine receptors are summarized.

The unsubstituted *N*-[4-(2-pyridyl)thiazol-2-yl]benzamide 17a showed affinities in the micromolar range at the three adenosine receptors ($A_1 > A_3 > A_{2A}$). Introduction of a halogen atom at the *para*-position (17b,c) decreased the A_{2A} affinity and did not influence the adenosine A₃ receptor affinity. However, the 4-chloro-substituted benzamide 17b possessed an 8-fold increased affinity at the adenosine A₁ receptor compared to 17a, with a K_i value of 200 nM. Introduction of a methyl group (17d) does not influence adenosine receptor affinities, whereas the stronger electron-donating methoxy analogue (17e) increased adenosine A₃ receptor

Table 1. Affinities of Isoquinoline and Quinazoline Analogues in Radioligand Binding Assays at Adenosine Receptors

Compound	X	Y	$rA_1^{a,c}$	$rA_{2A}^{a,c}$	$hA_3^{a,c}$
1	CH	N	3.2 ± 0.3	0 %	$0.20 \pm 0.04^{a,c}$
(VUF8507)					
2	CH	CH	1.2 ± 0.2	0 %	1.2 ± 0.3
3	N	N	16 %	9 %	$0.23 \pm 0.02^{a,c}$
4	N	CH	34 %	17 %	0.24 ± 0.06

^a Displacement of specific [³H]DPCPX binding in rat brain cortical membranes, expressed as $K_i \pm$ SEM in μ M ($n = 3$) or percentage displacement of specific binding at a concentration of 10 μ M ($n = 2$). ^b Displacement of specific [³H]CGS 21680 binding in rat striatal membranes, expressed as percentage displacement of specific binding at a concentration of 10 μ M ($n = 2-3$). ^c Displacement of specific [¹²⁵I]AB-MECA binding at human adenosine A₃ receptors expressed in HEK 293 cells, expressed as $K_i \pm$ SEM in μ M ($n = 3$). ^d As published in ref 16.

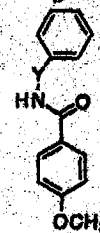
affinity and decreased adenosine A₁ receptor affinity. The methoxy group has a prominent role in different classes of adenosine A₃ receptor antagonists,^{3,4,14-17} indicating that it could play an important role in the molecular recognition of the adenosine A₃ receptor.

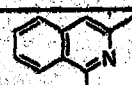
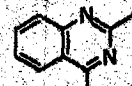
The 3,4-dichlorobenzamide analogue 17f, 3-chlorobenzamide 17g, and 4-nitrobenzamide 17h showed affinities comparable to that of the unsubstituted benzamide 17a toward adenosine A₁ and A₃ receptors. *m*-Chloro-substituted compound 17g showed also A_{2A} affinity with a K_i value of 1.3 μ M. Increasing the size of the ether group of 17e resulting in isopropyl ether 17i diminished both the adenosine A₁ and A₃ receptor affinities by 2-fold.

Furthermore we used a cyclopentyl group instead of the phenyl ring. This moiety showed A₁ selectivity in other classes of adenosine receptor ligands (DPCPX, N-0840, CPA, and CCPA).²⁹⁻³³ Compound 17j was also an adenosine A₁ receptor-selective ligand but showed also increased affinities at the adenosine A_{2A} and A₃ receptors compared to benzamide 17a. This is surprising, since *N*-[3-(2-pyridyl)isoquinolin-1-yl]alkyl amides were hardly active at adenosine receptors with K_i values in the range of 10–50 μ M,¹⁶ whereas a benzamide instead of an alkylamide as in VUF8507 led to 55- and 10-fold increased adenosine A₃ and A₁ affinity, respectively. Thus the SAR of this class of *N*-[4-(2-pyridyl)thiazol-2-yl]amides is not the same as the SAR of the *N*-[3-(2-pyridyl)isoquinolin-1-yl]amides. This observation has a precedent in the SAR of pyran derivatives and dihydropyridines not being parallel.¹⁰ On the other hand, the *p*-methoxy-substituted compound 17e was as expected the most active compound at the adenosine A₃ receptor within the series of benzamides.

Thiadiazolylbenzamide Analogues. We continued our investigations on the monocyclic thiadiazole adenosine ligands. In addition to the 4-methoxybenzamide

Table 2. Affinities of 4-Methoxybenzamide Analogues in Radioligand Binding Assays at Adenosine Receptors



Compound	Y	$rA_1^{a,c}$	$rA_{2A}^{b,d}$	$hA_3^{e,f}$
5		3.0 ± 0.7	35 %	0.079 ± 0.02
6		1.8 ± 0.8	44 %	0.027 ± 0.02
7 (LUF5433)		0.076 ± 0.008	1.9 ± 0.5	0.67 ± 0.10
8e (LUF5417)		0.032 ± 0.005	2.34 ± 1.1	0.082 ± 0.004
9		26 %	19 %	41 %
10		20 %	16 %	35 %
11		0.20 ± 0.1	31 %	0.80 ± 0.05
12		46 %	16 %	8.7 ± 0.3
13		30 %	41 %	10 ± 1.6

^a Displacement of specific [³H]DPCPX binding in rat brain cortical membranes, expressed as $K_i \pm \text{SEM}$ in μM ($n = 3$) or percentage displacement of specific binding at a concentration of $10 \mu\text{M}$ ($n = 2$). ^b Displacement of specific [³H]CGS 21680 binding in rat striatal membranes, expressed as percentage displacement of specific binding at a concentration of $10 \mu\text{M}$ ($n = 2-3$) or $K_i \pm \text{SEM}$ in μM ($n = 3$). ^c Displacement of specific [¹²⁵I]AB-MECA binding at human adenosine A_3 receptors expressed in HEK 293 cells, expressed as $K_i \pm \text{SEM}$ in μM ($n = 3$) or percentage displacement of specific binding at a concentration of $10 \mu\text{M}$ ($n = 2$).

8e we prepared other benzamides 8a–i to explore the structure–affinity relationships (Table 3).

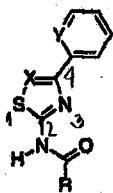
Unsubstituted benzamide 8a showed adenosine A_1 and A_{2A} receptor affinities comparable with 8e but a 20-fold decreased adenosine A_3 receptor affinity. This is compatible with our earlier observation on the importance of the methoxyphenyl moiety.

At the adenosine A_1 receptor small substituents on the *para*-position were allowed, as in compounds

8a,b,d,e. Introduction of more or less lipophilic substituents or changing their electronic nature did not influence the relatively high adenosine A_1 receptor affinity (K_i values 30–40 nM). However, larger substituents such as *tert*-butoxy in 8c and nitro in 8f decreased the adenosine A_1 receptor affinity tremendously.

Compounds 8a–f showed little affinity for the adenosine A_{2A} receptor with the exception of the 4-methoxy-substituted thiadiazolobenzamide 8e ($K_i = 2 \mu\text{M}$).

Table 3. Affinities of Thiazole and Thiadiazole Derivatives in Radioligand Binding Assays at Adenosine Receptors



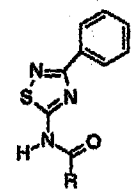
Compound	X	Y	R	$RA_1^{a,b}$	$RA_{2A}^{a,b}$	$hA_3^{a,c}$
17a	CH	N	C_6H_5	1.7 ± 0.5	8.7 ± 0.6	3.4 ± 1
17b	CH	N	4- ClC_6H_4	0.20 ± 0.05	30 %	3.2 ± 2
17c	CH	N	4- IC_6H_4	2.4 ± 1	50 %	2.8 ± 1
17d	CH	N	4- $CH_3C_6H_4$	1.6 ± 0.4	44 %	3.2 ± 0.3
17e	CH	N	4- $OCH_3C_6H_4$	3.2 ± 0.7	40 %	1.8 ± 0.6
17f	CH	N	3,4-di ClC_6H_4	1.6 ± 0.6	20 %	2.5 ± 1
17g	CH	N	3- ClC_6H_4	1.7 ± 0.7	1.3 ± 0.7	4.6 ± 1
17h	CH	N	4- $NO_2C_6H_4$	1.5 ± 0.4	29 %	3.5 ± 0.9
17i	CH	N	4- $OCH(CH_3)_2C_6H_4$	5.8 ± 1	44 %	3.7 ± 0.7
17j	CH	N	cyclopentyl	0.92 ± 0.08	1.3 ± 0.7	2.1 ± 0.8
8a	N	CH	C_6H_5	0.031 ± 0.007	4.4 ± 1.2	0.41 ± 0.1
8b	N	CH	4- ClC_6H_4	0.041 ± 0.02	36 %	0.52 ± 0.3
8c	N	CH	4- IC_6H_4	49 %	19 %	1.1 ± 0.9
8d	N	CH	4- $CH_3C_6H_4$	0.030 ± 0.002	38.2 %	0.14 ± 0.03
8e (LUF5417)	N	CH	4- $OCH_3C_6H_4$	0.032 ± 0.005	2.3 ± 1.1	0.082 ± 0.004
8f	N	CH	4- $NO_2C_6H_4$	34 %	5 %	28 %
8g	N	CH	3- CH_3 -4- $OCH_3C_6H_4$	48 %	8 %	0.58 ± 0.2
8h (LUF5437)	N	CH	4- OHC_6H_4	0.0073 ± 0.001	0.57 ± 0.07	0.13 ± 0.01
8i	N	CH	4- $OCH_2CO_2HC_6H_4$	0.10 ± 0.01	15 ± 3.0	1.2 ± 0.81
VUF8504 ^d				37 %	19 %	0.017 ± 0.002
XAC				0.0012	0.063	$0.11 \pm 0.003^{e,f}$
L-249313						$0.17 \pm 0.009^{g,h}$
CGS 15943				$0.021 \pm 0.003^{i,j}$	$0.0033 \pm 0.002^{k,l}$	$0.14 \pm 0.02^{m,n}$

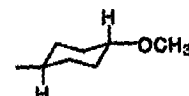
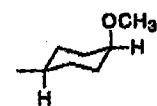
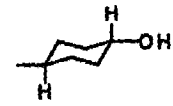
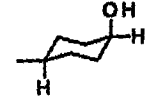
^a Displacement of specific [³H]DPCPX binding in rat brain cortical membranes, expressed as $K_i \pm SEM$ in μM ($n = 3$) or percentage displacement of specific binding at a concentration of $10 \mu M$ ($n = 2$). ^b Displacement of specific [³H]ZM241385 binding in rat striatal membranes, expressed as percentage displacement of specific binding at a concentration of $10 \mu M$ ($n = 2-3$) or $K_i \pm SEM$ in μM ($n = 3$). ^c Displacement of specific [¹²⁵I]AB-MECA binding at human adenosine A_3 receptors expressed in HEK 293 cells, expressed as $K_i \pm SEM$ in μM ($n = 3$) or percentage displacement of specific binding at a concentration of $10 \mu M$ ($n = 2$). ^d As published in ref 15. ^e As published in ref 16. ^f As published in ref 41.

At the adenosine A_3 receptor a quite different SAR was established. In addition to the steric restriction (an iodo atom or nitro moiety at the *para*-position appeared to be too large) electronic effects play an important role in the molecular recognition. The A_3 receptor potency order of 4-substituents is $Cl < H < Me < OMe$. The strong electron-donating methoxy substituent afforded a high K_i value of 82 nM. This SAR is similar as seen

in adenosine A_3 receptor antagonizing *N*-isoquinolinebenzamides¹⁶ and *N*¹-isoquinolinebenzamides¹⁵ and also to the SAR present in the adenosine A_3 receptor agonist class of *N*⁶-(phenylcarbamoyl)adenosine-5'-*N*-ethyluronamides.³⁴

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-3-methyl-4-methoxybenzamide (**8g**) was proof that the introduction of an extra 3-methyl next to the 4-methoxybenzamide **8e**

Table 4. Affinities of *N*-(3-Phenyl-1,2,4-thiadiazol-5-yl)cyclohexanamide Derivatives in Radioligand Binding Assays at Adenosine Receptors


Compound	R	$rA_1^{a/}$	$rA_{2A}^{a/}$	$hA_3^{a/}$
8j		1.4 ± 0.5	16 %	16 ± 8
8k (trans)		0.032 ± 0.002	1.9 ± 0.8	1.7 ± 0.6
8l (cis)		0.11 ± 0.02	2.0 ± 0.5	5.3 ± 2
8m (trans) (VUF5472)		0.020 ± 0.007	37 %	1.9 ± 0.4
8n (cis)		0.042 ± 0.006	41 %	2.7 ± 0.6

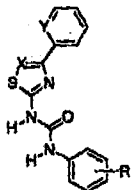
^a Displacement of specific [³H]DPCPX binding in rat brain cortical membranes, expressed as $K_i \pm \text{SEM}$ in μM ($n = 3$) or percentage displacement of specific binding at a concentration of $10 \mu\text{M}$ ($n = 2$). ^b Displacement of specific [³H]ZM241385 binding in rat striatal membranes, expressed as percentage displacement of specific binding at a concentration of $10 \mu\text{M}$ ($n = 2-3$) or $K_i \pm \text{SEM}$ in μM ($n = 3$). ^c Displacement of specific [¹²⁵I]AB-MECA binding at human adenosine A_3 receptors expressed in HEK 293 cells, expressed as $K_i \pm \text{SEM}$ in μM ($n = 3$) or percentage displacement of specific binding at a concentration of $10 \mu\text{M}$ ($n = 2$).

is adverse for binding to all three receptors. We also prepared compound **8l**, bearing the same oxyacetate substituent as in I-ABOPX, the only xanthine derivative with appreciable affinity for human adenosine A_3 receptors.³⁵ However, at all three receptors **8l** had decreased receptor affinities compared to the unsubstituted thiadiazole **8a**.

We also tested the 4-hydroxyl-substituted benzamide **8h**. This compound showed an increase in affinities at all three receptor subtypes when compared to **8a** and appeared to be a highly potent and selective adenosine A_1 receptor antagonist. *N*-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-hydroxybenzamide (LUF5437, **8h**) had a K_i value of 7.3 nM at the A_1 receptor and possessed 18- and 78-fold selectivity over the A_3 and A_{2A} receptors, respectively. A specific role for the *p*-hydroxyl group in binding to the A_1 receptor seems therefore likely, whereas the *p*-methoxy group plays an important role in binding to the A_3 receptor. We therefore further investigated the influence of these substituents on binding adenosine receptors by preparing *N*-(3-phenyl-1,2,4-thiadiazol-5-yl)cyclohexanamide **8j** and its 4-substituted derivatives **8k-n**. In the thiadiazole series the cyclopentanamide analogue **17j** showed relatively high adenosine receptor affinities (better than benzamide **17a**), and therefore we chose also a cycloalkyl group to direct the hydroxy or methoxy substituent, as *cis*- and *trans*-isomers, respectively. The results are summarized in Table 4.

The cyclohexyl group of **8j** proved less favorable than the phenyl group of **8a** in binding adenosine receptors, which disagrees with the SAR of **17a,j**. This suggests that either a cyclopentyl group fits the adenosine receptor pocket better or the thiadiazole ligands behave differently, compared to the thiazole analogues. Introduction of a 4-*trans*-methoxy substituent increased adenosine A_3 receptor affinity. It also increased the adenosine A_1 and A_{2A} receptor affinities as in the thiadiazolobenzamides (**8e** vs **8a**), unlike the methoxy group in the benzamide analogues (**17e** vs **17a**). Introduction of a 4-*cis*-methoxy substituent (**8l**) led to similar changes, but to a lesser extent than observed for the *trans*-analogue. Apparently, adenosine A_1 and A_3 receptors slightly prefer the 4-*trans*-methoxycyclohexanamide over the *cis*-analogue.

The 4-*trans*-hydroxy analogue **8m** had an adenosine A_3 receptor affinity comparable to that of the 4-*trans*-methoxy analogue **8k**, a decreased A_{2A} receptor affinity, and a slightly increased A_1 receptor affinity. The *cis*-analogue **8n** showed lower affinity again at all three adenosine receptors. From Table 4 we concluded that all three receptor subtypes prefer 4-*trans*-substituted cyclohexanamides and, second, that a hydroxyl group is (slightly) favored over a methoxy group for binding the adenosine A_1 receptor. Furthermore, these investigations provided another potent adenosine A_1 receptor antagonist (VUF5472, **8m**). This 4-*trans*-hydroxycyclo-

Table 5. Affinities of Thiazole and Thiadiazole Urea Derivatives in Radioligand Binding Assays at Adenosine Receptors


Compound	X	Y	R	$K_i^{A_1}$ ^a	rA_{2A} ^a	hA_3 ^a
20a	N	CH	H	1.0 ± 0.9	48 %	4.0 ± 1
20b	N	CH	4-OCH ₃	44 %	16 %	3.3 ± 2
20c	N	CH	2-OCH ₃	27 %	38 %	20 %
21a	CH	N	H	0.93 ± 0.2	0.92 ± 0.06	5.0 ± 0.7
21b	CH	N	4-OCH ₃	4 %	11 %	147 ± 159
22	CH	CH	H	37 %	19 %	9.9 ± 2

^a Displacement of specific [³H]DPCPX binding in rat brain cortical membranes, expressed as $K_i \pm$ SEM in μ M ($n = 3$) or percentage displacement of specific binding at a concentration of 10 μ M ($n = 2$). ^b Displacement of specific [³H]ZM241385 binding in rat striatal membranes, expressed as percentage displacement of specific binding at a concentration of 10 μ M ($n = 2-3$) or $K_i \pm$ SEM in μ M ($n = 3$). ^c Displacement of specific [¹²⁵I]AB-MECA binding at human adenosine A₃ receptors expressed in HEK 293 cells, expressed as $K_i \pm$ SEM in μ M ($n = 3$) or percentage displacement of specific binding at a concentration of 10 μ M ($n = 2$).

hexanamide analogue showed a K_i value of around 20 nM and a 100-fold selectivity versus the adenosine A₃ receptor and even more than 500-fold versus the A_{2A} receptor.

Thiazolyl- and Thiadiazolylurea Analogues. Earlier studies in a series of isoquinoline and quinazoline adenosine A₃ receptor antagonists have proven that a urea moiety as spacer increased adenosine A₃ receptor affinity compared to an amide moiety.¹⁷ We therefore applied the template approach again and replaced the quinazoline ring of VUF5574 by a thiazole or thiadiazole moiety and investigated a urea series of compounds (Figure 1).

First, we prepared *N*-phenyl-*N*-(3-phenyl-1,2,4-thiadiazol-5-yl)urea (20a) and determined its affinities at the three adenosine receptors (Table 5). Unsubstituted urea analogue 20a had a K_i value of 1 and 4 μ M at the adenosine A₁ and A₃ receptor, respectively, and possessed only 48% displacement at a concentration of 10 μ M at the adenosine A_{2A} receptor. Second, we prepared the *o*- and *p*-methoxy-substituted phenylurea analogues according to the positive contributions of these substituents toward adenosine A₃ receptor affinity in the *N*-phenyl-*N*-(2-phenylquinazolin-4-yl)urea¹⁷ and various benzamide series, respectively. The SAR of this class of thiadiazole ureas differed from the SAR of the quinazoline urea analogues to a large extent. The 4-methoxyphenyl analogue 20b showed a decrease in the adenosine A₁ and A_{2A} receptor affinities and did not affect the adenosine A₃ receptor affinity, compared to unsubstituted urea 20a. Introduction of a 2-methoxy substituent as in 20c decreased the binding at all three receptor subtypes substantially.

We also prepared *N*-phenyl-*N*-[4-(2-pyridyl)thiazol-2-yl]urea analogues 21a,b. Unsubstituted analogue 21a had adenosine receptor affinities comparable to that of

the amide analogue 17a and the thiadiazole urea analogue 20a. Introduction of a 4-methoxy substituent diminished adenosine receptor affinities. Finally, we studied the influence of the substituent on the 4-position of the thiazole ring and prepared compound 22. A comparison of analogues 22 and 21a revealed that a 2-pyridyl moiety at position 4 slightly improved binding to the adenosine A₃ receptor compared to a phenyl ring and is apparently essential for the adenosine A₁ receptor. Furthermore, compounds 22 and 20a differ in the heterocyclic ring system only, and a comparison of the thiazole and thiadiazole analogues revealed that the lack of the nitrogen atom in 22 is detrimental toward the adenosine A₁ receptor, while also decreasing the adenosine A₃ receptor affinity.

Molecular Modeling. The binding data in Tables 1 and 5 show that for binding the adenosine A₁ and A₃ receptor ligands needed an additional nitrogen atom either in the heterocyclic central ring (as in thiadiazole rather than thiazole) or in the substituent at the 4-position of the thiazole ring (2-pyridyl instead of phenyl).

In earlier studies¹⁷ it had been shown that in low-energy conformations of 3-(2-pyridyl)isoquinoline analogues, the nitrogen of the pyridyl group pointed "upward", i.e. the pyridyl group was turned away from the nitrogen of the isoquinoline ring. Therefore we built the structures of compounds 20a and 21a in Spartan,³⁶ and after conformational optimization we calculated their molecular electrostatic potentials (MEPs) semiempirically and ab initio. Indeed, also in this case, the low-energy conformation of 21a has a pyridyl group in which the nitrogen atom is pointed "upward" (Figure 2). Both compounds showed comparable MEPs in the ab initio calculations as well as in the semiempirical study, indicating that the high electron density present in the plane of the thia(dia)zole or 2-pyridyl ring may function as proton acceptor for amino acid residues of the adenosine receptor (arrows in Figure 2). This could then also be the reason for the loss of adenosine receptor affinities of 22 compared to 20a and 21a and of 2 compared to 1 and 4.

We have shown that our template approach yields thiazolo and thiadiazolo analogues as novel classes of adenosine receptor antagonists, and subsequently several potent *c.q.*-selective ligands were developed. These compounds contribute to a better understanding of the structural requirements necessary for the molecular recognition by adenosine A₁ and A₃ receptors.

Experimental Section

Abbreviations: APT, attached proton test; CGS 15943, 9-fluoro-2-(2-furyl-5,6-dihydro[1,2,4]triazolo[1,5-*c*]quinazolin-5-imine; CHO cells, Chinese hamster ovary cells; CI, chemical ionization; COSY, correlated spectroscopy; DCC, dicyclohexylcarbodiimide; DEPT, distortionless enhancement by polarization transfer; DMAP, *N,N*-(dimethylamino)pyridine; DMSO, dimethyl sulfoxide; DPCPX, 1,3-dipropyl-8-cyclopentylxanthine; EA, ethyl acetate; [³H]CGS 21680, [³H]-2-[[4-(2-carboxy-ethyl)phenyl]ethylamino]-5'-*N*-(ethylcarbamoyl)adenosine; [³H]-DPCPX, [³H]-1,3-dipropyl-8-cyclopentylxanthine; [³H]ZM 241385; HEK cells, human embryonic kidney cells; [¹²⁵I]-AB-MECA, [¹²⁵I]-*N*-(4-amino-3-iodobenzyl)-5'-(*N*-methylcarbamoyl)adenosine; K_i , equilibrium inhibition constant; L-249313, 6-carboxymethyl-5,9-dihydro-9-methyl-2-phenyl-[1,2,4]triazolo[5,1-*a*][2,7]naphthopyridine; L-268605, 3-(4-meth-

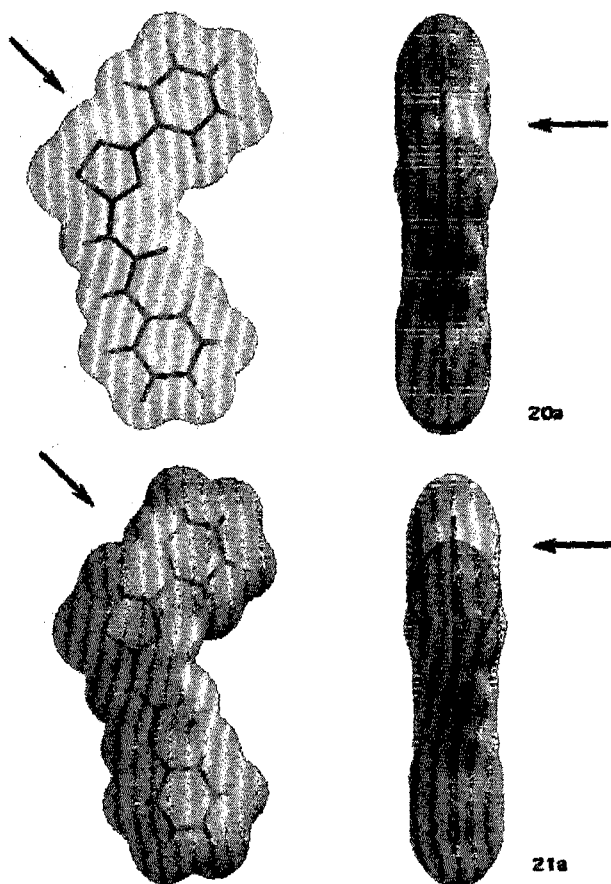


Figure 2. Molecular electrostatic potential energy isosurfaces of low-energy conformations of compounds 20a and 21a. Color coding is in the range from -60 (deepest red) to 60 kcal/mol (deepest blue).

oxyphenyl)-5-amino-7-oxothiazolo[3,2]pyrimidine; MEP, molecular electrostatic potential; MRS1191, 3-ethyl-5-benzyl-2-methyl-6-phenyl-4-(phenylethynyl)-1,4-($\pm$)dihydropyridine-3,5-dicarboxylate; MRS1220, 9-chloro-2-(2-furyl)-5-phenyl-acetyl-amino[1,2,4]triazolo[1,5-c]quinazoline; N-0840, *N*-cyclopentyl-9-methyladenine; VUF8504, 4-methoxy-*N*-(3-(2-pyridinyl)isoquinolin-1-yl)benzamide; VUF5574, *N*-(2-methoxyphenyl)-*N*-(2-(3-pyridyl)quinazolin-4-yl)urea; XAC, 8-[4-(((2-aminoethyl)amino)carbonyl)methoxy]oxyphenyl]-1,3-dipropylxanthine.

Materials. DMF was distilled and stored under linde type 4 Å molecular sieves. Dioxane, triethylamine, pyridine, and DMSO were distilled over CaH_2 and stored under linde type 4 Å molecular sieves as well. All other solvents used were analytical grade. 5-Amino-3-phenyl-1,2,4-thiadiazole, cyclohexanoic acid, *N,N*-dimethylaminopyridine (DMAP), 3- and 4-chlorobenzoic acid, *p*-anisoyl chloride, *p*-anisic acid, *p*-toluic acid, 3,4-dichlorobenzoic acid, 4-methoxyphenyl isocyanate and 4-nitrobenzoic acid were purchased from ACROS. 3-Amino-5-phenylpyrazole, 3-methyl-4-methoxybenzaldehyde, and 4-methoxycyclohexanoic acid were commercially available from Aldrich. Alumina tribromide, 4-iodobenzoic acid, 4-isopropoxybenzoic acid, and 2-amino-4-(4-chlorophenyl)thiazole were purchased from Merck, *n*-butyllithium and phenyl isocyanate from Fluka, and 3-amino-4,5-dihydro-1-phenylpyrazole, 2-amino-4-phenylthiazole and 1-(2-aminophenyl)pyrrole from Lancaster. Thionyl chloride was purchased from Riedel de Haen and 4-amino-6-phenylpyrimidine from SPECS. Compounds 2 and 4 were prepared as described previously¹⁰ and 2-amino-4-(2-pyridyl)thiazole (16) was prepared by the method as described by Taurins and Blaga.¹⁸

Synthesis. Reaction scales were used as mentioned in the general methods, unless otherwise specified. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-FX 200 spectrometer equipped with a PG 200 computer operating in the Fourier transform mode, with tetramethylsilane as an internal standard or on a Bruker AC 200 (^1H NMR: 200 MHz; ^{13}C NMR: 50.29 MHz). 2D-NMR (H-H and C-H) COSY techniques were frequently used to support interpretation of 1D spectra. The multiplicity of the carbon signals was determined by DEPT or APT spectra or by a combination of a normal decoupled carbon spectrum and a CH correlation. The symbols used are (p) for primary, (s) for secondary, (t) for tertiary and (q) for quaternary carbon signals. Mass spectra were measured on a Finnigan MAT TSQ-70 mass spectrometer, equipped with an electrospray interface (EI). Spectra were collected by constant infusion of the analyte dissolved in 80/20 methanol water (sometimes with 1% acetic acid). Experiments were done in positive ionization mode. Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected or measured on a Electrothermal IA9200 apparatus. Reactions were routinely monitored by thinlayer chromatography on Merck silica gel F₂₅₄ plates and spots were visualized with UV light at 254 nm or iodine or aqueous potassium permanganate staining. Elemental analyses were performed by the analytical department of Organic and Molecular Inorganic Chemistry at the University of Groningen (The Netherlands) or at the Leiden University Gorlaeus Laboratories (The Netherlands) and are within $\pm 0.4\%$ of theoretical values unless otherwise specified.

Method A: General Procedure for the Synthesis of 8b,c. 0.5 g (2.8 mmol) of 5-amino-3-phenyl-1,2,4-thiadiazole, 0.52 g of DMAP (4.2 mmol), 4.2 mmol of the apparent benzoic acid and 0.87 g (4.2 mmol) of DCC were dissolved in 35 mL of dry dioxane. After stirring at 60°C for 16 h, the yellow mixture was filtered and concentrated in vacuo. Recrystallization from a mixture of methanol and ethanol yielded white crystals.

Method B: 8a. 0.5 g (2.8 mmol) of 5-amino-3-phenyl-1,2,4-thiadiazole was dissolved in 20 mL of dry dioxane, containing 0.39 mL (2.8 mmol) of triethylamine. A solution of 0.5 mL (4.3 mmol) in 5.0 mL of dry dioxane was added and the solution stirred at 80°C for 16 h. After filtration, the solution was concentrated in vacuo and recrystallized from methanol.

Method C: General Procedure for the Synthesis of 6, 8d,e,j-1, 9, and 10. 1.0 g (5.6 mmol) of 5-amino-3-phenyl-1,2,4-thiadiazole was dissolved in 2.5 mL of dry pyridine in a flame-dried 10-mL three-neck flask. This mixture was cooled to 0°C and 8.2 mmol of acid chloride was added dropwise. The clear solution solidified. After 0.5 h, the solid was dissolved in a mixture of 50 mL of ethyl acetate and 50 mL of water. The H_2O layer was discarded and the ethyl acetate layer washed subsequently with 50 mL of 1 M HCl, 50 mL of 5% NaHCO_3 solution and 50 mL of brine. The organic layer was dried on MgSO_4 and concentrated under reduced pressure. The remaining oil was stirred with 50 mL of *n*-pentane and a white solid resulted. Recrystallization from methanol resulted in white crystals.

Method D: General Procedure for the Synthesis of 5, 8f,g, and 11-13. 0.50 g (2.8 mmol) of 5-amino-3-phenyl-1,2,4-thiadiazole was dissolved in 1.0 mL of dry pyridine in a flame-dried 25-mL three-neck flask. This mixture was cooled to 0°C and 3.2 mmol of acid chloride in 14 mL of dry pyridine was added dropwise. After stirring at room temperature for 1 h the mixture was refluxed for 5 h. After cooling to room temperature, a precipitate was formed which was filtrated and washed 3 times with methanol. Addition of methanol to the filtrate yielded a second batch of solidified product.

***N*-(3-Phenylisoquinolin-1-yl)benzamide (2):** yield 28% yellow-white crystals; mp $162-164^\circ\text{C}$; R_f (MeOH) = 0.8; ^1H NMR (CDCl_3) δ 7.27–8.12 (m, 12H), 8.48 (d, 2H, $^3J_{\text{BA}} = 7.8$ Hz, 2H, benzamide-2H), 8.98 (d, $^3J_{\text{B7}} = 8.0.3$ Hz, 1H, H8), and 14.76 (s, 1H, NH). Anal. ($\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}$) C, H, N.

***N*-(2-Phenylquinazolin-4-yl)benzamide (4):** yield 32% white crystals; mp 166°C (lit.³⁷ mp $168-169^\circ\text{C}$); ^1H NMR ($\text{DMSO}-d_6$) δ 7.31–7.84 (m, 9H, H5 + H6 + H7 + H8 +

259
266

benzamide 2H + benzamide 3H + benzamide 4H), 7.93–8.22 (m, 5H, phenyl-2H + phenyl-3H + phenyl-4H), and 11.05 (s, 1H, NH). Anal. ($C_{21}H_{15}N_3O$) C, H, N.

N-(3-Phenylisoquinolin-1-yl)-4-methoxybenzamide (5): method D; yield 47% white crystals; mp 144–146 °C; 1H NMR ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 6.98 (d, 2H, $^3J_{AB} = 8.8$ Hz, 2H, benzamide-3H), 7.24–7.88 (m, 9H, H5 + H6 + H7 + phenyl-2H + phenyl-3H + phenyl-4H + NH), 8.42–8.52 (m, 3H, H8 + benzamide-2H), and 8.80–8.98 (m, 1H, H4). Anal. ($C_{23}H_{18}N_2O_2 \cdot 0.2H_2O$) C, H, N.

N-(2-Phenylquinazolin-4-yl)-4-methoxybenzamide (6): method C used for 2.20 mmol of 4-amino-2-phenylquinazoline; yield 38% white powder; mp 165–168 °C; R_f (EA) = 0.6; 1H NMR ($DMSO-d_6$) δ 3.87 (s, 3H, OCH_3), 7.12 (d, 2H, $^3J_{AB} = 8.8$ Hz, 2H, benzamide-3H), 7.54–7.70 (m, 4H, H5 + H6 + H7 + H8), 7.95–8.18 (m, 5H, phenyl-2H + phenyl-3H + phenyl-4H), 8.45 (d, 2H, $^3J_{BA} = 8.6$ Hz, 2H, benzamide-2H), and 11.21 (s, 1H, NH). Anal. ($C_{22}H_{17}N_3O_2$) C, H, N.

N-(4-Phenylthiazol-2-yl)-4-methoxybenzamide (7, LUF5433): 47.0 mg (0.27 mmol) of 2-amino-4-phenylthiazole was dissolved in 5.0 mL of dry DMF and added to a solution of 155.0 mg (1.0 mmol) of *p*-anisic acid in 0.5 mL of dry DMF in a 2.2-mL Eppendorf cup. A solution of 210.0 mg (1.0 mmol) of DCC and 15.0 mg (0.12 mmol) of DMAP in 1.0 mL of DMF was added. After stirring at room for 4 days, the precipitate was removed and the solution concentrated under reduced pressure. Recrystallization of the residue from PE (40/60) and methanol resulted in 21% white crystals; mp 172 °C; 1H NMR ($DMSO-d_6$) δ 3.85 (s, 3H, OCH_3), 7.08 (d, 2H, $^3J_{AB} = 8.9$ Hz, benzamide-3H), 7.33 (d, 1H, $^3J_{43} = 7.2$ Hz, phenyl-4H), 7.44 (dd, 1H, $^3J_{34} = 7.2$ Hz, $^3J_{32} = 7.6$ Hz, phenyl-3H), 7.7 (s, 1H, thiazolyl-5H), 7.9 (d, 2H, $^3J_{23} = 7.9$ Hz, phenyl-2H), 8.13 (d, 2H, $^3J_{BA} = 8.9$ Hz, benzamide-2H), and 12.6 (s, 1H, NH); MS (EI) m/z 311 (MH^+ , 100%). Anal. ($C_{17}H_{14}N_2O_2S$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)benzamide (8a): method B; crystallization from CCl_4 /MeOH yielded 35% white crystals; mp 145 °C; R_f value TLC (2.5% EA in CH_2Cl_2) 0.56; 1H NMR ($DMSO-d_6$) δ 7.50–7.73 (m, 6H, phenyl-3H + phenyl-4H + benzamide-3H + benzamide-4H), 8.16–8.32 (m, 4H, phenyl-2H + benzamide-2H); MS (EI) m/z 282 (MH^+ , 100%). Anal. ($C_{15}H_{11}N_3OS \cdot 0.03CCl_4$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-chlorobenzamide (8b): method A; yield white crystals 38%; mp 258 °C; R_f value TLC (2.5% EA in CH_2Cl_2) 0.72; 1H NMR ($DMSO-d_6$) δ 7.48–7.56 (m, 3H, phenyl-3H + phenyl-4H), 7.66 (ddd, 2H, $J = 8.6$; 2.8; 1.7 Hz, benzamide-3H), 8.15–8.22 (m, 4H, phenyl-2H + benzamide-2H); MS (EI) m/z 316 ($M^{(35)Cl}H^+$, 100%), 318 ($M^{(37)Cl}H^+$, 20%). Anal. ($C_{15}H_{10}ClN_3O_2S$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-iodobenzamide (8c): method A; yield white crystals 34%; mp 269 °C; R_f value TLC (2.5% EA in CH_2Cl_2) 0.63; 1H NMR ($DMSO-d_6$) δ 7.51–7.54 (m, 3H, phenyl-3H + phenyl-4H), 7.90–8.02 (m, 4H, phenyl-2H + benzamide-2H), 8.18–8.22 (m, 2H, benzamide-3H); MS (EI) m/z 408 (MH^+ , 100%). Anal. ($C_{15}H_{10}IN_3OS$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-methylbenzamide (8d): method C; yield needlelike white crystals 17%; mp 177 °C; R_f value TLC (EA/tol) 0.69; 1H NMR ($CDCl_3$) δ 2.38 (s, 3H, CH_3), 7.22 (ddd, 2H, $J = 8.25$; 2.04; 2.06 Hz, benzamide-3H), 7.24–7.40 (m, 3H, phenyl-3H + phenyl-4H), 7.71 (ddd, 2H, $J = 8.25$; 2.06; 2.05 Hz, benzamide-2H), 8.11–8.16 (m, 2H, phenyl-2H), 10.58 (bs, 1H, NH). Anal. ($C_{12}H_{13}N_3OS$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-methoxybenzamide (LUF5417, 8e): method C; yield needlelike white crystals 77%; mp 177 °C; R_f value TLC (CH_2Cl_2) 0.36; 1H NMR ($CDCl_3$) δ 3.84 (s, 3H, CH_3), 6.88 (ddd, 2H, $J = 8.93$; 2.06 Hz, benzamide-3H), 7.38–7.43 (m, 3H, phenyl-3H + phenyl-4H), 7.88 (ddd, 2H, $J = 8.93$; 2.06; 2.06 Hz, benzamide-2H), 8.12–8.16 (m, 2H, phenyl-2H). ^{13}C NMR ($CDCl_3$) δ 55.56 (CH_3), 114.44 (benzamide-3C), 122.53 (benzamide-1C), 127.78 + 128.63 + 129.88 + 130.26 (benzamide-2C + phenyl-3,4-C), 132.45 (phenyl-1C), 16402 (benzamide-4C), 165.08 (amide-C), 166.97 (thiadiazolyl-3C), 175.88 (thiadiazolyl-5C); MS (EI) m/z 312 (MH^+ , 100%). Anal. ($C_{16}H_{13}N_3O_2S$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-nitrobenzamide (8f): method D; recrystallization of the combined solids from dichloromethane/methanol yielded 33% needlelike white crystals; mp >300 °C; R_f value TLC (CH_2Cl_2) 0.33; 1H NMR ($DMSO-d_6$) δ 7.50–7.56 (m, 3H, phenyl-3H + phenyl-4H), 8.20–8.22 (m, 2H, benzamide-2H), 8.37–8.42 (m, 4H, phenyl-2H + benzamide-3H), 10.60 (bs, 1H, NH). Anal. ($C_{15}H_{10}N_4O_3S \cdot 0.3CH_2Cl_2$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-methoxy-3-methylbenzamide (8g): method D; purification by column chromatography (EA/tol as eluent) followed by recrystallization from methanol yielded 11% white needles; mp 160 °C; R_f value TLC (EA/tol) 0.90; 1H NMR ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.73–6.78 (d, 1H, benzamide-5H), 7.34–7.37 (m, 3H, phenyl-3H + phenyl-4H), 7.67 (s, 1H, benzamide-2H), 7.71–7.75 (m, 1H, benzamide-6H), 8.10–8.15 (m, 2H, phenyl-2H), 10.64 (bs, 1H, NH). Anal. ($C_{17}H_{15}N_3O_2S$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-4-hydroxybenzamide (LUF5437, 8h): 0.5 g (1.6 mmol) of **8e** was dissolved in 5.0 mL of dry DMSO in a flame-dried pressure tube. 0.40 g (8.2 mmol) of NaCN was added and a nitrogen flow was let in the tube before closing. The solution was stirred at 165 °C for 90 h. The resulting black solution was poured on 30 mL of ice and acidified (carefully in a hood with good ventilation) with 6 N HCl. The black precipitate was collected by filtration and subsequently washed with water and *n*-pentane. A short Kieselgel column was used for purification with CH_2Cl_2 as eluent. 0.08 g of **8e** was recovered (pure). After this ethyl acetate was used as eluent and the product was isolated as a white/yellow solid, which was recrystallized from CCl_4 /toluene; yield white crystals 70% (corrected for recovery of **8e**); mp 117 °C; 1H NMR (CD_3OD) δ 6.93 (d, 2H, $J = 8.6$ Hz, benzamide-3H), 7.45 (m, 3H, phenyl-3H + phenyl-4H), 8.00 (d, 2H, $J = 8.9$ Hz, benzamide-2H), 8.24 (m, 2H, phenyl-2H); MS (EI) m/z 298 (MH^+ , 100%). Anal. ($C_{15}H_{11}N_3O_2S \cdot 0.2CCl_4$) C, H, N.

2-(4-[(3-Phenyl-1,2,4-thiadiazol-5-yl)amino]carbonyl]phenoxy)acetic Acid (8i): 100.0 mg of **8h** was dissolved in 5.0 mL of dry dioxane in a flame-dried pressure tube under nitrogen gas. 200 μ L of triethylamine and 200 μ L of bromoethyl acetate were added. This light yellow solution was stirred overnight at ambient temperature. A precipitate was formed. A mixture of 20 mL of water and 20 mL of ethyl acetate was added. The ethyl acetate layer was collected, washed with a 1 M HCl solution (20 mL) and a brine solution (20 mL), dried on $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in 10 mL of ethanol (96%) and 10 mL of 1 M KOH (aq) was added. After 10 min 6 M HCl was added to acidify the solution. A precipitate formed and a mixture of 20 mL of ethyl acetate and 10 mL of water was added. The ethyl acetate layer was collected and washed with brine (20 mL). After drying and concentrating the ethyl acetate layer, a white "solid" oil remained (yield 100%), which was recrystallized twice from toluene with a little acetone; yield white needlelike crystals, 10% after recrystallization; mp >265 °C; 1H NMR ($DMSO-d_6$) δ 4.82 (s, 2H, CH_2), 7.10 (d, 2H, $J = 8.2$ Hz, benzamide-3H), 7.52 (m, 3H, phenyl-3H + phenyl-4H), 8.17 (d, 2H, $J = 8.2$ Hz, benzamide-2H), 8.21 (m, 2H, phenyl-2H); MS (EI) m/z 356 (MH^+ , 100%). Anal. ($C_{17}H_{13}N_3O_4S$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)cyclohexanamide (8j): method C; crystallization from CCl_4 /MeOH yielded 10% off-white crystals; mp 250 °C dec; R_f value TLC (EA/tol 4:1) 0.65; 1H NMR ($CDCl_3$) δ 1.24–2.14 (m, 10H, chex), 2.70–2.82 (m, 1H, chex-H1), 7.44–7.61 (m, 3H, phenyl-3H + phenyl-4H), 8.52 (dd, 2H, $3J = 7.1$ Hz, phenyl-2H), and 13.48 (bs, 1H, NH). Anal. ($C_{15}H_{17}N_3OS$) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-trans-4-methoxycyclohexanamide (8k): method C; purification by column chromatography (EA/ CH_2Cl_2 1:7 as eluent) yielded the pure isomer; recrystallization from PE60–80/EA yielded 48% white crystals (corrected for *cis/trans*-mixture of starting material); mp 177 °C; R_f value TLC (2.5% EA/ CH_2Cl_2) 0.31; 1H NMR (400 MHz, $DMSO-d_6$) δ 1.12–1.21 (m, 2H, H3-ax), 1.46–1.56 (m, 2H, H2-ax), 1.93–1.96 (m, 2H, H2-eq), 2.05–2.09 (m, 2H, H3-

260

261

eq), 2.52–2.56 (m, 1H, H1-ax), 3.06–3.13 (m, $^3J_{\text{axax}} = 15$ Hz, 1H, H4-ax), 3.26 (s, 3H, OCH₃), 7.35–7.42 (m, 3H, phenyl-3H + phenyl-4H), 7.87–7.93 (m, 1H, phenyl-2H), 8.10–8.14 (m, 1H, phenyl-2H), 12.77 (bs, 1H, NH). Anal. (C₁₆H₁₅N₃O₂S) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-cis-4-methoxycyclohexanamide (8l): method C; purification by column chromatography (EA/CH₂Cl₂ 1:7 as eluent) yielded the pure isomer; recrystallization from PE60–80/EA yielded 32% (corrected for cis/trans-mixture of starting material); mp 221 °C; *R_f* value TLC (2.5% EA in CH₂Cl₂) 0.50; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.42–1.48 (m, 2H, H3-ax), 1.60–1.64 (m, 2H, H2-eq), 1.74–1.83 (m, 2H, H2-ax), 1.86–1.91 (m, 2H, H3-eq), 2.58–2.65 (m, 1H, H1), 3.39 (dd, $^3J_{\text{eqeq}} = 2.1$ Hz, 1H, H4-eq), 3.22 (s, 3H, OCH₃), 7.38–7.45 (m, 3H, phenyl-3H + phenyl-4H), 8.09–8.17 (m, 2H, phenyl-2H), 12.83 (bs, 1H, NH). Anal. (C₁₆H₁₉N₃O₂S) C, H, N.

General Procedure for the Synthesis of 8m,n. 100 mg of methoxy derivative 8k or 8l was added to a mixture of 0.80 g of AlBr₃ and 5.0 mL of EtSH and stirred for 3 h at room temperature. After quenching with 10 mL of water the solution was acidified with 3 drops of HCl (concentrated) and three times extracted with 15 mL of ethyl acetate. The combined organic layers were dried on Na₂SO₄, concentrated under reduced pressure, and purified by column chromatography (EA/CH₂Cl₂ 1:1 as eluent).

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-trans-4-hydroxycyclohexanamide (8m): yield 78%; mp 236 °C; ¹H NMR (DMSO-*d*₆) δ 1.05–1.30 (m, 2H, H3-ax), 1.40–1.60 (m, 2H, H2-ax), 1.75–1.95 (m, 4H, H2-eq + H3-eq), 2.12–2.48 (m, 1H, H1-ax), 3.30–3.50 (m, $^3J_{\text{axax}} = 15$ Hz, 1H, H4-ax), 4.64 (d, $^3J = 6$ Hz, 1H, OH), 7.50–7.60 (m, 3H, phenyl-3H + phenyl-4H), 8.60–8.70 (m, 2H, phenyl-2H), 13.08 (bs, 1H, NH). Anal. (C₁₅H₁₇N₃O₂S) C, H, N.

N-(3-Phenyl-1,2,4-thiadiazol-5-yl)-cis-4-hydroxycyclohexanamide (8n): yield 47%; mp 175 °C; *R_f* value TLC (EA/CH₂Cl₂) 0.43; ¹H NMR (DMSO-*d*₆) δ 1.43–1.70 (m, 6H, H3-ax + H2-ax + H2-eq), 1.81–1.96 (m, 2H, H3-eq), 2.50–2.64 (m, 1H, H1), 3.46–3.50 (m, 1H, H4-eq), 3.74 (d, $^3J = 7$ Hz, 1H, OH), 7.50–7.55 (m, 3H, phenyl-3H + phenyl-4H), 8.14–8.19 (m, 2H, phenyl-2H), 13.04 (bs, 1H, NH). Anal. (C₁₅H₁₇N₃O₂S) C, H, N.

N-(4,5-Dihydro-1-phenylpyrazol-3-yl)-4-methoxybenzamide (9): Method C yielded the dibenzoyl analogue, which was dissolved in 5 mL of dioxane. Subsequently 1.5 mL of 1 M NaOMe was added and the mixture stirred at room temperature for 48 h. Purification by column chromatography (EA/*n*-hexane 3:1) yielded 3% yellow crystals: ¹H NMR (CDCl₃) δ 3.22 (t, $^3J = 10$ Hz, 2H, CH₂), 3.81–3.93 (s + t, $^3J = 7.3$ Hz, 5H, CH₂ + OCH₃), 6.73–6.88 (m, 5H, phenyl-2H, phenyl-4H, benzamide-3H), 7.19 (m, 2H, phenyl-3H), and 7.74 (d, 2H, $^3J_{\text{BA}} = 8.6$ Hz, benzamide-2H). Anal. (C₁₇H₁₇N₃O₂) C, H, N.

N-(5-Phenylpyrazol-3-yl)-4-methoxybenzamide (10): Method C was used for 2.08 mmol of 3-amino-5-phenylpyrazole and 2.28 mmol of anisoyl chloride. The white solid contained the desired product as well as the diamide and was purified by column chromatography (EA/tol 1:1). Recrystallization from methanol of the second fraction yielded 13% of 31 as white needles: mp >300 °C; ¹H NMR (CDCl₃) δ 3.84 (s, 3H, OCH₃), 7.04–7.06 (m, 3H, benzamide-3H + pyrazol-4H), 7.37–7.46 (m, 3H, phenyl-3H + phenyl-4H), 7.72–7.76 (m, 2H, phenyl-2H), 8.0 (d, 2H, $^3J_{\text{BA}} = 8.7$ Hz, benzamide-2H), 10.70 (bs, 1H, NH), and 12.92 (bs, 1H, pyrazol-NH). Anal. (C₁₇H₁₅N₃O₂·0.2CH₃OH) C, H, N.

N-(6-Phenylpyrimidin-4-yl)-4-methoxybenzamide (11): method D used for 0.292 mmol of 4-amino-6-phenylpyrimidine and 0.704 mmol of *p*-anisic acid; reflux period 12 h; preparative TLC (EA/CH₂Cl₂/TEA 1:1 0.01) yielded 26% white solid; mp 160 °C; ¹H NMR (CDCl₃) δ 3.85 (s, 3H, OCH₃), 6.98 (d, 2H, $^3J_{\text{AB}} = 9$ Hz, benzamide-3H), 7.40–7.50 (m, 3H, phenyl-3H + phenyl-4H), 7.85 (d, 2H, $^3J_{\text{BA}} = 9$ Hz, benzamide-2H), 8.02–8.12 (m, 2H, phenyl-2H), 8.61 (bs, 1H, NH), 8.75 (s, 1H, pyrimidine-H), and 8.88 (s, 1H, pyrimidine-H). Anal. (C₁₈H₁₅N₃O₂) C, H, N.

N-(6-Phenylpyridin-2-yl)-4-methoxybenzamide (12): method D used for 3.00 mmol of 2-amino-6-phenylpyridine; yield 22% white crystals; mp 130 °C; ¹H NMR (CDCl₃) δ 3.82 (s, 3H, OCH₃), 6.93 (d, 2H, $^3J_{\text{AB}} = 7$ Hz, benzamide-3H), 7.36–7.47 (m, 4H, H5 + phenyl-3H + phenyl-4H), 7.76 (dd, 1H, $^3J_{\text{A5}} = 8.0$ Hz, $^3J_{\text{A3}} = 8.2$ Hz, H4), 7.85–7.93 (m, 4H, benzamide-2H, phenyl-2H), 8.26 (d, $^3J_{\text{A4}} = 8.2$ Hz, 1H, H3), and 8.55 (bs, 1H, NH). Anal. (C₁₉H₁₆N₂O₂) C, H, N.

N-(Biphen-3-yl)-4-methoxybenzamide (13): method D used for 1.20 mmol of 3-aminobiphenyl; reflux period 8 h; yield 70% white powder; mp 137–138 °C; ¹H NMR (CDCl₃) δ 3.86 (s, 3H, OCH₃), 6.97 (d, 2H, $^3J_{\text{AB}} = 8$ Hz, benzamide-3H) and 7.38–7.87 (m, 11H, H2 + H4 + H5 + H6 + phenyl-2H + phenyl-3H + phenyl-4H + benzamide-2H). Anal. (C₂₀H₁₇NO₂) C, H, N.

General Procedure for 17a–j. **N-[4-(2-Pyridyl)thiazol-2-yl]benzamide Hydrochloride (17a).** 1.0 mmol of the appropriate benzoic acid was dissolved in 0.5 mL of dry DMF in a 2.2-mL Eppendorf vial. 45.0 mg (0.25 mmol) of 2-amino-4-phenylthiazole in 0.5 mL of dry DMF was added, together with a solution of 0.21 g (1.0 mmol) of DCC in 0.5 mL of dry DMF and 14.0 mg (0.1 mmol) of DMAP. This was stirred for 4 days with a small stirring bar. The precipitate was removed by centrifugation, washed with 1.0 mL of DMF, and the combined DMF solutions were concentrated in vacuo. The residue was dissolved in 10 mL of ethyl acetate (clear solution) and a stream of HCl gas was bubbled through the solution. A white precipitate formed, which was collected by centrifugation. The solid was recrystallized twice from EA/CCl₄/MeOH: yield off-white powder 49%; mp 176 °C; ¹H NMR (CD₃OD) δ 7.53–7.70 (m, 3H, benzamide-3H + benzamide-4H), 7.96 (ddd, 1H, *J* = 6.0; 6.0; 3.1 Hz, pyridyl-5H), 8.06 (dd, 2H, *J* = 7.2; 1.4 Hz, benzamide-2H), 8.42 (s, 1H, thiazolyl-5H), 8.57–8.64 (m, 2H, pyridyl-3H + pyridyl-4H), 8.78 (d, 1H, *J* = 5.8 Hz, pyridyl-6H); MS (EI) *m/z* 282 (MH⁺ (–HCl), 100%). Anal. (C₁₅H₁₁N₃OS·HCl) C, H, N.

N-[4-(2-Pyridyl)thiazol-2-yl]-4-chlorobenzamide Hydrochloride (17b): yield white crystals 59%; mp 245 °C; ¹H NMR (CD₃OD) δ 7.60 (ddd, 2H, *J* = 8.6; 2.4; 2.1 Hz, benzamide-3H), 7.97 (ddd, 1H, *J* = 6.2; 6.2; 2.7 Hz, pyridyl-5H), 8.06 (ddd, 2H, *J* = 8.9; 2.4; 2.1 Hz, benzamide-2H), 8.42 (s, 1H, thiazolyl-5H), 8.57–8.64 (m, 2H, pyridyl-3H + pyridyl-4H), 8.78 (ddd, 1H, *J* = 5.5; 1.0; 1.0 Hz, pyridyl-6H); MS (EI) *m/z* 316 (M^(35Cl)H⁺ (–HCl), 100%), 318 (M^(37Cl)H⁺ (–HCl), 28%). Anal. (C₁₅H₁₀ClN₃OS·HCl·0.2CCl₄) C, H, N.

N-[4-(2-Pyridyl)thiazol-2-yl]-4-iodobenzamide Hydrochloride (17c): yield off-white powder 63%; mp 212 °C; ¹H NMR (CD₃OD) δ 7.81 (ddd, 2H, *J* = 8.6; 2.8; 2.1 Hz, benzamide-2H), 7.89 (m, 1H, pyridyl-5H), 7.98 (ddd, 2H, *J* = 8.6; 2.8; 2.1 Hz, benzamide-3H), 8.41 (s, 1H, thiazolyl-5H), 8.56–8.64 (m, 2H, pyridyl-3H + pyridyl-4H), 8.78 (ddd, 1H, *J* = 5.5; 1.0; 1.0 Hz, pyridyl-6H); MS (EI) *m/z* 408 (MH⁺ (–HCl), 100%). Anal. (C₁₅H₁₀IN₃OS·HCl·0.2CCl₄) C, H, N.

N-[4-(2-Pyridyl)thiazol-2-yl]-4-methylbenzamide Hydrochloride (17d): yield white crystals 78%; mp 221 °C; ¹H NMR (CD₃OD) δ 2.44 (s, 3H, CH₃), 7.38 (d, 2H, *J* = 7.9 Hz, benzamide-3H), 7.90–8.00 (m, 1H, pyridyl-5H), 7.94 (d, 2H, *J* = 8.2 Hz, benzamide-2H), 8.39 (s, 1H, thiazolyl-5H), 8.52–8.64 (m, 2H, pyridyl-3H + pyridyl-4H), 8.76 (d, 1H, *J* = 5.4 Hz, pyridyl-6H); MS (EI) *m/z* 296 (MH⁺ (–HCl), 100%). Anal. (C₁₆H₁₃ClN₃OS·HCl·0.2CCl₄) C, H, N.

N-[4-(2-Pyridyl)thiazol-2-yl]-4-methoxybenzamide Hydrochloride (17e): yield slightly yellow crystals 67%; mp 197 °C; ¹H NMR (CD₃OD) δ 3.90 (s, 3H, CH₃), 7.09 (ddd, 2H, *J* = 8.9; 3.1; 2.1 Hz, benzamide-3H), 7.97 (m, 1H, pyridyl-5H), 8.04 (ddd, 2H, *J* = 8.9; 3.1; 2.1 Hz, benzamide-2H), 8.40 (s, 1H, thiazolyl-5H), 8.62 (m, 2H, pyridyl-3H + pyridyl-4H), 8.78 (dm, 1H, *J* = 5.8 Hz, pyridyl-6H); MS (EI) *m/z* 312 (MH⁺ (–HCl), 100%). Anal. (C₁₆H₁₃N₃O₂S) C, H, N.

N-[4-(2-Pyridyl)thiazol-2-yl]-3,4-dichlorobenzamide Hydrochloride (17f): yield white crystals 72%; mp 257 °C; ¹H NMR (CD₃OD) δ 7.75 (d, 1H, *J* = 8.6 Hz, benzamide-5H), 7.97 (ddd, 1H, *J* = 6.2; 5.8; 2.7 Hz, pyridyl-5H), 8.00 (dd, 1H, *J* = 8.6, 2.1 Hz, benzamide-6H), 8.22 (d, 1H, *J* = 2.1 Hz, pyridyl-

261
262

262
263

2H), 8.42 (s, 1H, thiazolyl-5H), 8.56–8.63 (m, 2H, pyridyl-3H + pyridyl-4H), 8.78 (ddd, 1H, $J = 5.8$; 1.0; 1.0 Hz, pyridyl-6H); MS (EI) m/z 350 ($M^{35}Cl$, ^{35}Cl)H⁺ (–HCl), 100%), 352 ($M^{35}Cl$, ^{37}Cl)H⁺ (–HCl), 70%), 354 ($M^{37}Cl$, ^{37}Cl)H⁺ (–HCl), 18%). Anal. ($C_{15}H_{10}Cl_2N_3OS \cdot HCl \cdot 0.1CCl_4$) C, H, N.

N-[4-(2-Pyridyl)thiazol-2-yl]-3-chlorobenzamide Hydrochloride (17g): yield white crystals 62%; mp 188 °C; ¹H NMR (CD_3OD) δ 7.58 (dd, 1H, $J = 8.2$; 7.6 Hz, benzamide-5H), 7.78 (ddd, 1H, $J = 7.9$; 1.9; 1.9 Hz, benzamide-4H), 7.98 (ddd, 1H, $J = 6.4$; 5.7; 2.7 Hz, pyridyl-5H), 8.00 (m, 1H, benzamide-6H), 8.06 (t, 1H, $J = 1.7$ Hz, pyridyl-2H), 8.43 (s, 1H, thiazolyl-5H), 8.57–8.68 (m, 2H, pyridyl-3H + pyridyl-4H), 8.78 (ddd, 1H, $J = 5.5$; 1.4; 1.4 Hz, pyridyl-6H); MS (EI) m/z 316 ($M^{35}Cl$)H⁺ (–HCl), 100%), 318 ($M^{37}Cl$)H⁺ (–HCl), 80%). Anal. ($C_{15}H_{10}ClN_3OS \cdot HCl$) C, H, N.

N-[4-(2-Pyridyl)thiazol-2-yl]-4-nitrobenzamide Hydrochloride (17h): recrystallization of the HCl salt from methanol yielded 53% white crystals; mp 261 °C; ¹H NMR (CD_3OD + 20% DMSO- d_6) δ 7.94 (m, 1H, pyridyl-5H), 8.30 (ddd, 2H, $J = 9.3$; 2.4; 2.1 Hz, benzamide-2H), 8.44 (ddd, 2H, $J = 8.9$; 2.4; 2.1 Hz, benzamide-3H), 8.45 (s, 1H, thiazolyl-5H), 8.56–8.62 (m, 2H, pyridyl-3H + pyridyl-4H), 8.80 (dm, 1H, $J = 6.1$ Hz, pyridyl-6H); MS (EI) m/z 327 (MH⁺ (–HCl), 100%). Anal. ($C_{15}H_{10}N_4O_3S \cdot HCl$) C, H, N.

N-[4-(2-Pyridyl)thiazol-2-yl]-4-isopropoxybenzamide Hydrochloride (17i): crystallization from methanol yielded 48% white needlelike crystals; mp 181 °C; ¹H NMR (CD_3OD) δ 1.37 (d, 6H, $J = 5.8$ Hz, CH₃), 4.75 (quin, 1H, $J = 5.8$ Hz, CH), 7.06 (ddd, 2H, $J = 8.9$; 2.1; 2.1 Hz, benzamide-3H), 7.95 (ddd, 1H, $J = 6.2$; 3.1 Hz, pyridyl-5H), 8.02 (ddd, 2H, $J = 8.9$; 2.1; 2.1 Hz, benzamide-2H), 8.38 (s, 1H, thiazolyl-5H), 8.53–8.63 (m, 2H, pyridyl-3H + pyridyl-4H), 8.78 (dm, 1H, $J = 5.8$ Hz, pyridyl-6H); MS (EI) m/z 340 (MH⁺ (–HCl), 100%). Anal. ($C_{18}H_{17}N_3O_2S \cdot HCl$) C, H, N.

N-[4-(2-Pyridyl)thiazol-2-yl]cyclopentanamide Hydrochloride (17j): yield white crystals 66%; mp 233 °C; ¹H NMR (DMSO- d_6 + 20% CD_3OD) δ 1.50–1.96 (m, 8H, cyclopentyl-2H + cyclopentyl-3H), 3.00 (m, 1H, cyclopentyl-1H), 7.73 (m, 1H, pyridyl-5H), 8.23–8.37 (m, 2H, pyridyl-3H + pyridyl-4H), 8.42 (s, 1H, thiazolyl-5H), 8.72 (d, 1H, $J = 5.5$ Hz, pyridyl-6H); MS (EI) m/z 274 (MH⁺ (–HCl), 100%). Anal. ($C_{14}H_{15}N_3OS$) C, H, N.

General Procedure for the Synthesis of 20a,b, 21a,b, and 22. 90.0 mg (0.5 mmol) of 5-amino-3-phenyl-1,2,4-thiadiazole or 2-amino-4-phenylthiazole was dissolved in 2.0 mL of acetonitrile. This slightly turbid mixture was filtered and the clear solution was transferred in a 2.2-mL Eppendorf vial. 100 μ L (0.9 mmol) of isocyanate was added and the solution was warmed at 56 °C for 2 h. Overnight a white solid precipitated from the reaction mixture, which was collected by centrifugation. The dry solid was recrystallized from PE (60/80) and methanol or absolute ethanol.

N-Phenyl-N-(3-phenyl-1,2,4-thiadiazol-5-yl)urea (20a): yield white crystals 38%; mp 218 °C; ¹H NMR (CD_3OD) δ 7.10 (t, 1H, $J = 7.6$ Hz, N-phenyl-4H), 7.34 (t, 2H, $J = 7.9$ Hz, N-phenyl-3H), 7.41–7.53 (m, 5H, N-phenyl-2H + thiazolphenyl-3H + thiazolphenyl-4H), 8.16–8.21 (m, 2H, thiazolphenyl-2H); MS (EI) m/z 297 (MH⁺, 100%). Anal. ($C_{15}H_{12}N_4OS$) C, H, N.

N-(4-Methoxyphenyl)-N-(3-phenyl-1,2,4-thiadiazol-5-yl)urea (20b): yield white crystals 43%; mp 210 °C; ¹H NMR ($CDCl_3$ + 10% CD_3OD) δ 3.81 (s, 3H, OCH₃), 6.90 (d, 2H, $J = 8.6$ Hz, N-phenyl-3H), 7.40 (d, 2H, $J = 8.6$ Hz, N-phenyl-2H), 7.43–7.49 (m, 3H, thiazolphenyl-3H + thiazolphenyl-4H), 8.13–8.20 (m, 2H, thiazolphenyl-2H); MS (EI) m/z 327 (MH⁺, 100%). Anal. ($C_{16}H_{14}N_4O_2S$) C, H, N.

N-(2-Methoxyphenyl)-N-(3-phenyl-1,2,4-thiadiazol-5-yl)urea (20c): yield white crystals 37%; mp 178–179 °C; ¹H NMR ($CDCl_3$ + 10% CD_3OD) δ 3.71 (s, 3H, OCH₃), 6.95–7.15 (m, 4H, N-phenylH), 7.43–7.49 (m, 3H, thiazolphenyl-3H + thiazolphenyl-4H), 8.13–8.20 (m, 2H, thiazolphenyl-2H). Anal. ($C_{16}H_{14}N_4O_2S \cdot 0.2CH_3OH$) C, H, N.

N-Phenyl-N-[4-(2-pyridyl)thiazol-2-yl]urea (21a): yield white crystals 69%; mp 218 °C; ¹H NMR (DMSO- d_6) δ 7.10 (t,

1H, $J = 7.2$ Hz, N-phenyl-4H), 7.03–7.38 (m, 3H, N-phenyl-3H + pyridyl-5H), 7.50 (dm, 2H, $J = 8.6$ Hz, N-phenyl-2H), 7.64 (s, 1H, thiazolyl-5H), 7.88 (ddd, 1H, $J = 7.55$; 7.55; 1.8 Hz, pyridyl-4H), 7.99 (dm, 1H, $J = 7.9$ Hz, pyridyl-3H), 8.57 (dm, 1H, $J = 5.2$ Hz, pyridyl-6H); MS (EI) m/z 297 (MH⁺, 100%). Anal. ($C_{15}H_{12}N_4OS$) C, H, N.

N-(4-Methoxyphenyl)-N-[4-(2-pyridyl)thiazol-2-yl]urea (21b): recrystallization from methanol yielded 66% white crystals; mp 258 °C; ¹H NMR (DMSO- d_6) δ 3.72 (s, 3H, CH₃), 6.90 (d, 2H, $J = 8.6$ Hz, phenyl-3H), 7.30 (m, 1H, pyridyl-5H), 7.39 (d, 2H, $J = 0.86$ Hz, phenyl-2H), 7.71 (s, 1H, thiazolyl-5H), 7.82–7.96 (m, 2H, pyridyl-3H + pyridyl-4H), 8.58 (m, 1H, pyridyl-6H), 8.74 (s, 1H, NH), 10.66 (bs, 1H, NH); MS (EI) m/z 327 (MH⁺, 100%), 296 (MH⁺ – OCH₃, 95%). Anal. ($C_{16}H_{14}N_4O_2S$) C, H, N.

N-Phenyl-N-(4-phenylthiazol-2-yl)urea (22): yield white crystals 80%; mp 214 °C; ¹H NMR (DMSO- d_6) δ 7.03 (t, 1H, $J = 7.2$ Hz, N-phenyl-4H), 7.28–7.54 (m, 8H, N-phenyl-2H + N-phenyl-3H + thiazolphenyl-3H + thiazolphenyl-4H + thiazolyl-5H), 7.88 (d, 2H, $J = 7.6$ Hz, thiazolphenyl-2H), 8.91 (s, 1H, NH₂), 10.68 (bs, 1H, NH); MS (EI) m/z 296 (MH⁺, 100%). Anal. ($C_{16}H_{13}N_3OS$) C, H, N.

Molecular Modeling. Calculations were performed with SPARTAN version 5.0 (Wavefunction, Inc., Irvine)³⁶ running on a Silicon Graphics O2 workstation. Default values in the Merck force field³⁸ were used in molecular mechanics minimizations. Conjugate gradient energy minimizations were continued until the rms energy derivative was less than 0.01 kcal/mol.Å. The Monte Carlo method was used for conformational analysis (step size 15°). The semiempirical molecular orbital program AM1³⁹ with the AM1 Hamiltonian was used to optimize the conformation of the compounds. The keyword MMOK was used because the structures contain an amide moiety. The 3-21G* Gaussian basis set⁴⁰ (Hartree–Fock, closed shell) was used for ab initio calculations of the energy and the molecular electrostatic potential. The electrostatic potentials were sampled over the entire accessible surface of the molecules (corresponding roughly to a van der Waals contact surface). The most negative electrostatic potential is red, and the most positive electrostatic potential is blue.

Pharmacology. Materials: [³H]CGS 21680 and [³H]-DPCPX were commercially available from DuPont Nemours, (s Hertogenbosch, The Netherlands). [³H]ZM 241385 was purchased from TOCRIS (Bristol, U.K.). [¹²⁵I]AB-MECA was prepared as described by Olah et al.²⁸ Adenosine deaminase was from Boehringer Mannheim (Mannheim, Germany). HEK 293 cells stably expressing the human adenosine A₃ receptor were a gift from Dr. K.-N. Klotz (University of Würzburg, Germany).

Methods for receptor binding: Binding of [³H]DPCPX to adenosine A₁ receptors on rat cerebral cortex membranes and of [³H]CGS 21680 to adenosine A_{2A} receptors from rat striatal membranes was performed as described previously.^{28,27} Binding of [³H]ZM 241385 to adenosine A_{2A} receptors was performed in test tubes containing an aliquot of rat striatal membranes (100–200 μ g of protein/mL) in incubation buffer (50 mM Tris-HCl, adjusted to pH 7.4 at 25 °C) with approximately 2 nM [³H]ZM 241385 in a final volume of 1 mL. After incubation at 25 °C for 120 min the binding reaction was terminated by filtration through Whatman GF/B filters under reduced pressure (200 mbar) using a Brandell cell harvester (Brandell Gaithersburg, MD). Filters were washed twice with ice-cold buffer (5 mL) and placed in scintillation vials. Bound radioactivity was determined using conventional liquid scintillation spectroscopy techniques in a LKB1219 counter.

Binding of [¹²⁵I]AB-MECA to membranes of HEK 293 cells stably expressing the human adenosine A₃ receptor was determined as described.^{28,29}

Acknowledgment. This research was financially supported by Byk Gulden (Zwanenburg, The Netherlands).

Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Alexander, S. P. H.; Peters, J. A. Receptor & ion channel nomenclature supplement. *Trends Pharmacol. Sci.* **1998**, 7–8.
- (2) Robeva, A. S.; Woodard, R. L.; Jin, X.; Gao, Z.; Bhattacharya, S.; Taylor, H.; Roisin, D. L.; Linden, J. *Drug Dev. Res.* **1996**, 39, 243–253.
- (3) Jacobson, M. A.; Chakravarty, P. K.; Johnson, R. G.; Norton, R. Novel selective nonxanthine A_3 adenosine receptor antagonists. *Drug Dev. Res.* **1996**, 37, 131.
- (4) Jacobson, M. A.; Norton, R.; Chakravarty, P. K. Method for inhibiting activation of the human adenosine A_3 receptor to treat asthma. U.S. Patent 5,780,481-A, 1998; *Chem. Abstr.* **129**, 117841.
- (5) Rhee, A. M. van; Jiang, J. L.; Melman, N.; Olah, M. E.; Stiles, G. L.; Jacobson, K. A. Interaction of 1,4-dihydropyridine and pyridine derivatives with adenosine receptors: selectivity for A_3 receptors. *J. Med. Chem.* **1996**, 39, 2980–2989.
- (6) Jiang, J.; Rhee, A. M. van; Melman, N.; Ji, X.; Jacobson, K. A. 6-Phenyl-1,4-dihydropyridine derivatives as potent and selective A_3 adenosine receptor antagonists. *J. Med. Chem.* **1996**, 39, 4667–4675.
- (7) Jiang, J. L.; Rhee, A. M. van; Chang, L.; Patchornik, A.; Ji, X. D.; Evans, P.; Melman, N.; Jacobson, K. A. Structure–Activity Relationships of 4-(phenylethynyl)-6-phenyl-1,4-dihydropyridines as highly selective A_3 adenosine receptor antagonists. *J. Med. Chem.* **1997**, 40, 2596–2608.
- (8) Li, A. H.; Moro, S.; Melman, N.; Ji, X. D.; Jacobson, K. A. Structure–Activity Relationships and molecular modeling of 3,5-diacyl-2,4-dialkylpyridine derivatives as selective A_3 adenosine receptor antagonists. *J. Med. Chem.* **1998**, 41, 3186–3201.
- (9) Xie, R. Y.; Li, A. H.; Ji, X. D.; Melman, N.; Olah, M. E.; Stiles, G. L.; Jacobson, K. A. Selective A_3 adenosine receptor antagonists: Water-soluble 3,5-diacyl-1,2,4-trialkylpyridinium salts and their oxidative generation from dihydropyridine precursors. *J. Med. Chem.* **1999**, 42, 4232–4238.
- (10) Li, A. H.; Ji, X. D.; Kim, H. S.; Melman, N.; Jacobson, K. A. Pyran template approach to the design of novel A_3 adenosine receptor antagonists. *Drug Dev. Res.* **1999**, 48, 171–177.
- (11) adenosine antagonist (CGS15943) are selective for the human A_3 receptor subtype. *J. Med. Chem.* **1996**, 39, 4142–4148.
- (12) Kim, Y.-C.; Zwart, M. de; Chang, L.; Moro, S.; Frijtag von Drabbe Künzel, J.; Melman, N.; IJzerman, A. P.; Jacobson, K. A. Derivatives of the triazoloquinazoline adenosine antagonist (CGS 15943) having high potency at the human A_{2B} and A_3 receptor subtypes. *J. Med. Chem.* **1998**, 41, 2835–2845.
- (13) Karton, Y.; Jiang, J. L.; Ji, X. D.; Melman, N.; Olah, M. E.; Stiles, G. L.; Jacobson, K. A. Synthesis and biological activities of flavonoid derivatives as adenosine receptor antagonists. *J. Med. Chem.* **1996**, 39, 2293–2301.
- (14) Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Spalluto, G.; Klotz, K. N.; Leung, E.; Varani, K.; Gessi, S.; Merighi, S.; Borea, P. A. Pyrrolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine derivatives as highly potent and selective human A_3 adenosine receptor antagonists. *J. Med. Chem.* **1999**, 42, 4473–4478.
- (15) van Muijlwijk-Koezen, J. E.; Timmerman, H.; Link, R.; van der Goot, H.; IJzerman, A. P. A novel class of adenosine A_3 receptor ligands. I. 3-(2-Pyridinyl)isoquinoline derivatives. *J. Med. Chem.* **1998**, 41, 3987–3993.
- (16) van Muijlwijk-Koezen, J. E.; Timmerman, H.; Link, R.; van der Goot, H.; IJzerman, A. P. A novel class of adenosine A_3 receptor ligands. II. Structure Affinity Profile of a series of isoquinoline and quinazoline compounds. *J. Med. Chem.* **1998**, 41, 3994–4000.
- (17) van Muijlwijk-Koezen, J. E.; Timmerman, H.; van der Goot, H.; Menge, W. M. P. B.; Frijtag von Drabbe Künzel, J.; de Groote, M.; IJzerman, A. P. Isoquinoline and quinazoline urea analogues as antagonists for the human adenosine A_3 receptor. *J. Med. Chem.* **2000**, 43, 2227–2238.
- (18) Taurins, A.; Blaga, A. Synthesis of pyridyl- and quinolyl-substituted 2-aminothiazoles. *J. Heterocycl. Chem.* **1970**, 7, 1137–1141.
- (19) Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fujii, K.; Fujita, E. Aluminum halide-thiol system: a useful reagent for demethylation of aliphatic and aromatic methyl ethers and demethylation of methylenedioxy compounds. *Chem. Lett.* **1979**, 97–98.
- (20) Demethylation of methyl ethers of alcohol and phenol with an aluminum halide-thiol system. *J. Org. Chem.* **1980**, 45, 4275–4277.
- (21) Rice, K. C. A rapid, high-yield conversion of codeine to morphine. *J. Med. Chem.* **1977**, 20, 164–165.
- (22) Niwa, H.; Hida, T.; Yamada, K. A new method for cleavage of aliphatic methyl ethers. *Tetrahedron Lett.* **1981**, 22, 4239–4240.
- (23) Jung, M. E.; Lyster, M. A. Quantitative dealkylation of alkyl ethers via treatment with trimethylsilyl iodide. A new method for ether hydrolysis. *J. Org. Chem.* **1977**, 42, 3761–3764.
- (24) Klemmer, A.; Bieber, M.; Wilbers, H. Eine neue Methode zur Spaltung von Kohlenhydrat-triphenylmethyl- und -benzyl-ethern. *Liebigs Ann. Chem.* **1983**, 1416–1421.
- (25) Pawson, B. A.; Cheung, H.-C.; Gurbaxani, S.; and Saucy, G. Synthesis of natural (+)-juvabione, its enantiomer (–)-juvabione, and their diastereoisomers (+)- and (–)-epjuvabione. *J. Am. Chem. Soc.* **1970**, 92, 336–343.
- (26) Pirovano, I. M.; IJzerman, A. P.; Galen, P. J. M. van; Soudijn, W. The influence of molecular structure of N^6 -(ω -aminoalkyl)-adenosines on adenosine receptor affinity and intrinsic activity. *Eur. J. Pharmacol.* **1989**, 172, 185–193.
- (27) Jarvis, M. F.; Schulz, R.; Hutchison, A. J.; Do, U. H.; Sills, M. A.; Williams, M. [3H]CGS 21680, A selective A_2 adenosine receptor agonist directly labels A_2 receptors in rat brain. *J. Pharmacol. Exp. Ther.* **1989**, 251, 888–893.
- (28) Olah, M. E.; Gallo-Rodriguez, C.; Jacobson, K. A.; Stiles, G. L. [^{125}I]-4-aminobenzyl-5'- N -methylcarbamidoadenosine, a high affinity radioligand for the rat A_3 adenosine receptor. *Mol. Pharmacol.* **1994**, 45, 978–982.
- (29) P. J. M.; van Bergen, A. H.; Gallo-Rodriguez, C.; Melman, N.; Olah, M. E.; IJzerman, A. P.; Stiles, G. L.; Jacobson, K. A. A binding site model and structure–activity relationships for the rat A_3 adenosine receptor. *Mol. Pharmacol.* **1994**, 45, 1101–1111.
- (30) Barrett, R. J.; May, J. M.; Martin, P. L.; Miller, J. R. In vitro and in vivo pharmacological characterization of N^6 -cyclopentyl-9-methyladenine(N-0840) – a selective, orally active A_1 adenosine receptor antagonist. *J. Pharmacol. Exp. Ther.* **1993**, 265, 227–236.
- (31) Jacobson, K. A.; Suzuki, F. Recent developments in selective agonists and antagonists acting at purine and pyrimidine receptors. *Drug Dev. Res.* **1996**, 39, 289–300.
- (32) Klotz, K. N.; Hessling, J.; Hegler, J.; Owman, C.; Kull, B.; Fredholm, B. B.; Lohse, M. J. Comparative pharmacology of human adenosine receptor subtypes – characterization of stably transfected receptors in CHO cells. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1998**, 357, 1–9.
- (33) Ukena, D.; Padgett, W. L.; Hong, O.; Daly, J. W.; Daly, J. T.; Olsson, R. A. N^6 -substituted 9-methyladenines: a new class of adenosine receptor antagonists. *FEBS Lett.* **1987**, 215, 203–208.
- (34) Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Ji, X. D.; Olah, M. E.; Stiles, G. L.; Dionisotti, S.; Zocchi, C.; Ongini, E.; Jacobson, K. A. Novel N^6 -(substituted-phenylcarbamoyl)adenosine 5'-uronamides as potent agonists for A_3 adenosine receptors. *J. Med. Chem.* **1996**, 39, 802–806.
- (35) Kim, H. O.; Ji, X. D.; Melman, N.; Olah, M. E.; Stiles, G. L.; Jacobson, K. A. Structure–activity relationships of 1,3-dialkyl-xanthine derivatives at rat A_3 adenosine receptors. *J. Med. Chem.* **1994**, 37, 3373–3382.
- (36) SPARTAN 5.0; Wavefunction, Inc., Irvine, CA 92612; 1995.
- (37) Korbonits, D.; Kiss, P.; Simon, K.; and Kolonits, P. Synthesis of 4-aminopyridines from 1,2,4-oxadiazoles. I. A novel general method for the preparation of 4-aminoquinazolines and their hetero analogues. *Chem. Ber.* **1984**, 117, 3183–3193.
- (38) (a) Halgren, T. A. Merck molecular force field. 1. Basis, form, scope, parametrization, and performance of MMFF94. *J. Comput. Chem.* **1996**, 17, 490–519. (b) Halgren, T. A. Merck molecular force field. 2. MMFF94 van der Waals and electrostatic parameters for intermolecular interactions. *J. Comput. Chem.* **1996**, 17, 520–552. (c) Halgren, T. A. Merck molecular force field. 3. Molecular geometries and vibrational frequencies for MMFF94. *J. Comput. Chem.* **1996**, 17, 553–586. (d) Halgren, T. A.; Nachbar, R. B. Merck molecular force field. 4. Conformational energies and geometries for MMFF94. *J. Comput. Chem.* **1996**, 17, 587–615. (e) Halgren, T. A. Merck molecular force field. 5. Extension of MMFF94 using experimental data, additional computational data, and empirical rules. *J. Comput. Chem.* **1996**, 17, 616–641.
- (39) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. AM1: A new general purpose quantum mechanical molecular model. *J. Am. Chem. Soc.* **1985**, 107, 3902–3909.
- (40) Hehre, W. J.; Radam, L.; Schleyer, P. R.; Pople, J. A. *Ab initio molecular orbital theory*; Wiley: New York, 1986.
- (41) de Zwart, M.; Vollinga, R. C.; Beukers, M. W.; Sleegers, D. F.; Frijtag von Drabbe Künzel, J.; de Groote, M.; IJzerman, A. P. Potent antagonists for the human adenosine A_{2B} receptor. Derivatives of the triazoloquinazoline adenosine receptor antagonist ZM241385 with high affinity. *Drug Dev. Res.* **1999**, 48, 95–103.

JM0003945

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

(19) World Intellectual Property Organization
International Bureau



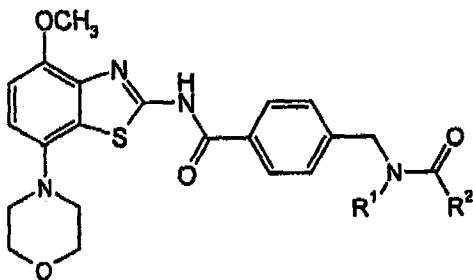
(43) International Publication Date
5 June 2003 (05.06.2003)

PCT

(10) International Publication Number
WO 03/045386 A1

- (51) International Patent Classification: A61K 31/428, C07D 277/82 (74) Agent: POPPE, Regina; 124 Grenzacherstrasse, CH-4070 Basle (CH).
- (21) International Application Number: PCT/EP02/13046 (81) Designated States (national): AE, AG, AI, 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, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date:
21 November 2002 (21.11.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
01128338.9 29 November 2001 (29.11.2001) EP
- (71) Applicant: F.HOFFMANN-LA ROCHE AG [CH/CH];
124 Grenzacherstrasse, CH-4070 Basle (CH).
- (72) Inventors: FLOHR, Alexander; 142 St. Galler-Ring, CH-4054 Basle (CH). JAKOB-ROETNE, Roland; Oberer Baselblick 37, 79595 Inzlingen (DE). NOR-CROSS, Roger, David; 20 Alte Saline, CH-4310 Rheinfelden (CH). RIEMER, Claus; Optizstrasse 5, 79110 Freiburg (DE).
- (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, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- 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.

(54) Title: BENZOTHAZOLE DERIVATIVES



(57) Abstract: The present invention relates to compounds of the general formula (I) wherein R¹ is hydrogen or lower alkyl; R² is lower alkyl, -(CH₂)_n-O-lower alkyl, -C₃₋₆-cycloalkyl or -(CH₂)_n-NR'₂; R' is hydrogen, lower alkyl or -(CH₂)_n-O-lower alkyl, independently from each other for R'₂, or R'₂ may form together with the N atom a pyrrolidine ring; n is 1, 2 or 3; and to pharmaceutically acceptable acid addition salts thereof. It has surprisingly been found that the compounds of general formula I are adenosine receptor ligands. Specifically, the compounds of the present invention have a good affinity to the A_{2A}-receptor and they are therefore useful in the treatment of diseases, related to this receptor.

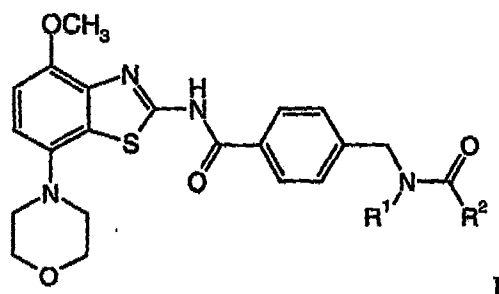
WO 03/045386 A1

265

266

Case 21018Benzothiazole derivatives

The present invention relates to compounds of the general formula



wherein

- 5 R^1 is hydrogen or lower alkyl;
- R^2 is lower alkyl, $-(CH_2)_n-O$ -lower alkyl, $-C_{3-6}$ -cycloalkyl or $-(CH_2)_n-NR'_2$;
- R' is hydrogen, lower alkyl or $-(CH_2)_n-O$ -lower alkyl, independently from each other
 for R'_2 , or R'_2 may form together with the N atom a pyrrolidine ring;
- n is 1, 2 or 3;
- 10 and to pharmaceutically acceptable acid addition salts thereof.

It has surprisingly been found that the compounds of general formula I are adenosine receptor ligands. Specifically, the compounds of the present invention have a good affinity to the A_{2A} -receptor and a high selectivity to the A_1 - and A_3 receptors.

- 15 Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors. The potential of adenosine receptors as drug targets was first reviewed in 1982. Adenosine is related both structurally and metabolically to the bioactive nucleotides adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP) and cyclic adenosine monophosphate (cAMP); to the biochemical methylating agent S-adenosyl-L-methione (SAM); and structurally to the coenzymes NAD,

267
268

4-[(cyclopropanecarbonyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide or

4-[(cyclobutanecarbonyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide.

- 5 6. Compounds in accordance with claim 1, wherein R^2 is lower alkyl and R^1 is hydrogen or lower alkyl.

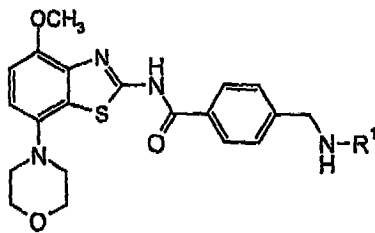
7. Compounds in accordance with claim 6, wherein the compound is
- 10 N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-[(methyl-propionyl-amino)-methyl]-benzamide,
- N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-(propionylamino-methyl)-benzamide,
- 4-[(acetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide,
- 15 4-(acetylamino-methyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide or
- 4-[(ethyl-propionyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide.

8. Compounds in accordance with claim 1, wherein R^2 is the group $-(CH_2)_n-NR'_2$
- 20 and R^1 is lower alkyl.

9. Compounds in accordance with claim 8, wherein the compound is
- 4-[(dimethylaminoacetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide
- N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-[[methyl-(pyrrolidin-1-yl-acetyl)-
- 25 amino]-methyl]-benzamide

10. A process for preparing a compound of formula I as defined in claims 1 - 9, which process comprises

- a) reacting a compound of formula



DERIVATIVES OF 4-AMINO-5-ALKYL SULPHONYL ORTHOANISAMIDES

This is a continuation of application Ser. No. 004,397, 5
filed Jan. 18, 1979, now U.S. Pat. No. 4,294,828, issued
Oct. 13, 1981.

BACKGROUND OF THE INVENTION

The compounds of the present invention fall within 10
the general disclosure of U.S. Pat. No. 3,342,826. It
should be noted however that none of the compounds
prepared in said patent nor the specifically named ben-
zoic acids utilized for preparing the prior art com-
pounds contain the 4-amino-5-lower alkylsulphonyl
benzoyl moiety.

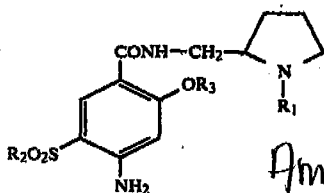
The disclosure of utility set forth in column 1 lines 33
through 43 of the prior art patent make no mention
whatsoever of the surprising antiapomorphine and an-
tiserotonin activities of the compounds of the present
invention.

The prior art patent is assigned to applicant's as-
signee.

SUMMARY OF THE INVENTION

There are provided novel compounds having anti-
apomorphine and antiserotonin activity.

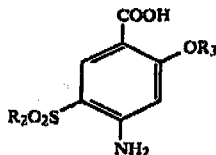
The novel compounds of the present invention have
the formula:



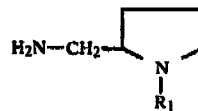
wherein R₁ is lower alkyl of 1 to 5 carbon atoms or
lower alkenyl of 2 to 5 carbon atoms, R₂ and R₃ are
lower alkyl of 1 to 5 carbon atoms.

The novel compounds of the present invention also
include the N-oxides, the quaternary ammonium salts
and the salts with pharmacologically acceptable acids
of the foregoing compounds. The dextrorotatory and
levorotatory isomers of all of the foregoing are also
included within the scope of the invention.

The compounds of the present invention are readily
prepared by either of two routes, the appropriate 2-
alkoxy-4-amino-5-mercaptobenzoic acid is treated with
a lower alkyl sulphate to provide the corresponding
5-lower alkylthiobenzoic acid which is then oxidized to
provide the 2-alkoxy-4-amino-5-alkylsulphonyl benzoic
acid of the formula:



The acid II is then reacted with an amine of the for-
mula:



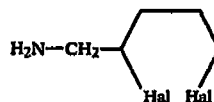
the reaction is carried out by activating either the acid
moiety or the amino moiety by means known in the art.
Thus the acid moiety may be converted into the corre-
sponding acyl halide, alkyl ester, reactive ester, aryl
ester, N-hydroxy imide ester, symmetrical anhydride,
or mixed anhydride with an ester of a carbonic acid or
a haloformic ester, azide, hydrazide, azolide, acid isothi-
ocyanate, trichloroacetophenone, or triphenylphos-
phine derivative.

Alternatively, the acid moiety is left intact and the
amine activated by reaction with phosphorus chloride,
phosphorus oxychloride, a dialkyldiaryl-, or ortho-
phenylenechlorophosphite, an alkyl- or aryldichloro-
phosphite, or the formation of an isothiocyanate of the
amine or a substituted urea or sulphamide.

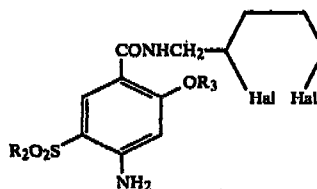
The activated compound is then reacted with the
unactivated component by means well-known in the
art.

In a further embodiment the free acid and the free
amine may be reacted together in the presence of a
condensing agent such as, for example, silicon tetra-
chloride, trichlorophenylsilane, phosphoric anhydride,
a carbodiimide or an alkoxyacetylene.

In yet another embodiment of this synthetic proce-
dure of the present invention there is provided a diaha-
loalkylamine of the formula:



the diahaloalkylamine (IV) is then reacted with an acid
of formula (II) as above or one of its active derivatives
again as defined above to provide a compound of the
formula:



The compound of formula (V) is then reacted with a
primary amine of the formula:



The thus produced compounds of the present inven-
tion may be reacted with pharmaceutically acceptable
acids to yield acid addition salts; with alkyl halides or
alkyl sulphates to give the corresponding quaternary
ammonium salts; or oxidized with the usual oxidizing
agents to provide the corresponding N-oxide.

(III)

(IV)

(V)

(II)

60

(VI)

65

270
241

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Especially preferred among the compounds of the present invention are the compounds of formula I, wherein R₁ is methyl, ethyl, propyl, allyl, R₂ is methyl, ethyl, propyl, or isopropyl, R₃ is methyl.

Among the pharmaceutically acceptable acids which form salts with the compounds of formula I may be mentioned inclusively but not in a limiting manner, inorganic or organic acids such as hydrochloric, hydrobromic, sulphuric, phosphoric, oxalic, acetic, tartaric, citric, or methane sulphonc acid.

The method of activating compounds of formula II in order to react them with compounds of formula III and of activating compounds of formula III to react them with compounds of formula II are well-known in the art. The amidation reaction may be carried out either by mixing the reactant in situ or, if desired, after previously separating the intermediate reactants.

In the second embodiment of the procedure wherein an acid formula II is reacted with a dihaloalkylamine the amidation reaction may be carried out with or without a solvent. It has however, been found useful to carry out the reaction utilizing either inert solvents or an excess of the haloalkylamine, as the solvent. In both cases the reaction is most suitably carried out under solvent reflux although the procedure is by no means limited thereto.

As inert solvents for the amidation reaction there may be mentioned alcohols, polyols, ketones, benzene, toluene, dioxane, chloroform or diethylene glycol dimethyl-ether.

The N-oxides of the present invention may be prepared in the usual manner by reacting with suitable oxidizing agent such as hydrogen peroxide and magnesium dioxide.

PHARMACOLOGICAL DATA

The acute toxicity of the compounds according to the invention has been studied in mice. The lethal doses 50 are set out in the table which follows:

Compounds	Intravenous	I.P.	Subcutaneous	Oral
1	56-60	173-180	224-250	1024-1054
2	56-57	210-217	280	1326-1330
3	106-107	216-217	312-330	2232-2375
4	39.8	188	254-263	1564-1621
5	44.8	122-128	137-149	1109-1160
6	62-64	304-322	380-396	1186-1260
7	43-46.8	160-165	140-144	570-629
8	46.5-50	234-238	208-225	625-660
9	54	200-216	202.5	996-105

1 N-(1-ethyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-ethylsulphonylbenzamide
 2 N-(1-methyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-ethylsulphonylbenzamide
 3 N-(1-allyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-ethylsulphonylbenzamide
 4 dextrorotatory N-(1-ethyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-ethylsulphonylbenzamide tartrate
 5 levorotatory N-(1-ethyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-ethylsulphonylbenzamide tartrate
 6 dextrorotatory N-(1-methyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-ethylsulphonylbenzamide
 7 N-(1-ethyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-propylsulphonylbenzamide
 8 N-(1-ethyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-methylsulphonylbenzamide
 9 N-(1-methyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-methylsulphonylbenzamide

The cataleptic action has been studied as follows.

Benzamides are administered subcutaneously to male rats. The criterion taken for the cataleptic state is that

the animal should be immobile for 30 seconds with its rear limbs apart, arranged carefully on wooden cubes 4 cm high, which thus puts the animal in an unaccustomed and uncomfortable position.

The cataleptic action is measured when the effect is at its maximum, i.e. 5 to 7 hours after the substance has been administered.

With a dose of 200 mg/kg given subcutaneously, benzamides 1 to 4 and 6 to 8 are found to have absolutely no cataleptic action, and compound 5 is found to produce a cataleptic state in only 30% of the animals, after 7 hours.

The compounds of the invention have undergone other pharmacodynamic tests, and in particular their antiemetic power relative to apomorphine has been measured.

The test has been carried out on dogs by the method of Chen and Ensor.

The compounds of the invention are administered subcutaneously, 30 minutes before the apomorphine, which is administered subcutaneously in a dose of 100 µg/kg.

The results obtained are as follows:

Antipomorphine ED ₅₀ in the dog expressed in µg/kg/s.c.									
Compound	1	2	3	4	5	6	7	8	9
ED ₅₀	0.29	0.8	0.65	12	0.28	8	1.6	2.7	7

The results of this test, which prove an antagonism to apomorphine 5 to 20 times greater than that of known compounds in the same series, have led us to think that the compounds according to the invention have a strong action on the central nervous system. The pharmacodynamic study of the compounds of the invention was concluded with antiserotonin tests inter alia in connection with stomach ulceration in the rat and bronchospasm in the guinea-pig.

The antiserotonin action in connection with stomach ulceration has been studied in the rat under the following conditions:

30 mg/kg of serotonin is administered subcutaneously to female rats in two stages, with an interval of 16 hours. The product being studied is administered subcutaneously at the same time as the serotonin, in two stages with increasing doses. A group of 30 animals is used for each dose and a group of 60 animals is used as the control. The animals are sacrificed 22 hours after the first injection of serotonin, and their stomachs are taken out and examined. The percentage protection for each dose studied is determined, then the DE₅₀, the dose protecting 50% of the animals, from gastric ulceration, is measured graphically.

The results obtained are as follows:

Antiserotonin ED ₅₀ in respect of stomach ulceration, in the rat - expressed in mg/kg/s.c.									
Compound	1	2	3	4	6	7	8	9	
ED ₅₀	1	0.4	0.65	0.46	0.34-0.44	3.2	3	1.14	

The antiserotonin action in respect of bronchospasm has been studied in the guinea-pig under the following conditions:

The bronchospasm is recorded by the method of Konzett and Rossler, which comprises connecting the

trachea of the guinea-pig to an artificial respiration pump, which passes a constant volume of air, slightly greater than the respiratory capacity of the animal, into the bronchi at a physiological rhythm. The excess quantity of air, which varies according to the diameter of the bronchi, is discharged to a special manometric device which measures the volume of air at each inhalation.

The serotonin is administered intravenously to the guinea-pigs in a dose of 20 $\mu\text{g/kg}$. The guinea-pigs have previously been anaesthetised with ethyl carbamate, thus producing a bronchial spasm.

The product to be studied is then administered intravenously, after which the administration of serotonin is repeated one minute later. The percentage inhibition of bronchospasm is measured for each dose of the product to be studied, then the antiserotonin ED_{50} relative to bronchospasm in the guinea-pig is determined:

The results obtained are as follows:

Antiserotonin ED_{50} relative to bronchospasm in the guinea-pig - expressed in $\mu\text{g/kg/IV}$		
COMPOUND	1	4
ED_{50}	74	106

These antiserotonin properties very clearly distinguish the compounds of the invention from sulpiride, for which the antiserotonin ED_{50} relative to stomach ulceration in the rat is 110 mg/kg .

The low toxicity of the compounds according to the invention and the absence of any undesirable side effects such as catalepsy, which normally accompany this type of product, have made it possible to proceed to clinical tests. These have revealed powerful psychotropic properties of the compounds according to the invention, as follows (their originality has to do with the combination of antiapomorphine and antiserotonin properties, which is surprising at this degree in the benzamide series):

effect of removing inhibitions; in particular this makes it the preferred treatment for autism treatment for sudden attacks of delirium antimigraine action

In addition, these derivatives have proved valuable in weaning drug addicts.

Because of their psycho stimulating properties they reduce the danger of relapse during the deficiency period which follows weaning. They are not addictive.

Finally, the sedative effect is zero: these derivatives are not recommended for acute psychoses with agitation.

Clinical studies carried out on several hundred patients taking daily doses of 50 to 750 mg have brought out the therapeutic properties of the compounds according to the invention and shown that they can be tolerated extremely well.

Thus for example, 200 mg per day of compound (1) was administered orally or by intramuscular injection to 30 patients who were alcoholic or heroin addicts. In 28 cases the product acted rapidly and the drug addicts asked for more. Its effect is different from that of opiates and the main analgesics. The patients did not suffer any dependency syndrome when the treatment was suddenly stopped. No neurological side effect was observed.

41 patients suffering from sudden attacks of delirium were treated with 350 mg per day of compound (2), administered orally or by intramuscular injection. In 38 cases a very good antipsychotic action was observed in

the sudden attacks of delirium; there was an antidepressive action and excellent tolerance in all cases.

21 patients suffering from catatonic hebephrenia were treated with compound (1), a daily dose of 100-300 mg being given orally or by intramuscular injection. In 13 cases removal of inhibitions was observed, sometimes with a reversal of mood, which made it possible to make contact with the patient.

Compound (1) was administered in a dose of three tablets per day (300 mg) to a patient suffering from frequent migraines; these obliged hereto interrupt any professional activity for three or four days per month. The migraines decreased from the first month and disappeared altogether from the second month, with a continuous dosage of only one tablet per day (100 mg).

Compound (1) was administered in a daily dose of 300 mg taken in three portions, to two twin brothers who suffered each month from attacks of migraine accompanied by vomiting. For one of the twins the migraine disappeared immediately. For the other the pain disappeared from the second method and only a few attacks of nausea persisted.

Compound (2) was administered continuously, in doses of two tablets per day (200 mg), to a woman who had suffered from attacks of migraine for four years. The attacks had not responded to curative treatment (ergotamine and caffeine) or preventive treatment. The attacks are becoming rare (1 or 2 per month instead of 10 to 15), their intensity is decreasing and they can regularly be dealt with by taking two tablets of ergotamine and caffeine.

Compound (2) was administered in doses of three tablets per day (300 mg) to a woman suffering from quasi permanent occipital cephalalgia and several times a week from attacks of migraine with right hemiparesis, photophobia and nausea. From the third week the migraine attacks disappeared completely.

EXPERIMENTAL

In order to illustrate the technical features of the invention some examples will now be described. It should be made clear that the invention is not restricted to these, either in respect of the method used or the possible applications.

EXAMPLE 1

N-(1-ethyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide

2-methoxy 4-amino 5-ethylthiobenzoic acid

159 g of 2-methoxy 4-amino 5-mercaptobenzoic acid, 355 cm^3 of water and 160 cm^3 of caustic soda solution are placed in a flask fitted with a condenser. The mixture is heated until the solid dissolves, then 123 g of ethyl sulphate is added. The mixture is heated to reflux, treated with 10 cm^3 of 30% caustic soda solution, then heated to reflux for 1 hour. After cooling, 800 cm^3 of water is added and the solution is filtered. The precipitate obtained by adding 100 cm^3 of concentrated hydrochloric acid in the presence of ether is drained, washed with water and dried.

162 g of 2-methoxy 4-amino 5-ethylthio benzoic acid is obtained (yield=88%).

2-methoxy 4-amino 5-ethylsulphonyl benzoic acid

123 g of 2-methoxy 4-amino 5-ethylthiobenzoic acid is dissolved hot in 542 cm^3 of acetic acid. The solution obtained is cooled to 35° C., then 185 cm^3 of 131 vol.

272
273

hydrogen peroxide is added in small quantities while the temperature is raised to 80° C.

The temperature is lowered to 40° C. and the mixture is kept at that temperature for some hours then cooled to 10° C.

The precipitate formed is drained, washed with acetic acid and dried, then dissolved in 600 cm³ of water and 100 cm³ of 20% ammonia.

The precipitate formed by adding 70 cm³ of concentrated hydrochloric acid is cooled, drained, washed with water and dried.

61.5 g of 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid hydrate is obtained (yield 42%—M.P. 95°–100° C.).

N-[1-ethyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide

81 g of 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid and 297 cm³ of acetone are placed in a flask fitted with an agitator, a thermometer and a dropping funnel, followed by 33 g of triethylamine. The solution is cooled to 0° C., then 30 g of ethyl chloroformate is added drop by drop between 0° and 5° C.

When the mixture has been agitated 51 g of 1-ethyl 2-amino methyl pyrrolidine is added drop by drop between 5° and 10° C. The mixture is agitated at 10° C. then at ambient temperature. The triethylamine hydrochloride which precipitates is drained, then the acetone is distilled. The residue is dissolved in 600 cm³ of water in the presence of caustic soda solution. The base crystallises after seeding and is drained, washed with water and dried.

When the crystals have been purified by passing them through hydrochloride and re-crystallising them in acetone, 66 g of N-[1-Methyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (yield 61%—M.P.=126° to 127° C.).

EXAMPLE II

N-[1-methyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide

144 g of 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid, 440 cm³ of acetone and 44.5 g of triethylamine are placed in a flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to 0° C., then 48 g of ethyl chloroformate is added drop by drop between 0° and 15° C.

The mixture is agitated for 30 minutes between 0° and 5° C., then 67 g of 1-methyl 2-aminomethylpyrrolidine is added drop by drop between 5° and 10° C. The mixture is then agitated firstly at 10° C. then at room temperature. The product obtained is drained, washed with acetone, treated with 500 cm³ of water, then drained, washed with water and dried.

The substance obtained is re-crystallised in absolute alcohol and purified by passing it through hydrochloride. After further re-crystallisation in absolute alcohol, 101 g of N-[1-methyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (yield=157°–158° C.).

EXAMPLE III

N-[1-allyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide

132 g of 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid, 510 cm³ acetone and 51.5 g of triethylamine are placed in a flask fitted with an agitator, a thermometer and a dropping funnel. The solution obtained is cooled

to 0° C., then 55.5 g of ethyl chloroformate is added drop by drop, between 0° and 5° C.

The mixture is agitated for 30 minutes at 5° C., then 96 g of 1-allyl 2-aminomethylpyrrolidine is added drop by drop, between 5° and 10° C. The mixture is agitated at 10° C. then at room temperature.

The triethylamine hydrochloride which is precipitated is drained and washed with acetone, then the acetone is distilled. The residue is dissolved in water and 60 cm³ of concentrated hydrochloric acid, then the solution obtained is filtered and treated with the 30% caustic soda solution. The oil formed is extracted with methylene chloride, then the organic solution is dried over potassium carbonate and the methylene chloride is distilled.

After purification 131 g of N-[1-allyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (yield=67%—M.P. 111°–112° C.).

EXAMPLE IV

Dextrorotatory tartrate of N-[1-ethyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide

Dextrorotatory N-[1-ethyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide

Following the same procedure as in Example I, 95 g of 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid dissolved in 370 ml of acetone, in the presence of 37 g of triethylamine, is treated with 40 g of ethyl chloroformate then with 57 g of dextrorotatory 1-ethyl 2-aminomethylpyrrolidine.

115 g of dextrorotatory N-[1-ethyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (yield=84%).

Dextrorotatory tartrate of N-1-ethyl 2-pyrrolidylmethyl 2-methoxy 4-amino 5-ethylsulphonyl benzamide

133 g of dextrorotatory N-[1-ethyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide is dissolved in 500 ml of methanol, then 54 g of dextrorotatory tartaric acid dissolved in 80 ml of methanol is added. The crystals which form after seeding are drained, washed with methanol then dried.

After re-crystallisation in methanol, 106 g of dextrorotatory tartrate of N-[1-ethyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (yield=56%—N.P.=98°–108° C.—[α]_D²⁰ C. in 5% aqueous solution=+7°, 5).

EXAMPLE V

Levorotatory tartrate of N-[1-ethyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide

Levorotatory N-[1-ethyl 2-pyrrolidylmethyl] 2-methoxy 4-amino 5-ethylsulphonyl benzamide

Following the same procedure as in Example I, 104 g of 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid dissolved in 380 ml of acetone, in the presence of 38 g of triethylamine, is treated with 41 g of ethyl chloroformate then with 58 g of levorotatory 1-ethyl 2-aminomethyl pyrrolidine.

273
274

140 g of levorotatory N-[1-ethyl 2-pyrrolidylmethyl]2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (yield 100%).

Levorotatory tartrate of N-[1-ethyl 2-pyrrolidylmethyl]2-methoxy 4-amino 5-ethylsulphonyl benzamide

136 g of levorotatory N-[1-ethyl 2-pyrrolidylmethyl]2-methoxy 4-amino 5-ethylsulphonyl benzamide is dissolved in 500 ml of methanol, then 58 g of levorotatory tartaric acid dissolved in 70 ml of methanol is added. The crystals formed are drained, washed with methanol and dried.

After re-crystallisation in methanol, 103 g of levorotatory tartrate of N-[1-ethyl 2-pyrrolidylmethyl]2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (yield=54%; M.P.=100° C.; $[\alpha]$ 20° C. in 5% aqueous solution = -6°, 3).

EXAMPLE VI

Dextrorotatory N-1-methyl 2-pyrrolidylmethyl 2-methoxy 4-amino 5-ethylsulphonyl benzamide

Following the same procedure as in Example I, 117 g of 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid dissolved in 450 ml of acetone, in the presence of 46 g of triethylamine, is treated with 49 g of ethyl chloroformate then with 69 g of dextrorotatory 1-methyl 2-aminomethylpyrrolidine.

69 g of dextrorotatory N-1-methyl 2-pyrrolidylmethyl 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (yield=44%—M.P.=125°-126° C.— $[\alpha]$ 20° C. in a 5% dimethylformamide solution=35.3°).

EXAMPLE VII

N-(1-methyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-propylsulphonyl benzamide

2-methoxy 4-amino 5-propylthio benzoic acid

Following the same procedure as in Example I and starting with 2-methoxy 4-amino 5-mercapto benzoic acid, 2-methoxy 4-amino 5-propylthio benzoic acid is obtained (M.P.=104°-105° C.).

2-methoxy 4-amino 5-propylsulphonyl benzoic acid

Following the same procedure as in Example I, 137 g of 2-methoxy 4-amino 5-propylthio benzoic acid dissolved in 570 ml of acetic acid is treated with 233 ml of 110 vol. hydrogen peroxide. 108 g of 2-methoxy 4-amino 5-propylsulphonyl benzoic acid is obtained (yield=69%—N.P.=165°-166° C.).

N-(1-ethyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-propylsulphonyl benzamide

Following the same procedure as in Example I, 160 g of 2-methoxy 4-amino 5-propylsulphonyl benzoic acid dissolved in 590 ml of acetone, in the presence of 59 g of triethylamine, is treated with 64 g of ethyl chloroformate then with 101 g of 1-ethyl 2-aminomethylpyrrolidine.

After purification, 151 g of N-[1-ethyl 2-pyrrolidylmethyl]2-methoxy 4-amino 5-propylsulphonyl benzamide is obtained (yield=67%—M.P.=105°-106° C.).

EXAMPLE VIII

N-[1-methyl 2-pyrrolidylmethyl]2-methoxy 4-amino 5-methylsulphonyl benzamide

2-methoxy 4-amino 5-methylthio benzoic acid

Following the same procedure as in Example I and starting with 2-methoxy 4-amino 5-mercapto benzoic acid, 2-methoxy 4-amino 5-methylthio benzoic acid is obtained (M.P.=151°-152° C.).

2-methoxy 4-amino 5-methylsulphonyl benzoic acid

Following the same procedure as in Example I, 158 g of 2-methoxy 4-amino 5-methylthio benzoic acid dissolved in 742 ml of acetic acid is treated with 310 ml of 110 vol. hydrogen peroxide.

114.5 g of 2-methoxy 4-amino 5-methylsulphonyl benzoic acid is obtained (yield=63%—M.P.=178°-180° C.).

N-(1-methyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-methylsulphonyl benzamide

Following the same procedure as in Example I, 131 g of 2-methoxy 4-amino 5-methylsulphonyl benzoic acid dissolved in 538 ml of acetone, in the presence of 54 g of triethylamine, is treated with 58.5 g of ethyl chloroformate then with 73 g of 1-methyl 2-aminomethylpyrrolidine.

When the substance formed has been purified, 114 g of N-[1-methyl 2-pyrrolidylmethyl]2-methoxy 4-amino 5-methylsulphonyl benzamide is obtained (yield=62%—M.P.=190°-191° C.).

EXAMPLE IX

N-[1-ethyl 2-pyrrolidylmethyl]2-methoxy 4-amino 5-methylsulphonyl benzamide

Following the same procedure as in Example I, 129 g of 2-methoxy 4-amino 5-methylsulphonyl benzoic acid dissolved in 526 ml of acetone, in the presence of 53 g of triethylamine, is treated with 57 g of ethyl chloroformate then with 81 g of 1-ethyl 2-aminomethyl pyrrolidine.

When the substance formed has been purified, 96 g of N-[1-ethyl 2-pyrrolidyl methyl]2-methoxy 4-amino 5-methylsulphonyl benzamide is obtained (yield=52%—M.P.=151°-151.5° C.).

EXAMPLE X

N-oxide of N-(1-ethyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide

258.3 g of N-(1-ethyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide and 875 ml of absolute ethanol are placed in a 2 liter flask fitted with an agitator and a thermometer, and 142 ml of 110 vol. hydrogen peroxide is added with agitation. The mixture is heated to 45° C. for a few hours then cooled to 40° C., and 2 g of manganese dioxide is added in stages.

After the addition of vegetable black and filtration, the solvent is removed under vacuum. The residue obtained is dissolved in 200 ml of ethanol and 150 ml of acetone, then the solution is filtered and the filtrate poured into 21 of sulphuric ether. The crystals formed are drained, washed with ether and dried.

140 g of N-oxide of N-(1-ethyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (M.P.=190° C. with decomposition. Yield=52%).

274
275

EXAMPLE XI

N-oxide of N-(1-methyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide

248.5 g of N-(1-methyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide and 875 ml of absolute ethanol are placed in a 2 liter flask fitted with an agitator and a thermometer, then 142 ml of 110 vol. hydrogen peroxide is added with agitation. The mixture is heated to 45° C. for a few hours then cooled to 40° C., and 2 g of manganese dioxide is added in stages.

The solution is filtered, after which the solvent is removed under vacuum and the residue dissolved in 500 ml of acetone. The crystals formed are drained and dried, then dissolved hot in 1 liter of ethanol.

Following the addition of 20 g of vegetable black, the solution is cooled then poured into 1 liter of sulphuric ether. The crystals formed are drained, washed and dried.

190 g of N-oxide of N-(1-methyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (M.P.=200°-210° C. with decomposition—yield=73%).

EXAMPLE XII

N-(1-ethyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide

Composite anhydride of ethylbicarbonate and 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid

77.7 g of 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid and 500 ml of anhydrous dioxane are placed in a flask fitted with an agitator, a thermometer, a condenser and a dropping funnel, and 30.3 g of triethylamine is dripped in.

The mixture is cooled to 20° C. then 32.5 g of ethyl chloroformate is poured in drop by drop while the temperature is kept at 20° C.

The mixture is agitated and filtered, and the filtrate is evaporated under vacuum. The residue is dissolved in 500 ml of carbon tetrachloride then crystallisation is initiated by seeding.

The crystals which form when the mixture has cooled are filtered, washed and then dried.

74 g of anhydride is obtained (M.P.=77° C.—yield=74.5%).

N-(2,5-dichloropentyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide

4.33 g of 2,5-dichloropentylamine hydrochloride, 65 ml of dimethylformamide and 2.27 g of triethylamine are placed in a flask fitted with an agitator, a thermometer and a condenser, followed by 7.47 g of composite anhydride of ethylbicarbonate and 2-methoxy 4-amino 5-ethylsulphonyl benzoic acid.

The mixture is agitated for 1 hour at room temperature, after which 100 ml of water and 10 ml of hydrochloric acid are added.

The suspension obtained is evaporated dry under vacuum then the residue is dissolved in 100 ml of water. The crystals formed are filtered, washed with water then dried in an oven at 50° C.

6.5 g of N-(2,5-dichloropentyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (M.P.=109° C.—yield=73%).

N-(1-ethyl 2-pyrrolidyl methyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide

5.95 g of N-(2,5-dichloropentyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide and 22 ml of a 56% aqueous solution of ethyl amine are placed in a flask fitted with an agitator.

The mixture is agitated until the solids are completely dissolved, after which the solution is heated in an oven to 40°-45° C. until the reaction is over.

The solvent is evaporated, then the residue is treated with 100 ml of water and 5 ml of caustic soda solution.

After being twice extracted with methylene chloride, the organic phase is dried over magnesium sulphate and filtered, then the solvent is evaporated under vacuum.

The residue is dissolved at boiling point in 10 ml of acetone, then the crystals which form after cooling are filtered and dried in an oven at 50° C.

3 g of N-(1-ethyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide is obtained (M.P.=125° C.—yield=54%).

The substances according to the invention are used in the form of capsules, tablets, pills, in granular form or as an injectable solution; the preparation of these is known per se. It is possible to use substances which are inert relative to the compounds of the invention, such as levilite, alkali metal lauryl sulphates, saccharose, and the vehicles customarily used in medicinal preparations.

The compounds according to the invention may be administered in doses of 50 to 750 mg per day in one or more portions. The preferred doses are from 150 to 200 mg per day.

The following examples concern pharmaceutical preparations prepared in the conventional manner from compounds according to the invention.

EXAMPLE XIII

Tablets

N-(1-ethyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide	100 mg
Dried starch (féculé)	20 mg
lactose	100 mg
methylcellulose 1500 cps.	1.5 mg
levilite	9.5 mg
magnesium stearate	4 mg

for 1 tablet

EXAMPLE XIV

Tablets

N-(1-methyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide	50 mg
lactose	50 mg
dried starch	10 mg
methylcellulose 1500 cps.	0.687 mg
3% water	
levilite	6.803 mg
magnesium stearate	2.51 mg

for 1 tablet

EXAMPLE XV

Injectable Solution

N-(1-allyl 2-pyrrolidylmethyl) 2-methoxy 4-amino 5-ethylsulphonyl benzamide	100 mg
---	--------

-continued

1N hydrochloric acid	0.26 ml
sodium chloride	8 mg
water for injectable preparations	q.s. 2 ml

To prepare the tablets, the selected compound is mixed with the starch and lactose by the method of successive dilutions; the mixture is granulated with methylcellulose. The levilite, magnesium stearate and talc are added to the granulated substances before proceeding to the compression stage.

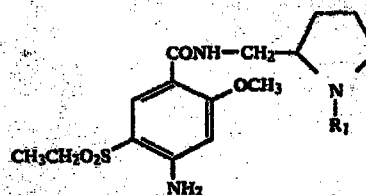
It is possible to replace the methyl cellulose with any other appropriate granulating agent, such as ethyl cellulose, polyvinylpyrrolidone or starch paste.

The magnesium stearate may be replaced by stearic acid. To prepare injectable solutions, it is possible to dissolve the compound according to the invention in the following acids: hydrochloric, levulinic, gluconic or glucoheptonic.

The solution, prepared under sterile conditions, is made isotonic by an alkali metal chloride such as sodium chloride, then preservatives are added. It is equally possible to prepare the same solution without adding any preservatives: the ampoule is filled in a nitrogen atmosphere and sterilised for $\frac{1}{2}$ hour at 100° C.

We claim:

1. A compound of the formula



wherein R₁ is methyl, ethyl or allyl and the acid addition salts thereof with pharmacologically acceptable acids, the quaternary ammonium salts thereof and the levorotatory and dextrorotatory optical isomers thereof.

2. N-(1-ethyl-2-pyrrolidylmethyl) 2-methoxy-4-amino-5-ethylsulphonyl benzamide, being a compound of claim 1.

3. N-(1-methyl-2-pyrrolidylmethyl) 2-methoxy-4-amino-5-ethylsulphonyl benzamide, being a compound of claim 1.

4. N-(1-allyl-2-pyrrolidylmethyl) 2-methoxy-4-amino-5-ethylsulphonyl benzamide, being a compound of claim 1.

5. Dextrorotatory N-(1-ethyl-2-pyrrolidylmethyl) 2-methoxy-4-amino-5-ethylsulphonyl benzamide tartrate, being a compound of claim 1.

6. Levorotatory N-(1-ethyl-2-pyrrolidylmethyl) 2-methoxy-4-amino-5-ethylsulphonyl benzamide tartrate, being a compound of claim 1.

7. Dextrorotatory N-(1-methyl-2-pyrrolidyl methyl) 2-methoxy-4-amino-5-ethylsulphonyl benzamide, being a compound of claim 1.

* * * * *

276.
277

277
258

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

2020
Bogotá, D.C., 08/04/2010

Abogado
Emilio Ferrero
(Apoderado)

ASUNTO	Radicación	06 39105
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	05084
	Folios	010

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒ Cap. II ☐

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 le comunica:

1. Documentos estudiados

- | | | |
|------|-----------------------------------|---|
| 1.1. | <u>Descripción:</u> | Folios: 78 a 150 |
| 1.2. | <u>Reivindicaciones:</u> | Folios: 151 a 161
Folios: 178 a 197 Memorial de 30/04/2007
Folios: 243 a 246 Memorial de 07/12/2009 |
| 1.3. | <u>Datos PCT:</u> | Solicitud Internacional: PCT/DK04/000733
Capítulo II
Fecha Sol. Internacional: 25/10/2004
Publicación. Internacional: WO05/039572
Fecha Pub. Internacional: 06/05/2005
Fecha Inicio Fase Nacional: 27/05/2006
Fecha Sol. Nacional: 26/04/2006 |
| 1.4. | <u>Prioridad:</u> | DK PA200301579 de 27/10/2003
DK PA200400229 de 13/02/2004 |
| 1.5. | <u>Respuesta del solicitante:</u> | Folios 285 a 246 Memorial de 07/12/2009 |

2. Objeto de la invención

Título de la solicitud

Reivindicaciones

Reivindicación 1: Se reivindica un compuesto elegido entre:

- 4-butirilamino-N-tiazol-2-il-benzamida (1)
- rac*-3-metoxi-4-(3-metil-4-oxo-pentanoilamino)-N-tiazol-2-il-benzamida (2)
- rac*-4-(3-metil-pentanoilamino)-N-tiazol-2-il-benzamida (3)
- 4-hexanoilamino-3-metil-N-tiazol-2-il-benzamida (4)
- 4-(2-cicloheptil-acetilamino)-N-tiazol-2-il-benzamida (5)
- rac*-3-metoxi-4-(3-metil-pentanoilamino)-N-tiazol-2-il-benzamida (6)

Entre otros.

Sustento Descriptivo

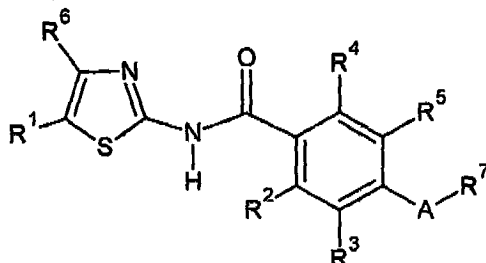
La solicitud hace alusión a compuestos derivados del núcleo de las N-tiazol-2-il-benzamidas que presentan afinidad por el receptor de adenosina 2A (A_{2A}). Los compuestos son útiles en el tratamiento de trastornos neurológicos y psiquiátricos donde hay compromiso del receptor de adenosina.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/426// A 61 P²⁵/16** de la **Clasificación Internacional de Patentes**.

3. Modificaciones aceptadas (artículo 34 D. 486)

En atención a las modificaciones que presenta el señor solicitante frente a la materia originalmente reivindicada y que reposan en los folios 243 a 246 esta Superintendencia se permite señalar lo siguiente:

- Aún cuando el señor solicitante hubiese decidido excluir la generalización estructural de la fórmula Markush que acompañaba toda la serie de compuestos reclamados en la cláusula 40 del pliego reivindicatorio contenido en los folios 178 a 197 es preciso aclarar que los mismos continúan presentando una estructura común derivada del núcleo:



Así las cosas, esta Superintendencia se permite aclarar que su exclusión no implica que el concepto común e inventivo de los 133 compuestos reivindicados hubiera sido realmente modificado, toda vez que un análisis detallado de las estructuras que presentan los compuestos, ahora denominados exclusivamente mediante su nombre IUPAC, permite concluir a una persona versada en ciencias químicas y farmacéuticas que todos conservan las características estructurales, químicas y funcionales definidas para dicho núcleo.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 27/10/2003, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de Publicación
D1	WO0026202	"2-amino-thiazole derivatives, process for their preparation, and their use as antitumor agents"	11/05/2000
D2	Artículo 1	"Thiazole and Thiadiazole analogues as a novel class of adenosine receptor antagonists"	18/01/2001
D3	WO03045386	"Benzothiazole derivatives"	05/06/2003
D4	US4401822	"Derivatives of 4-amino-5-alkyl sulphonyl orthoanisimides"	30/08/1983

Anterioridades D1 en los folios 200 a 225, anterioridades D2 a D4 en los folios 247 a 276

5. Análisis de patentabilidad (artículo 14 D. 486)

5.1 Nivel Inventivo (artículo 18 D. 486)

El nivel inventivo del objeto se evaluó mediante comparación técnica entre los elementos característicos de la fórmula (I) y las anticipaciones cercanas a la invención reveladas las publicaciones del estado del arte.

- Se reivindican los compuestos:

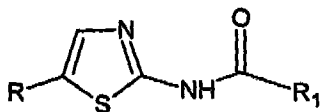
4-butilamino-*N*-tiazol-2-il-benzamida (1)
rac-3-metoxi-4-(3-metil-4-oxo-pentanoilamino)-*N*-tiazol-2-il-benzamida (2)
rac-4-(3-metil-pentanoilamino)-*N*-tiazol-2-il-benzamida (3)
4-hexanoilamino-3-metil-*N*-tiazol-2-il-benzamida (4)
4-(ciclopentanocarbonil-amino)-*N*-tiazol-2-il-benzamida (35)
4-[(2-ciclopentil-acetil)-propil-amino]-*N*-tiazol-2-il-benzamida (73)
3,5-dicloro-4-(3,3-dimetil-butilamino)-*N*-tiazol-2-il-benzamida (131)

Entre otros.

- El estado del arte presenta los siguientes documentos:

Anterioridad D1:

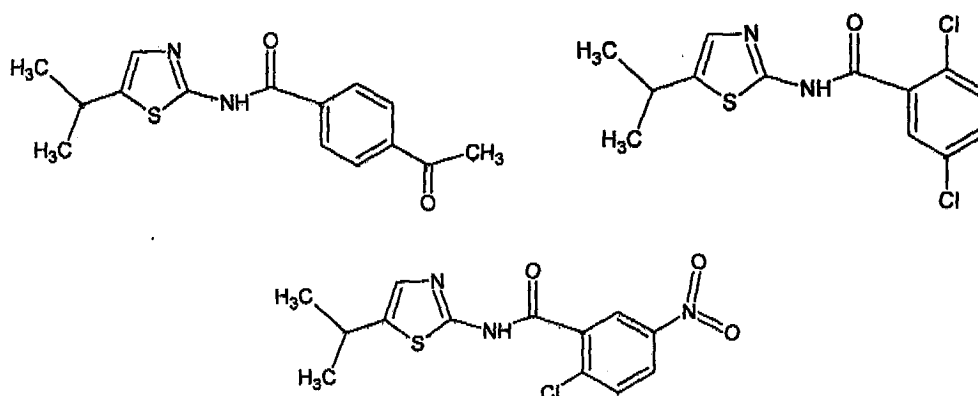
En el documento D1 se revelan derivados del núcleo de 2-amino tiazol:



Para la cual:

R₁ es un aril-alkilo.

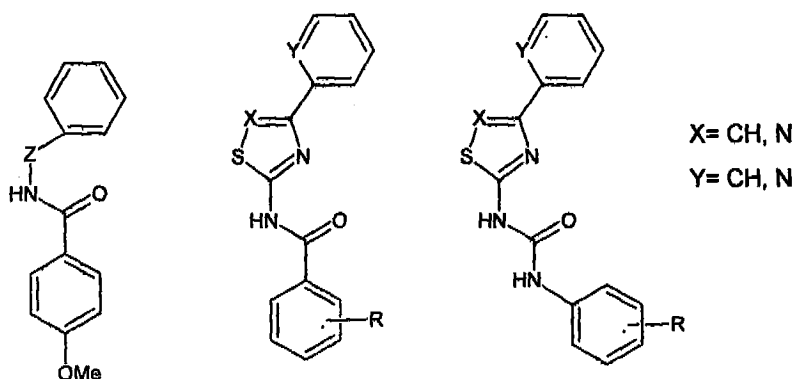
Y dentro de los ejemplos más representativos se encuentran las especies químicas:



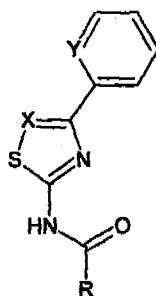
Y de acuerdo con el folio 201 del antecedente los compuestos resultan útiles en el tratamiento del cáncer, enfermedad de Alzheimer, infecciones virales y trastornos autoinmunes, así como en trastornos neurodegenerativos.

Anterioridad D2:

La publicación D2 hace referencia a estructuras tipo tiazol y tiadiazol que presentan actividad como antagonistas del receptor de adenosina.



En particular se presenta la serie de la tabla 3 (folio 256) que presenta las siguientes características funcionales y químicas:



Compuesto	X	Y	R	rA ₁	rA _{2A}	hA ₃
17a	CH	N	C ₆ H ₅	1,7 ± 0,5	8,7 ± 0,6	3,4 ± 1
17e	CH	N	4-OCH ₃ C ₆ H ₄	3,2 ± 0,7	40%	1,8 ± 0,6
17f	CH	N	3,4-diClC ₆ H ₄	1,6 ± 0,6	20%	2,5 ± 1
17i	CH	N	4-OCH(CH ₃) ₂ C ₆ H ₄	5,8 ± 1	44%	3,7 ± 0,7

Según la publicación los compuestos presentan actividad como antagonistas del receptor de adenosina y los ejemplos específicos 17a, 17e, 17f y 17i son capaces de modular la actividad de los subtipos A₁, A_{2A} y A₃.

Análisis de diferencias técnicas:

Teniendo en cuenta la definición de materia que presenta el pliego reivindicatorio y las anticipaciones reveladas en el documento D1 es posible concluir que la diferencia entre ellos estriba en la clase de grupos funcionales que sustituyen el anillo de fenilo que se enlaza al anillo de tiazol mediante el puente de carboxamido.

Con respecto a D2 las diferencias estriban en que los compuestos allí divulgados se acompañan de estructuras heterocíclicas como sustituyentes del anillo de tiazol en la posición 4. Y adicionalmente no presentan sustituciones tipo carboxamido sobre el anillo de fenilo sino de tipo 4-O-alkilo 8ver ejemplos (17a, 17e, 17f y 17i).

Y frente al contenido de la publicación D3 las diferencias estriban en que el anillo de tiazol se encuentra fusionado al anillo de benceno, por lo que los derivados allí divulgados que presentan actividad como moduladores de adenosina son de tipo benzotiazol y sustituidos por morfolina.

Con respecto a D4 las diferencias estructurales residen en que el compuesto allí divulgado no presenta un grupo tiazol sino de tipo pirrolidil y en el puente de carboxamido que une el anillo de fenilo y de pirrol se incluye un grupo metilen adicional. Por otra parte, el sustituyente que acompaña el anillo de fenilo sobre la posición 4 es de tipo amino y no carboxamido.

Del problema técnico objetivo y del efecto inesperado:

De acuerdo con el sustento descriptivo de la solicitud se pretende buscar alternativas terapéuticas para el control de enfermedades asociadas al receptor de adenosina 2A (A_{2A}).

Y la serie de compuestos reivindicados a lo largo de la cláusula 1 resultan útiles para el tratamiento de trastornos neurológicos y psiquiátricos donde hay compromiso del receptor A_{2A} , tal es el caso de la enfermedad de Alzheimer, enfermedad de Huntington, Parkinson o epilepsia.

Al respecto es preciso señalar que los compuestos divulgados por los antecedentes D1 a D4 se han aplicado efectivamente en el tratamiento de enfermedades mediadas por el receptor de adenosina. Por ejemplo, en la publicación D1 se menciona que el núcleo 2-carbamoil-tiazol presente en los derivados de la tabla del folio 226 es útil en el tratamiento de Alzheimer y trastornos neurodegenerativos. En la publicación científica D2 se presentan pruebas de actividad frente a los subtipos del receptor de adenosina A_1 , A_2 y A_3 aún cuando se encuentran tres anillos heteroaromáticos dentro de la estructura de los compuestos.

Por su parte la publicación D3 agrega que derivados fusionados del tiazol que contienen un sustituyente tipo alquil-carbamilo sobre la posición 4 del anillo de fenilo conservan la actividad moduladora del receptor de adenosina A_{2A} .

Y la publicación D4 señala que el compuesto amisulpride con estructura relacionada presenta actividad sobre los receptores serotoninérgicos pero se tiene evidencia de que los subtipos de receptores de adenosina (A_1 , A_{2A} , A_{2B} , A_3) y en particular el subtipo A_{2a} presenta un grado de interacción importante con otros neurotransmisores, entre ellos el receptor de dopamina D2, por lo que no es extraño que este compuesto sea utilizado como antipsicótico y en el tratamiento temprano de la enfermedad de Alzheimer.

285
296

En consecuencia, los compuestos que divulgan las publicaciones son análogos estructurales de los compuestos reivindicados, tal y como se comprueba a partir de la comparación estructural de la tabla 1. Y las diferencias encontradas no originan un efecto técnico inesperado o sorprendente, por lo que una persona versada en ciencias farmacéuticas se encontraba en capacidad de derivar los elementos técnicos estructurales de los compuestos y su actividad farmacológica a partir de las enseñanzas que en conjunto revelan las publicaciones del estado del arte: [D1 y D2] o [D1 y D3] o [D1 y D4].

Y como se mencionó en la oportunidad jurídica anterior ha quedado en evidencia que la actividad farmacológica deriva del grupo farmacofórico que se forma por el enlace entre un anillo de tiazol y un anillo de fenilo a través del puente carboxamido, como claramente se evidencia a partir de los resultados que acompañan los ensayos de actividad divulgados por D2.

Y como se mencionó en el examen anterior el objeto original de la solicitud corresponde al uso de los compuestos como moduladores del receptor de adenosina y sólo incluía una cláusula de compuestos como puede entenderse de la lectura del pliego reivindicatorio que reposa en los folios 151 a 161. Sin embargo mediante modificación presentada por el señor solicitante mediante memorial de fecha 01/10/2009 se incluye una cláusula relativas a la serie de compuestos que presentan en su estructura un anillo de tiazol enlazada a fenilo a través de un puente carboxamido, cuando el sustento descriptivo de la solicitud y el planteamiento del problema técnico objetivo deriva de la investigación de aplicaciones terapéuticas diferentes a las reportadas previamente para núcleos similares, tal y como se entiende de la lectura del capítulo descriptivo en los folios 78 a 85, razón por la cual esta Superintendencia continúa considerando que las enseñanzas reveladas por el documento D1 y sus combinaciones afectan la altura inventiva de la materia reivindicada, dada la cercanía estructural demostrada.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO0026202	1	Nivel Inventivo
D2	Artículo	1	Nivel Inventivo
D3	WO03/045386	1	Nivel Inventivo
D4	US4401822	1	Nivel Inventivo

7. Respuesta los argumentos del solicitante:

Mediante memorial de fecha 01/10/2009 el señor solicitante argumenta lo siguiente:

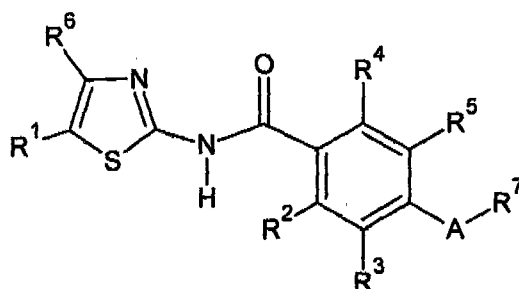
- *"(...) se presenta en esta oportunidad un pliego reivindicatorio claro, conciso, debidamente soportado en la descripción y que no incluye reivindicaciones de uso. Por lo tanto, consideramos que las objeciones formuladas a este respecto se deben tener por superadas".*

Al respecto es preciso señalar que aún cuando el señor solicitante excluya la generalización estructural de la fórmula Markush que originalmente acompañaba la serie de compuestos reclamados en la cláusula 40 en el pliego reivindicatorio de los

folio 178 a 197 es preciso aclarar que todos continúan presentando una estructura común derivada del núcleo:

286

287



Por lo que con el hecho de eliminar la estructura anular no se modifica el concepto común de los 133 compuestos reclamados en el nuevo juego de reivindicaciones de los folios 243 a 246 o se superan las objeciones de altura inventiva originalmente señaladas por esta Superintendencia.

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 sesenta 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 N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha
16 ABR. 2010

CONCEPTO TÉCNICO No. 1323

EXAMINADOR TÉCNICO
Código No. 202044

287
289

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

2020
Bogotá, D.C., 30/07/2010

Abogada
Luz Clemencia de Páez
(Apoderada)

ASUNTO

Radicación **06 39105**
Trámite **002**
Evento **001**
Actuación **430**
Oficio **10381**
Folios **010**

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

Mediante oficio N° 05084 notificado por fijación en lista de fecha 16 de abril de 2010, este Despacho en forma equivocada, requirió al Doctor Emilio Ferrero, en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que dentro del plazo de sesenta días presentara respuesta a las observaciones de carácter técnico, relacionadas con la patentabilidad y cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente que se tramita dentro del expediente de la referencia.

Teniendo en cuenta que mediante escrito radicado en esta entidad el 07 de Diciembre del 2009 bajo el número 06-39105, previamente el doctor Emilio Ferrero informa sobre el cambio de apoderado, adjuntado para tal efecto memorial de sustitución de poder, el cual reposa a folio 242, es procedente revocar en su totalidad el oficio N° 05084 de fecha 16 de abril de 2010 y en su lugar efectuar un nuevo requerimiento a su nombre, en los siguientes términos:

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 le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 78 a 150
- 1.2. Reivindicaciones: Folios: 151 a 161
Folios: 178 a 197 Memorial de 30/04/2007
Folios: 243 a 246 Memorial de 07/12/2009
- 1.3. Datos PCT: Solicitud Internacional: PCT/DK04/000733

Capítulo II
Fecha Sol. Internacional: 25/10/2004
Publicación. Internacional: WO05/039572
Fecha Pub. Internacional: 06/05/2005
Fecha Inicio Fase Nacional: 27/05/2006
Fecha Sol. Nacional: 26/04/2006

- 1.4. Prioridad: DK PA200301579 de 27/10/2003
DK PA200400229 de 13/02/2004
- 1.5. Respuesta del solicitante: Folios 285 a 246 Memorial de 07/12/2009

2. Objeto de la invención

Título de la solicitud

Derivados de N-tiazol-2il-benzamida

Reivindicaciones

Reivindicación 1: Se reivindica un compuesto elegido entre:

- 4-butilamino-N-tiazol-2-il-benzamida (1)
- rac-3-metoxi-4-(3-metil-4-oxo-pentanoilamino)-N-tiazol-2-il-benzamida (2)
- rac-4-(3-metil-pentanoilamino)-N-tiazol-2-il-benzamida (3)
- 4-hexanoilamino-3-metil-N-tiazol-2-il-benzamida (4)
- 4-(2-cicloheptil-acetilamino)-N-tiazol-2-il-benzamida (5)
- rac-3-metoxi-4-(3-metil-pentanoilamino)-N-tiazol-2-il-benzamida (6)

Entre otros.

Sustento Descriptivo

La solicitud hace alusión a compuestos derivados del núcleo de las N-tiazol-2-il-benzamidas que presentan afinidad por el receptor de adenosina 2A (A_{2A}). Los compuestos son útiles en el tratamiento de trastornos neurológicos y psiquiátricos donde hay compromiso del receptor de adenosina.

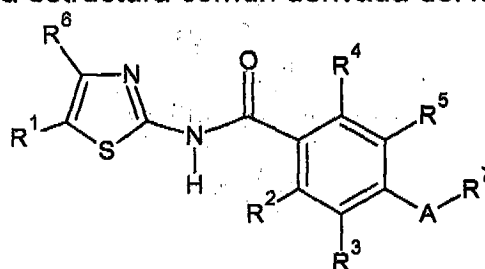
- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/426// A 61 P²⁵/16** de la **Clasificación Internacional de Patentes**.

3. Modificaciones aceptadas (artículo 34 D. 486)

En atención a las modificaciones que presenta el señor solicitante frente a la materia originalmente reivindicada y que reposan en los folios 243 a 246 esta Superintendencia se permite señalar lo siguiente:

- Aún cuando el señor solicitante hubiese decidido excluir la generalización estructural de la fórmula Markush que acompañaba toda la serie de compuestos reclamados en la cláusula 40 del pliego reivindicatorio contenido

en los folios 178 a 197 es preciso aclarar que los mismos continúan presentando una estructura común derivada del núcleo:



Así las cosas, esta Superintendencia se permite aclarar que su exclusión no implica que el concepto común e inventivo de los 133 compuestos reivindicados hubiera sido realmente modificado, toda vez que un análisis detallado de las estructuras que presentan los compuestos, ahora denominados exclusivamente mediante su nombre IUPAC, permite concluir a una persona versada en ciencias químicas y farmacéuticas que todos conservan las características estructurales, químicas y funcionales definidas para dicho núcleo.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 27/10/2003, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	WO0026202	"2-amino-thiazole derivatives, process for their preparation, and their use as antitumor agents"	11/05/2000
D2	Artículo 1	"Thiazole and Thiadiazole analogues as a novel class of adenosine receptor antagonists"	18/01/2001
D3	WO03045386	"Benzothiazole derivatives"	05/06/2003
D4	US4401822	"Derivatives of 4-amino-5-alkyl sulphonyl orthoanisimides"	30/08/1983

Anterioridades D1 en los folios 200 a 225; anterioridades D2 a D4 en los folios 247 a 276

5. Análisis de patentabilidad (artículo 14 D. 486)

5.1 Nivel Inventivo (artículo 18 D. 486)

El nivel inventivo del objeto se evaluó mediante comparación técnica entre los elementos característicos de la fórmula (I) y las anticipaciones cercanas a la invención reveladas las publicaciones del estado del arte.

- Se reivindican los compuestos:

4-butilamino-*N*-tiazol-2-il-benzamida (1)

rac-3-metoxi-4-(3-metil-4-oxo-pentanoilamino)-*N*-tiazol-2-il-benzamida (2)

rac-4-(3-metil-pentanoilamino)-*N*-tiazol-2-il-benzamida (3)

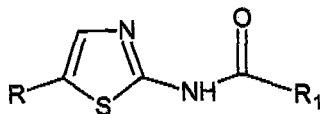
- 4-hexanoilamino-3-metil-*N*-tiazol-2-il-benzamida (4)
 4-(ciclopentanocarbonil-amino)-*N*-tiazol-2-il-benzamida (35)
 4-[(2-ciclopentil-acetil)-propil-amino]-*N*-tiazol-2-il-benzamida (73)
 3,5-dicloro-4-(3,3-dimetil-butilamino)-*N*-tiazol-2-il-benzamida (131)

Entre otros.

- El estado del arte presenta los siguientes documentos:

Anterioridad D1:

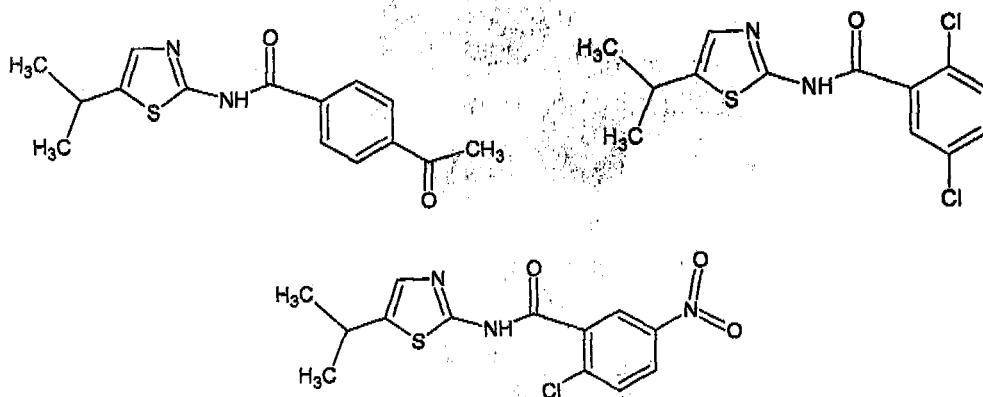
En el documento D1 se revelan derivados del núcleo de 2-amino tiazol:



Para la cual:

R_1 es un aril-alquilo.

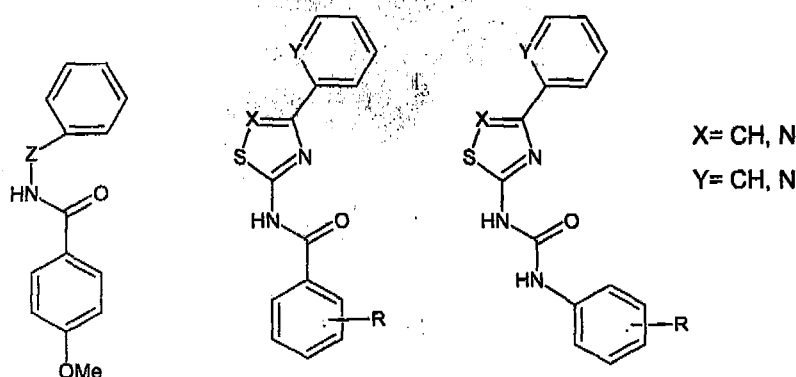
Y dentro de los ejemplos más representativos se encuentran las especies químicas:



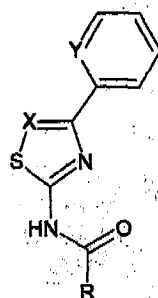
Y de acuerdo con el folio 201 del antecedente los compuestos resultan útiles en el tratamiento del cáncer, enfermedad de Alzheimer, infecciones virales y trastornos autoinmunes, así como en trastornos neurodegenerativos.

Anterioridad D2:

La publicación D2 hace referencia a estructuras tipo tiazol y tiadiazol que presentan actividad como antagonistas del receptor de adenosina.



En particular se presenta la serie de la tabla 3 (folio 256) que presenta las siguientes características funcionales y químicas:

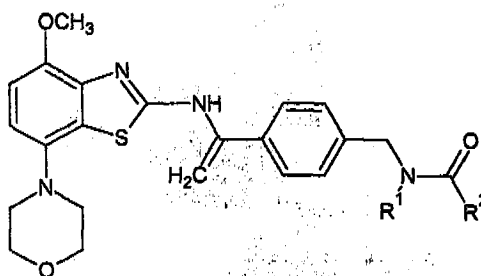


Compuesto	X	Y	R	rA ₁	rA _{2A}	hA ₃
17a	CH	N	C ₆ H ₅	1,7 ± 0,5	8,7 ± 0,6	3,4 ± 1
17e	CH	N	4-OCH ₃ C ₆ H ₄	3,2 ± 0,7	40%	1,8 ± 0,6
17f	CH	N	3,4-diClC ₆ H ₄	1,6 ± 0,6	20%	2,5 ± 1
17i	CH	N	4-OCH(CH ₃) ₂ C ₆ H ₄	5,8 ± 1	44%	3,7 ± 0,7

Según la publicación los compuestos presentan actividad como antagonistas del receptor de adenosina y los ejemplos específicos 17a, 17e, 17f y 17i son capaces de modular la actividad de los subtipos A₁, A_{2A} y A₃.

Anterioridad D3:

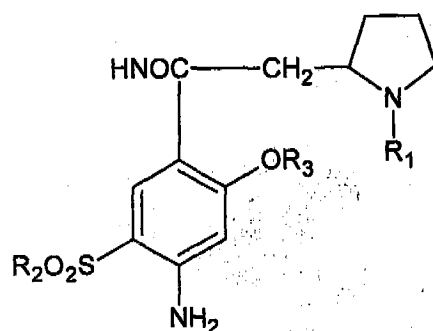
La publicación D3 hace referencia a derivados de benzotiazol que presentan la siguiente estructura:



Y de acuerdo con la publicación los compuestos derivados de benzotiazol presentan actividad como moduladores del receptor de adenosina, en particular, de los subtipos: A_{2A}, A₁ y A₃.

Anterioridad D4:

La publicación D4 hace referencia a derivados de 4-amino-5-alkil sulfonil ortoanisamidas que presentan la estructura:



De acuerdo con la publicación los compuestos son antiserotoninérgicos.

296

Análisis de diferencias técnicas:

Teniendo en cuenta la definición de materia que presenta el pliego reivindicatorio y las anticipaciones reveladas en el documento **D1** es posible concluir que la diferencia entre ellos estriba en la clase de grupos funcionales que sustituyen el anillo de fenilo que se enlaza al anillo de tiazol mediante el puente de carboxamido.

Con respecto a **D2** las diferencias estriban en que los compuestos allí divulgados se acompañan de estructuras heterocíclicas como sustituyentes del anillo de tiazol en la posición 4. Y adicionalmente no presentan sustituciones tipo carboxamido sobre el anillo de fenilo sino de tipo 4-O-alkilo ver ejemplos (17a, 17e, 17f y 17i).

Y frente al contenido de la publicación **D3** las diferencias estriban en que el anillo de tiazol se encuentra fusionado al anillo de benceno, por lo que los derivados allí divulgados que presentan actividad como moduladores de adenosina son de tipo benzotiazol y sustituidos por morfolina.

Con respecto a **D4** las diferencias estructurales residen en que el compuesto allí divulgado no presenta un grupo tiazol sino de tipo pirrolidil y en el puente de carboxamido que une el anillo de fenilo y de pirrol se incluye un grupo metilén adicional. Por otra parte, el sustituyente que acompaña el anillo de fenilo sobre la posición 4 es de tipo amino y no carboxamido.

Del problema técnico objetivo y del efecto inesperado:

De acuerdo con el sustento descriptivo de la solicitud se pretende buscar alternativas terapéuticas para el control de enfermedades asociadas al receptor de adenosina 2A (A_{2A}).

Y la serie de compuestos reivindicados a lo largo de la cláusula 1 resultan útiles para el tratamiento de trastornos neurológicos y psiquiátricos donde hay compromiso del receptor A_{2A} , tal es el caso de la enfermedad de Alzheimer, enfermedad de Huntington, Parkinson o epilepsia.

Al respecto es preciso señalar que los compuestos divulgados por los antecedentes **D1** a **D4** se han aplicado efectivamente en el tratamiento de enfermedades mediadas por el receptor de adenosina. Por ejemplo, en la publicación **D1** se menciona que el núcleo 2-carbamoil-tiazol presente en los derivados de la tabla del folio 226 es útil en el tratamiento de Alzheimer y trastornos neurodegenerativos. En la publicación científica **D2** se presentan pruebas de actividad frente a los subtipos del receptor de adenosina A_1 , A_2 y A_3 aún cuando se encuentran tres anillos heteroaromáticos dentro de la estructura de los compuestos.

Por su parte la publicación **D3** agrega que derivados fusionados del tiazol que contienen un sustituyente tipo alquil-carbamilo sobre la posición 4 del anillo de fenilo conservan la actividad moduladora del receptor de adenosina A_{2A} .

Y la publicación **D4** señala que el compuesto amisulpride con estructura relacionada presenta actividad sobre los receptores serotoninérgicos pero se tiene evidencia de que los subtipos de receptores de adenosina (A_1 , A_{2A} , A_{2B} , A_3) y en particular el subtipo A_{2A} presenta un grado de interacción importante con otros neurotransmisores, entre ellos el receptor de dopamina D_2 , por lo que no es extraño que este compuesto sea utilizado como antipsicótico y en el tratamiento temprano de la enfermedad de Alzheimer.

297

En consecuencia, los compuestos que divulgan las publicaciones son análogos estructurales de los compuestos reivindicados, tal y como se comprueba a partir de la comparación estructural de la tabla 1. Y las diferencias encontradas no originan un efecto técnico inesperado o sorprendente, por lo que una persona versada en ciencias farmacéuticas se encontraba en capacidad de derivar los elementos técnicos estructurales de los compuestos y su actividad farmacológica a partir de las enseñanzas que en conjunto revelan las publicaciones del estado del arte: [D1 y D2] o [D1 y D3] o [D1 y D4].

Y como se mencionó en la oportunidad jurídica anterior ha quedado en evidencia que la actividad farmacológica deriva del grupo farmacofórico que se forma por el enlace entre un anillo de tiazol y un anillo de fenilo a través del puente carboxamido, como claramente se evidencia a partir de los resultados que acompañan los ensayos de actividad divulgados por D2.

Y como se mencionó en el examen anterior el objeto original de la solicitud corresponde al uso de los compuestos como moduladores del receptor de adenosina y sólo incluía una cláusula de compuestos como puede entenderse de la lectura del pliego reivindicatorio que reposa en los folios 151 a 161. Sin embargo mediante modificación presentada por el señor solicitante mediante memorial de fecha 01/10/2009 se incluye una cláusula relativas a la serie de compuestos que presentan en su estructura un anillo de tiazol enlazada a fenilo a través de un puente carboxamido, cuando el sustento descriptivo de la solicitud y el planteamiento del problema técnico objetivo deriva de la investigación de aplicaciones terapéuticas diferentes a las reportadas previamente para núcleos similares, tal y como se entiende de la lectura del capítulo descriptivo en los folios 78 a 85, razón por la cual esta Superintendencia continúa considerando que las enseñanzas reveladas por el documento D1 y sus combinaciones afectan la altura inventiva de la materia reivindicada, dada la cercanía estructural demostrada.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO0026202	1	Nivel Inventivo
D2	Artículo	1	Nivel Inventivo
D3	WO03/045386	1	Nivel Inventivo
D4	US4401822	1	Nivel Inventivo

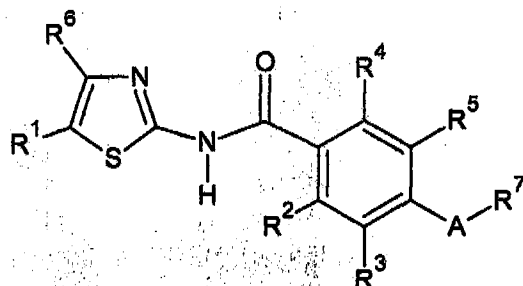
7. Respuesta los argumentos del solicitante:

Mediante memorial de fecha 01/10/2009 el señor solicitante argumenta lo siguiente:

- *"(...) se presenta en esta oportunidad un pliego reivindicatorio claro, conciso, debidamente soportado en la descripción y que no incluye reivindicaciones de uso. Por lo tanto, consideramos que las objeciones formuladas a este respecto se deben tener por superadas".*

Al respecto es preciso señalar que aún cuando el señor solicitante excluya la generalización estructural de la fórmula Markush que originalmente acompañaba la serie de compuestos reclamados en la cláusula 40 en el pliego reivindicatorio de los

folio 178 a 197 es preciso aclarar que todos continúan presentando una estructura común derivada del núcleo:



Por lo que con el hecho de eliminar la estructura anular no se modifica el concepto común de los 133 compuestos reclamados en el nuevo juego de reivindicaciones de los folios 243 a 246 o se superan las objeciones de altura inventiva originalmente señaladas por esta Superintendencia.

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 sesenta 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 N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

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

13 AGO. 2010

CONCEPTO TÉCNICO No. 2703

EXAMINADOR TÉCNICO
Código No. 202044