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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

P2007/000194

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☐

Capítulo I.

☒

Capítulo II.

2

SOLICITANTE (71)

Nombre: BAYER SCHERING PHARMA
AKTIENGESELLSCHAFT

Dirección: Müllerstrasse 178, 13353, Berlin Alemania

Nacionalidad o Domicilio: ALEMANA

Lugar de Constitución: ALEMANIA

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE O APODERADO

Nombre: J. IAN RAISBECK

Dirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.376.996 Btá
TP 135.799

4

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/EP2006/005608 Fecha Junio 7, 2006

Publicación Internacional No. WO 2006/131398 Fecha Diciembre 14, 2006

6

Título (54): INHIBIDORES DE LA ADENILATO CICLASA SOLUBLE

7

Clasificación Internacional (51) A61K 31/34, A61K 31/38, C07D 333/70, C07D
307/85, C07D 407/12, C07D 409/12, A61P 15/00, A61P 15/16.

8

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10 2005 027 274.6

9

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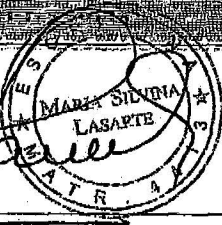
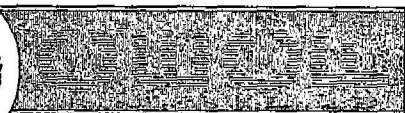
12/03/2007

1 FOLIO 85.- PRIMERA COPIA.- ESCRITURA NÚMERO: VEINTICUATRO.-
2 SUSTITUCIÓN PARCIAL DE PODER: MESSERER, Dagmar a favor de
3 OLARTE, Carlos Reinaldo y otro del Poder otorgado por BAYER SCHERING
4 PHARMA AG.- En la Ciudad Autónoma de Buenos Aires, Capital de la República
5 Argentina, el día NUEVE de MARZO del año DOS MIL SIETE, ante mí María
6 Silvina Lasarte, Escribana Autorizante, titular del Registro Notarial número 1788,
7 COMPARECE: Dagmar MESSERER, argentina, nacida el 28 de mayo de 1.968,
8 hija de Walter Messerer y Elsa Onelia Romanelli, soltera, titular del Documento Na-
9 cional de Identidad Número 20.383.892, Clave Única de Identificación Tributaria 27-
10 20383892-7, con domicilio especial en la Avenida Leandro N. Alem 1.134, Piso 10º,
11 de esta Ciudad de Buenos Aires.- La compareciente es mayor de edad.- INTERVIE-
12 NE: por su propio derecho.- Y la compareciente EXPRESA: PRIMERO: Que la
13 Sociedad "BAYER SCHERING PHARMA AG", con domicilio en Müllerstrasse
14 178, 13353, Berlín, Alemania, le confirió con fecha 22 de enero de 2007 en dicho pa-
15 ís, un Poder, el cual mediante escritura número 14 de fecha 16 de febrero de 2007,
16 otorgada ante la Escribana Mariela Vanina Scardaccione, al folio 44, protocolo co-
17 rriente de este Registro Notarial interinamente a su cargo, fue incorporado y transcrip-
18 to al mismo, cuya primera copia tengo para este acto a la vista, doy fe y en lo perti-
19 nente transcribiré en la presente.- SEGUNDO: Manifiesta bajo juramento que el refe-
20 rido poder se encuentra plenamente vigente en virtud de no haberle sido revocado,
21 suspendido ni limitado en ninguna de sus partes.- TERCERO: En consecuencia, DI-
22 CE: Que en uso de la facultad conferida SUSTITUYE PARCIALMENTE el poder
23 mencionado a favor de Carlos Reinaldo OLARTE y/o James Ian RAISBECK, al
24 solo y único objeto de que en nombre y representación de la Sociedad "BAYER
25 SCHERING PHARMA AG", y actuando en forma individual, indistinta y/o alterna-



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damente, se presente exclusivamente ante las autoridades de **COLOMBIA** que co- 26
respondan y realicen los actos enumerados en el citado poder y con las facultades que 27
surgen del mismo, el que transcripto en lo pertinente dice: "FOLIO 44.- PRIMERA 28
COPIA.- ESCRITURA NÚMERO: CATORCE.-- En la Ciudad Autónoma de 29
Buenos Aires, Capital de la República Argentina, el día DIECISÉIS de FEBRERO del 30
año DOS MIL SIETE, ante mí ..., Escribana Autorizante, ..., COMPARECE: Dagmar 31
MESSERER, argentina, nacida el 28 de mayo de 1.968, hija de Walter Messerer y 32
Elsa Onelia Romanelli, soltera, titular del Documento Nacional de Identidad Número 33
20.383.892, Clave Única de Identificación Tributaria 27-20383892-7, domiciliada 34
legalmente en la Avenida Leandro N. Alem 1.134, Piso 10º, de esta Ciudad de Buenos 35
Aires.- La compareciente es mayor de edad.- INTERVIENE: por su propio derecho.- 36
Y la compareciente EXPRESA: Que a los efectos que hubiere lugar, solicita de mí, la 37
Autorizante, LA INCORPORACIÓN y TRANSCRIPCIÓN en este protocolo del 38
PODER que le fuera conferido en Berlín, Alemania, el 22 de enero de 2007, por la 39
Sociedad "BAYER SCHERING PHARMA AG", con domicilio en Müllerstrasse 178, 40
13353, Berlín, Alemania, sobre cuya plena vigencia responde la requirente bajo jura- 41
mento.- Yo, la Autorizante, hago constar: a) Que el instrumento de poder cuya incor- 42
poración y transcripción a este protocolo solicita la compareciente, se encuentra ex- 43
tendido en idioma castellano, certificadas las firmas por notario en idioma alemán, 44
debidamente legalizado en idioma alemán (Sello de Apostilla de la Convención de La 45
Haya del 5 de octubre de 1961) y traducido en lo pertinente al idioma nacional por la 46
Traductora Pública Laura Thieberger.- b) Que la compareciente en virtud de lo mani- 47
festado tiene interés legítimo en su requerimiento.- En consecuencia, me hace entrega 48
en este acto del original del instrumento de poder relacionado con su respectiva tra- 49
ducción al idioma nacional, el que agrego a la presente y transcripto dice: "MOE- 50



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1 LLER & CO. (Sigue aclaración en idioma inglés) - PODER Los abajo firmante/s
2 BAYER SCHERING PHARMA AG domiciliados en Müllerstrasse 178 13353 Berlín
3 - Alemania declaran por el presente otorgar a Dagmar MESSERER poder general am-
4 plio y suficiente para recabar de las autoridades ..., sud y centroamericanas ... que co-
5 rrespondan, la obtención de patentes de invención, el registro y la renovación de mar-
6 cas y modelos y/o derechos de propiedad intelectual y/o nombres de dominio, a cuyo
7 efecto los faculta/n para llevar a cabo ante dichas autoridades todas las gestiones nece-
8 sarias al objeto indicado, presentar solicitudes, formular descripciones, oposiciones,
9 protestos, declaraciones, apelaciones y reclamos, oblar impuestos, justificar explota-
10 ciones, solicitar testimonios, aceptar transferencias, recibir documentos y valores, per-
11 cibir y hacer cuanto fuere necesario ante las autoridades administrativas de cualquier
12 orden. Por otra parte, les confieren mandato para que en su nombre y representación
13 puedan iniciar y proseguir cualquier juicio que actualmente los que suscriben tengan o
14 en el futuro tuvieran ..., en Sudamérica, Centroamérica ..., con motivo de su nombre,
15 marcas de fábrica o de comercio, patentes de invención y modelos y/o de sus derechos
16 de propiedad intelectual que actualmente posean o adquieran en lo sucesivo, promover
17 juicios de cualquier jurisdicción, criminales, correccionales, civiles o comerciales,
18 contra los falsificadores, usurpadores o imitadores y contra los tenedores de artículos
19 que infrinjan su nombre, marcas o patentes de invención, seguir los juicios por oposi-
20 ción u otros en que fueran parte como actores o demandados, defender el nombre, las
21 marcas, patentes y modelos y/o de derechos de propiedad intelectual y/o nombres de
22 dominio, haciendo las protestas del caso o diciendo de nulidad. Al efecto, podrán pre-
23 sentarse con escritos, querellas, pedidos, y lo que fuere necesario ante cualquier auto-
24 ridad judicial, presentar testigos, documentos y demás justificativos, rendir pruebas de
25 cualquier especie, pedir nombramientos de peritos, pedir y absolver posiciones, asistir



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a juicios verbales, declinar y prorrogar de jurisdicción, tachar, recusar, apelar, transar, 26
someter a arbitraje o mediación, hacer renunciaciones, exigir y dar cauciones, pedir embar- 27
gos preventivos, definitivos o inhibiciones y su levantamiento, pedir la venta de los 28
bienes de los deudores, solicitar y obtener el cumplimiento de sentencias, prestar ju- 29
ramentos, decir de nulidad, desistir, percibir, otorgar recibos y en general practicar 30
todos los actos y diligencias que sean precisos al desempeño de este mandato. Podrán 31
asimismo substituir el presente poder en todo o en parte.- Dado y firmado en Berlín 32
(Sigue fecha en idioma inglés). Bayer Schering Pharma AG (Sigue texto en idioma 33
inglés). ppa. Sigue una firma ilegible. (Aclarado:) Dr. Noeske-Jungblut. ppa. Sigue 34
otra firma ilegible. (Aclarado:) Dr. Klose". ES COPIA FIEL, doy fe.- En hoja adjunta 35
consta la certificación notarial de las firmas obrantes en el poder en idioma alemán, 36
efectuado el 22 de enero de 2007 por el Escribano Dimitri Rempen, de Berlín, Alema- 37
nia, y a continuación consta la respectiva legalización de la firma y sello del nombra- 38
do Notario (Sello de Apostilla de la Convención de La Haya del 5 de octubre de 39
1961), en idioma alemán, efectuado por el Presidente del Tribunal Regional de Berlín, 40
Alemania.- En hojas adjuntas sigue la referida traducción al idioma nacional la que 41
transcripta textualmente, dice: "TRADUCCIÓN PUBLICA - (Sobre papel con mem- 42
brete de "MOELLER y CO" - América Latina - Agentes de la Propiedad Intelectual - 43
figura un Poder otorgado por la Sociedad "BAYER SCHERING PHARMA AG", con 44
sede en Berlín, Alemania, redactado en idioma nacional, luego del que aparecen los 45
siguientes textos, que traducidos dicen:) "BAYER SCHERING PHARMA AG" - 46
Patentes y licencias - (Firmado y Aclarado:) pp Dr. Noeske-Jungblut - pp (Firmado y 47
Aclarado:) Dr. Klose.- La versión en inglés es para su información únicamente.- Re- 48
gistro de Actas N° R 17/2007.- Me he referido a la prohibición de intervención según 49
el artículo 3, párrafo 1, N° 7, de la Ley de Certificaciones. Mi pregunta de si ha existi- 50



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do una intervención previa en el sentido de la norma me fue contestaba por la negati-
va.- Las firmas trazadas ante mi por el Dr. Walter Klose, que nació el 26 de diciembre
de 1952, y de la Dra. Chistiane Noeske-Jungblut de soltera Noeske, que nació el 26 de
junio de 1957 – Ambos de mi personal conocimiento – Ambos con domicilio comer-
cial en 13353 Berlín, Müllerstrasse 178 son auténticas, de lo que doy fe.- Al mismo
tiempo certifico en base a que tuve a la vista en el día de hoy las actas del Registro de
Comercio del Tribunal de Primera Instancia de Charlottenburg, N° de Registro HR B
283, que la Sociedad “Bayer Schering Pharma Aktiengesellschaft”, con sede en Ber-
lín, está inscripta con el número mencionado arriba en el Registro de Comercio y que
la arriba mencionada Dra. Noeske-Jungblut y el arriba mencionado Dr. Walter Klose
están facultados en su carácter de mandatarios a representar en forma conjunta a la
Sociedad “Bayer Schering Pharma Aktiengesellschaft” de Berlín. Berlín, 22 de enero
de 2007.- El escribano (firma ilegible) y liquidación de derechos. (Hay un sello en
oblea sobre precinto:) Dimitri Rempen, Escribano de Berlín.- 9101ª E-F.- APOSTI-
LLA – (Convención de La Haya del 5 de Octubre de 1961) - País: República Federal
de Alemania - Este instrumento público fue firmado por Dimitri Rempen, actuando en
su carácter de escribano de Berlín, estando provisto del sello del escribano.- Certifica-
do en Berlín, el 24 de enero de 2007, por el Presidente del Tribunal Regional de Ber-
lín, con el N° 9101 a E-F 536/07 - Sello (hay un sello:) el Presidente del Tribunal Re-
gional de Berlín – Firma el Funcionario autorizado (firmado y aclarado:) Holldorf –
Juez Principal del Tribunal Regional.- ES TRADUCCIÓN FIEL de las partes perti-
nentes en los idiomas alemán e inglés del documento que se acompaña, que he vertido
al idioma nacional, en Buenos Aires, a 6 de febrero de 2007.- Hay una firma ilegible.
Hay un sello que dice: “LAURA THIEBERGER – MATRÍCULA DE TRADUCTO-
RES ALEMÁN – FRANCÉS – Tomo II Folio 254 (Cap.) Tomo III – 98 – (La Plata) –



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INGLÉS – Tomo III: Folio 14 (Cap.) – Tomo III Folio 329 (La Plata) – COLEGIO 26
DE TRADUCTORES PÚBLICOS N° 173”.- ES COPIA FIEL, doy fe.- A continua- 27
ción hay un sello que dice: “COLEGIO DE TRADUCTORES PÚBLICOS DE LA 28
CIUDAD DE BUENOS AIRES Corresponde a la Legalización N° T4-3278/07. Sigue 29
una firma ilegible: Esteban Santiago Allegretti”.- ES COPIA FIEL, doy fe.- Al dorso 30
en el margen superior hay un sello timbrador ...”.- A continuación sigue la legaliza- 31
ción de la firma de la nombrada traductora, ...”.- ES COPIA FIEL, doy fe.- En este 32
estado la compareciente DICE: que en la forma expresada deja INCORPORADO y 33
TRANSCRIPTO en este Protocolo el Poder que agrego a la presente, solicitando de 34
mí, la Escribana Autorizante, expida primera copia de la presente para la nombrada 35
apoderada Dagmar MESSERER.- Constancias Notariales: Identidad de la compare- 36
ciente (Artículo 1.002 del Código Civil): Se justifica la misma por conocimiento de la 37
Autorizante.- ...- LEO esta escritura a la compareciente, quien así la otorga y en prue- 38
ba de conformidad, la firma ante mí, doy fe.- Dagmar MESSERER. Ante mí: MA- 39
RIELA VANINA SCARDACCIONE. Escribana. Está mi sello. CONCUERDA con 40
su escritura matriz que pasó ante mí, al folio 44 del Registro Notarial número 1788, 41
interinamente a mi cargo.- PARA LA APODERADA expido la presente PRIMERA 42
COPIA en tres (3) sellos de actuación notarial numerados correlativamente desde el 43
número N 007376153 al presente inclusive, que sello y firmo en la fecha y lugar de su 44
otorgamiento, doy fe.- Sigue una firma ilegible y un sello que dice: Mariela V. Scar- 45
daccione – Escribana – Mat. 4527.”.- ES COPIA FIEL, de las partes pertinentes de la 46
escritura de referencia, doy fe.- CUARTO: Finalmente la compareciente expresa: a) 47
Que el presente otorgamiento no significa renunciar al ejercicio de las facultades sus- 48
tituidas; y b) Que los nombrados apoderados sustitutos no podrán sustituir el presente 49
poder en ninguna de sus partes.- Constancias Notariales: Identidad de la Compare- 50



N 007422054

1 ciente (Artículo 1.002 del Código Civil): Se justifica la misma por conocimiento de
2 la Autorizante.-Yo, la Escribana Autorizante impongo y advierto a la compareciente, a
3 tenor de lo dispuesto en el artículo 77 inciso h) de la Ley Orgánica Notarial Número
4 404, respecto de los alcances y consecuencias de las cláusulas contenidas en la presen-
5 te escritura y del derecho de leer por sí este instrumento.- LEO esta escritura a la
6 compareciente, quien así la otorga y en prueba de conformidad la firma ante mí, doy
7 fe.- Dagmar MESSERER. Ante mí: MARIA SILVINA LASARTE. Escribana. Está
8 mi sello. CONCUERDA con su escritura matriz que pasó ante mí, al folio 85 del Re-
9 gistro Notarial número 1788, a mi cargo. PARA LA PODERDANTE expido la pre-
10 sente PRIMERA COPIA en cuatro (4) sellos de actuación notarial numerados corre-
11 lativamente desde el número N 007422051 al presente inclusive, que sello y firmo en
12 la fecha y lugar de su otorgamiento, doy fe.-

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 C07D 333/70 (2006.01) A61P 15/00 (2006.01)
 C07D 307/85 (2006.01) A61P 15/16 (2006.01)

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(71) Applicant (for all designated States except US): SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstr. 178, 13353 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BUCHMANN, Bernd [DE/DE]; Erdmannstr. 44, 16540 Hohen Neuendorf (DE). NGUYEN, Duy [DE/DE]; Heinrich-Heine-Str. 27, 10179 Berlin (DE). FRITSCH, Martin [DE/DE]; Bochumer Str. 22, 10555 Berlin (DE). MENZENBACH, Bernd [DE/DE]; Hufelandweg 9, 07743 Jena (DE).

BOEMER, Ulf [DE/DE]; Leipziger Str. 49, 16548 Glienicke/Nordbahn (DE).

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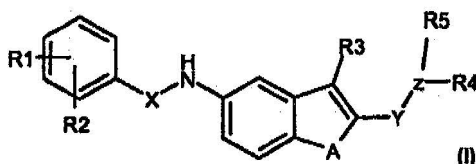
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT,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

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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: INHIBITORS OF SOLUBLE ADENYLATE CYCLASE



(57) Abstract: The invention relates to compounds of general Formula (I), the production thereof, and the use thereof as a medicinal product.

WO 2006/131398 A2

Inhibitors of soluble adenylate cyclase

The present invention relates to inhibitors of soluble adenylate cyclase, production thereof and use thereof for the production of a medicinal product for
5 contraception.

A large number of modern methods of contraception are currently available for women, but very few methods are available for male fertility control (condom and sterilization). Development of reliable new means of male fertility control is
10 urgently needed. The infertility brought about by a "male pill" should be reversible and should be just as effective as the existing methods available to women. Infertility should be developed relatively quickly and should persist for as long as possible. Such a method of contraception should have no side-effects, and the preparations may be non-hormonal as well as hormonal. A
15 possible starting point is regulation of the activity of an enzyme that plays an important role in fertilization of the ovum: soluble adenylate cyclase (sAC). This enzyme is mainly expressed in the testicular stem cells and is present in mature sperm.

20 In 1999, the authors Levin and Buck succeeded in purifying and cloning an isoform of sAC from rat testes (Proc. Natl. Acad. Sci. USA 96 (1): 79-84).

The recombinant rat enzyme can be stimulated by bicarbonate. It was demonstrated, using antibodies, that the catalytic domain of the enzyme is
25 localized in testes, sperm, kidneys and the choroid plexus. These disclosures are the subject of application WO01/85753, which was granted in the USA (US6544768).

WO01/21829 (Conti *et al.*) claims isolated polynucleotide sequences that code
30 for the human isoform of sAC, isolated sAC polypeptides and test systems, using which it is possible to identify substances that inhibit the activity of sAC. The possibility of using these substances to achieve a reversible reduction in

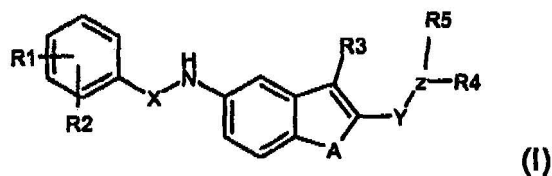
the motile sperm count, and their use as a means of controlling male fertility, is disclosed.

John Herr's group demonstrated the isolation and characterization of the human isoform of sAC from sperm. WO 02/20745 claims, in addition to nucleic acids that code for sAC, also test systems for identifying substances that modulate the expression or the activity of human sAC. Such compounds might, for example, selectively inhibit the activity of sAC, as a consequence of which the sperm would lose the capacity to fertilize an ovum. These sAC inhibitors might therefore serve as medicinal products for non-hormonal contraception.

However, the sAC inhibitors that are already known display specific problems: catechol estrogens (T. Braun, Proc Soc Exp Biol Med 1990, 194(1): 58ff) and gossypol (KL Olgati, Arch Biochem Biophys 1984, 231(2): 411ff) are inherently toxic, whereas adenosine analogs only have a very weak inhibitory action (MA Brown and ER Casillas, J Androl 1984, 5:361ff). The inhibitors of recombinant human sAC described by Zippin *et al.* are somewhat more potent ($IC_{50} \leq 10 \mu M$) (JH Zippin *et al.*, J Cell Biol 2004, 164(4): 527ff).

In order to provide a means for male fertility control, there is an increasing demand for substances that lead to infertility quickly, reversibly and successfully.

This problem is solved by the provision of the compounds of general Formula I,



where the following notation is used:

R¹ a hydrogen, halogen, CF₃, a C₃-C₆-cycloalkyl, which is optionally multiply saturated and optionally multiply substituted, or

-3-

the group C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-C₁-C₆-acyl, C₁-C₆-alkyl-C₁-C₆-aryl, C₁-C₆-aryl-C₁-C₆-alkyl or CF₃,

5

in which C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-C₁-C₆-acyl, C₁-C₆-alkyl-C₁-C₆-aryl or C₁-C₆-aryl-C₁-C₆-alkyl can optionally be interrupted singly or multiply,

identically or differently by oxygen, sulfur or nitrogen, or the group sulfonyl-C₁-C₆-alkyl, sulfonamide, or cyano,

10

R²

a halogen, CF₃, a C₃-C₆-cycloalkyl, which is optionally multiply saturated and optionally multiply substituted, or

the group C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-C₁-C₆-acyl, C₁-C₆-alkyl-C₁-C₆-aryl, C₁-C₆-aryl-C₁-C₆-alkyl or CF₃,

15

in which C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-C₁-C₆-acyl, C₁-C₆-alkyl-C₁-C₆-aryl or C₁-C₆-aryl-C₁-C₆-alkyl can optionally be interrupted singly or multiply,

20

identically or differently by oxygen, sulfur or nitrogen, or the group sulfonyl-C₁-C₆-alkyl, sulfonamide, or cyano,

R³

a C₆-C₁₂-aryl, which can optionally be substituted singly or multiply, identically or differently with halogen, with C₁-C₆-alkyl or C₁-C₆-acyl,

25

which can optionally be singly or multiply substituted,

or can be substituted with C₁-C₆-alkoxy, hydroxy, cyano,

CO₂-(C₁-C₆-alkyl), N-(C₁-C₆-alkyl)₂, CO-NR⁴R⁵ or with CF₃,

30

a C₅-C₁₂-heteroaryl, which can optionally be substituted singly or multiply, identically or differently with halogen, with C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, hydroxy, cyano, CO₂-(C₁-C₆-alkyl), N-(C₁-C₆-alkyl)₂, CO-NR⁴R⁵ or with CF₃ or

a C₃-C₆-cycloalkyl, which can optionally be substituted singly or multiply, identically or differently with halogen, CF₃, hydroxy, cyano, CO₂-(C₁-C₆-alkyl), C₁-C₆-alkyl, C₁-C₆-acyl, N-(C₁-C₆-alkyl)₂, CO-NR⁴R⁵ or C₁-C₆-alkoxy,

5

R⁴

a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy or CF₃,

10

a C₆-C₁₂-aryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, N-C₁-C₆-alkyl-C₁-C₆-alkyl, CF₃ or cyano, or

a C₅-C₁₂-heteroaryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, N-C₁-C₆-alkyl-C₁-C₆-alkyl, CF₃ or cyano, or

15

a C₁-C₆-alkyl, which can be substituted arbitrarily,

R⁵

a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy or CF₃,

20

a C₆-C₁₂-aryl, which is optionally substituted singly or multiply, identically or differently with halogen, with C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, N-C₁-C₆-alkyl-C₁-C₆-alkyl, CF₃ or cyano, or

a C₅-C₁₂-heteroaryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, N-C₁-C₆-alkyl-C₁-C₆-alkyl, CF₃ or cyano, or

25

a C₁-C₆-alkyl, which can be substituted arbitrarily,

R⁴ and R⁵

together form a 5-8-membered ring, which can contain further heteroatoms, and

30

X

the groups sulfonyl, (CH₂)_n or carbonyl,

Y

a -(CH₂)_n- or carbonyl group

Z a nitrogen,

A an oxygen or sulfur and

5

n 0 – 4,

as well as their isomers, diastereomers, enantiomers and salts, which overcome the known drawbacks and display improved properties, i.e. display good efficacy, good solubility and stability.

10

The compounds according to the invention inhibit soluble adenylate cyclase and so prevent capacitation of the sperm and thus provide male fertility control.

15

Alkyl means in each case a linear or branched alkyl residue, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec. butyl, tert. butyl, pentyl, isopentyl and hexyl.

20

Alkoxy means in each case a linear or branched alkoxy residue, such as methoxy-, ethoxy-, n-propoxy-, iso-propoxy-, n-butoxy-, sec-butoxy-, iso-butoxy-, tert. butyloxy-, pentoxy-, iso-pentoxy- and hexoxy-.

25

Acyl means in each case a linear or branched residue, such as formyl, acetyl, propionyl, butyryl, iso-butyryl, valeroyl and benzoyl.

30

Cycloalkyl means monocyclic alkyl rings such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The cycloalkyl residues can contain one or more heteroatoms, such as oxygen, sulfur and/or nitrogen, instead of the carbon atoms. Such heterocycloalkyls with 3 to 6 ring atoms are preferred. The ring systems, in which optionally one or more possible double bonds can be contained in the ring, mean for example cycloalkenyls such as cyclopropenyl, cyclobutenyl, cyclopentenyl,

cyclopentadienyl, cyclohexenyl, cycloheptenyl, where the coupling can take place both on the double bond and on the single bonds.

Halogen means in each case fluorine, chlorine, bromine or iodine.

5

In each case the aryl residue comprises 6-12 carbon atoms and can for example be benzocondensed. The following may be mentioned as examples: phenyl, troyl, cyclooctadienyl, indenyl, naphthyl, biphenyl, florenyl, anthracenyl etc.

10

In each case the heteroaryl residue comprises 5-16 ring atoms and can contain one or more, identical or different heteroatoms, such as oxygen, sulfur or nitrogen in the ring instead of carbon, and can be mono-, bi- or tricyclic and can additionally be benzocondensed in each case.

15

The following may be mentioned as examples:

thienyl, furanyl, pyrrolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, etc. and benzo derivatives thereof, e.g. benzofuranyl, benzothienyl, benzooxazolyl, benzimidazolyl, indazolyl, indolyl, isoindolyl, etc; or pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc. and benzo derivatives thereof, e.g. quinolyl, isoquinolyl, etc; or azozinyl, indoliziny, purinyl, etc. and benzo derivatives thereof; or quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, oxepinyl, etc.

25

The heteroaryl residue can be benzocondensed in each case. For example, the following may be mentioned as 5-ring heteroaromatics: thiophene, furan, oxazole, thiazole, imidazole, pyrazole and benzo derivatives thereof and as 6-ring-heteroaromatics pyridine, pyrimidine, triazine, quinoline, isoquinoline and benzo derivatives.

30

Heteroatoms is to be taken to mean oxygen, nitrogen or sulfur atoms.

If an acid function is present, the physiologically compatible salts of organic and inorganic bases are suitable as salts, such as the readily soluble alkali and alkaline-earth salts and N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, 1,6-hexadamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxymethylaminomethane, aminopropanediol, Sovak base, 1-amino-2,3,4-butanetriol.

If a basic function is present, the physiologically compatible salts of organic and inorganic acids are suitable, such as hydrochloric acid, sulfuric acid, phosphoric acid, citric acid, tartaric acid etc.

Compounds of general Formula I in which the symbols have the following meanings are especially preferred,

15

R^1 a hydrogen, halogen, CF_3 ,
a C_3 - C_6 -cycloalkyl, or the group C_1 - C_6 -alkyl, C_1 - C_6 -aryl, C_1 - C_6 -acyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- C_1 - C_6 -acyl, C_1 - C_6 -acyl- C_1 - C_6 -acyl, C_1 - C_6 -alkyl- C_1 - C_6 -aryl, C_1 - C_6 -aryl- C_1 - C_6 -alkyl or CF_3 ,

20

in which C_1 - C_6 -alkyl, C_1 - C_6 -aryl, C_1 - C_6 -acyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- C_1 - C_6 -acyl, C_1 - C_6 -acyl- C_1 - C_6 -acyl, C_1 - C_6 -alkyl- C_1 - C_6 -aryl or C_1 - C_6 -aryl- C_1 - C_6 -alkyl can optionally be interrupted singly or multiply,

25

identically or differently by oxygen, sulfur or nitrogen, or the group sulfonyl- C_1 - C_6 -alkyl, sulfonamide, or cyano,

30

R^2 a halogen, CF_3 , a C_3 - C_6 -cycloalkyl,
or the group C_1 - C_6 -alkyl, C_1 - C_6 -aryl, C_1 - C_6 -acyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- C_1 - C_6 -acyl, C_1 - C_6 -acyl- C_1 - C_6 -acyl, C_1 - C_6 -alkyl- C_1 - C_6 -aryl, C_1 - C_6 -aryl- C_1 - C_6 -alkyl or CF_3 ,

in which C_1 - C_6 -alkyl, C_1 - C_6 -aryl, C_1 - C_6 -acyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- C_1 - C_6 -alkyl, C_1 - C_6 -alkyl- C_1 - C_6 -acyl, C_1 - C_6 -acyl- C_1 - C_6 -acyl, C_1 - C_6 -alkyl- C_1 - C_6 -aryl or C_1 - C_6 -aryl- C_1 - C_6 -alkyl

alkyl can optionally be interrupted singly or multiply, identically or differently by oxygen, sulfur or nitrogen, or the group sulfonyl-C₁-C₆-alkyl, sulfonamide, or cyano,

- 5 **R³** a C₅-C₁₂-aryl, which can optionally be substituted singly or multiply, identically or differently with halogen, with C₁-C₆-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, cyano, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-NR⁴R⁵ or with CF₃,
- 10 a C₅-C₁₂-heteroaryl, which can optionally be substituted singly or multiply, identically or differently with chlorine and/or fluorine, with C₁-C₆-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, cyano, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-NR⁴R⁵ or with CF₃,
- 15 a C₃-C₆-cycloalkyl, which can optionally be substituted singly or multiply, identically or differently with chlorine and/or fluorine, CF₃, cyano, C₁-C₃-alkyl, C₁-C₃-acyl, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-NR⁴R⁵ or C₁-C₃-alkoxy,
- R⁴** a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy or CF₃,
- 20 a C₆-C₁₂-aryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or
- 25 a C₅-C₁₂-heteroaryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or
- a C₁-C₆-alkyl, which can be substituted arbitrarily,
- 30 **R⁵** a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy or CF₃,

5 a C₆-C₁₂-aryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or
a C₅-C₁₂-heteroaryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or
a C₁-C₆-alkyl, which can be substituted arbitrarily,

10 R⁴ and R⁵ together form a 5-8-membered ring, which can contain further heteroatoms, and

X the groups sulfonyl, (CH₂)_n or carbonyl,

15 Y a -(CH₂)_n- or carbonyl group,

Z a nitrogen,

A an oxygen or sulfur, and

20 n stands for 0 - 2,

as well as their isomers, diastereomers, enantiomers and salts.

25 Compounds of general Formula I in which the symbols have the following meanings are also preferred,

R¹ a hydrogen,

30 R² a C₃-C₆-cycloalkyl, C₁-C₆-alkyl, CF₃, cyano, bromine, or the group -OCF₃, -SO₂-CH₃,

-10-

- 5 R^3 a C_6 - C_{12} -aryl, which can optionally be substituted singly or multiply, identically or differently with halogen, C_1 - C_6 -alkyl, C_1 - C_3 -acyl, C_1 - C_3 -alkoxy, cyano, hydroxy, N -(CH_3)₂, CO_2 -(C_1 - C_3 -alkyl), $CO-NR^4R^5$ or CF_3 ,
- 10 a C_5 - C_{12} -heteroaryl, which can optionally be substituted singly or multiply, identically or differently with chlorine and/or fluorine, with C_1 - C_6 -alkyl, C_1 - C_3 -acyl, C_1 - C_3 -alkoxy, cyano, hydroxy, N -(CH_3)₂, CO_2 -(C_1 - C_3 -alkyl), $CO-NR^4R^5$ or with CF_3 ,
- 15 a C_3 - C_6 -cycloalkyl, which can optionally be substituted singly or multiply, identically or differently with chlorine and/or fluorine, CF_3 , cyano, C_1 - C_3 -alkyl, C_1 - C_3 -acyl, hydroxy, N -(CH_3)₂, CO_2 -(C_1 - C_3 -alkyl), $CO-NR^4R^5$ or C_1 - C_3 -alkoxy,
- 20 R^4 a hydrogen, a C_3 - C_6 -cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C_1 - C_3 -alkyl, C_1 - C_3 -acyl, C_1 - C_3 -alkoxy or CF_3 ,
- a C_6 - C_{12} -aryl, which is optionally substituted singly or multiply, identically or differently with halogen, C_1 - C_3 -alkyl, C_1 - C_3 -acyl, C_1 - C_3 -alkoxy, N - C_1 - C_3 -alkyl- C_1 - C_3 -alkyl, CF_3 or cyano, or
- 25 a C_5 - C_{12} -heteroaryl, which is optionally substituted singly or multiply, identically or differently with halogen, C_1 - C_3 -alkyl, C_1 - C_3 -acyl, C_1 - C_3 -alkoxy, N - C_1 - C_3 -alkyl- C_1 - C_3 -alkyl, CF_3 or cyano, or
- a C_1 - C_6 -alkyl, which can be substituted arbitrarily,
- 30 R^5 a hydrogen,
- X a sulfonyl or carbonyl group or $-(CH_2)_n$,
- 35 Y a $-(CH_2)_n$ - or carbonyl group,
- Z a nitrogen,

A an oxygen or sulfur and

n 0 – 2

5 as well as their isomers, diastereomers, enantiomers and salts.

Compounds of general Formula I in which the symbols have the following meanings are also preferred,

10

R¹ a hydrogen,

R² a C₃-C₆-cycloalkyl, C₁-C₆-alkyl, CF₃, cyano, bromine, or the group -OCF₃, -SO₂-CH₃ in the para-position,

15

R³ a C₆-C₁₂-aryl, which can optionally be substituted singly or doubly, identically or differently with halogen, C₁-C₃-alkyl, acetyl, methoxy, ethoxy, cyano, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-NHR⁵ or CF₃,

20

a C₅-C₁₂-heteroaryl, which can optionally be substituted singly or doubly, identically or differently with chlorine and/or fluorine, with C₁-C₃-alkyl, acetyl, methoxy, ethoxy, cyano, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-NHR⁵ or with CF₃,
a C₃-C₆-cycloalkyl,

25

R⁴ a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy or CF₃,

30

a C₆-C₁₂-aryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or

- X a sulfonyl or carbonyl group, or $-(CH_2)_n-$
- Y a $-(CH_2)_n-$ or carbonyl group,
- 5 Z a nitrogen,
- A an oxygen or sulfur and
- 10 n 1 - 2

as well as their isomers, diastereomers, enantiomers and salts.

15 The following compounds according to the present invention are quite especially preferred:

- (+/-)-5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(2-hydroxypropyl)amide
- 20 - (+/-)-5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(2-hydroxymethylethyl)amide
- 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(tetrahydropyran-4-yl)amide
- 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-
- 25 carboxylic acid-(2-morpholin-4-yl-ethyl)amide
- 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(tetrahydropyran-4-yl)amide
- 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(2-morpholin-4-yl-ethyl)amide
- 30 - 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(3-morpholin-4-yl-propyl)-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-cyclopentyl-amide

- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(4-pyridyl)-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(2-methoxy-ethyl)-amide
- 5 - 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-cyclohexyl-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(2-hydroxy-ethyl)-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(2-propen-1-yl)-amide
- 10 - 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(2-acetylamino-ethyl)-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(5-hydroxy-4,4-dimethyl-pentyl)-amide
- 15 - (+/-)-5-(4-tert-Butylphenylsulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(2-hydroxypropyl)amide
- (+/-)-5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(2-hydroxy-1-methylethyl)amide.

20

The compounds according to the invention inhibit soluble adenylylase, and this is also the basis of their action for example in male fertility control.

Adenylylases are the effector molecules for one of the most-used signal-transduction pathways, they synthesize the second messenger molecule cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP) with splitting-off of pyrophosphate (PP). cAMP mediates numerous cellular responses to a large number of neurotransmitters and hormones. Soluble, sperm-specific adenylylase (sAC, human mRNA sequence

25 (GenBank) nm_018417, human gene ADCY X) is one out of ten adenylylases described in the human genome. sAC exhibits some specific properties that distinguish it from the other adenylylases. In contrast to all

30 other adenylylases, sAC is stimulated by the concentration of bicarbonate

in the surrounding medium and not by G proteins. sAC does not possess any transmembrane regions in its amino acid sequence, it cannot be inhibited by forskolin, can be stimulated much more strongly by manganese than by magnesium, and only displays slight sequence homologies to the other
5 adenylate cyclases ($\leq 26\%$ identity of the catalytic domains I and II of sAC with other adenylate cyclases at the amino acid level).

Specific, manganese-dependent activity of sAC was first described by T. Braun *et al.* (1975, PNAS 73:1097ff) in rat testis and sperm. N. Okamura *et al.* (1985,
10 J. Biol. Chem 260(17):9699ff) showed that the substance which stimulates the activity of sAC in boar seminal fluid is bicarbonate. It was also shown that AC activity that can be stimulated by bicarbonate can only be detected in rat testis and sperm, but not in other tissues. sAC was purified from rat testis and sequenced for the first time by the Buck and Levin group (J. Buck *et al.* 1999,
15 PNAS 96:79ff, WO 01/85753). The expected properties (e.g. capacity to be stimulated by bicarbonate and magnesium) were confirmed on recombinantly expressed protein (Y. Chen *et al.* 2000, Science 289:625ff).

Testis-specific and sperm-specific expression of the enzymes can be concluded
20 from data on the distribution of sAC mRNA and on sAC activity that can be stimulated by bicarbonate (ML Sinclair *et al.* 2000, Mol Reprod Develop 56:6ff; N Okamura *et al.* 1985, J. Biol. Chem 260(17):9699ff; J. Buck *et al.* 1999, PNAS 96:79ff). In the testis, sAC mRNA is only expressed in later stages, of the gametes developing to sperm, but not in somatic cells (ML Sinclair *et al.* 2000,
25 Mol Reprod Develop 56:6ff).

There have been a number of pharmacological investigations into the function of sAC in sperm in mammals. Before sperm can penetrate the zona pellucida of the ovum and then fuse with the oolemma of the ovum, sperm must be
30 prepared for this functionality. This process, sperm capacitation, has been thoroughly investigated. A capacitated sperm is characterized by an altered pattern of movement and by the ability to go through the process of the acrosome reaction (release of lytic enzymes which presumably serve for



penetration of the zona pellucida by the sperm) when suitably stimulated. Sperm capacitation takes place *in vivo* and *in vitro* and among other things independently of a raised bicarbonate concentration in the medium (PE Visconti & GS Kopf (1998), Biol Reprod 59:1ff; E de Lamirande *et al.* 1997, Mol Hum
5 Reprod 3(3):175ff). Sperm capacitation can also be stimulated by adding suitable membrane-passing cAMP analogs, e.g. db-cAMP, and an inhibitor that prevents their degradation (e.g. IBMX). The presumed dependence of sperm function on sAC was confirmed only recently by a genetic deletion model, a so-called knock-out mouse (G Esposito *et al.* 2004, PNAS 101(9):2993ff). Male
10 mice lacking the gene for sAC exhibit spermatogenesis that proceeds normally, but are infertile. The sperm have motility defects and are not capable of fertilizing an egg. The animals did not display any other defects or abnormal findings, which contradicts other hypothesized functions of sAC (JH Zippin *et al.* 2003, FASEB 17:82ff).

15

sAC has a unique sequence and only slight homology to other somatic adenylate cyclases. It is the only adenylate cyclase in mammalian sperm and the activity is essential for sperm motility and capacitation. Specific sAC inhibitors accordingly represent an important possibility for controlling male
20 fertility.

20

The present invention therefore relates to medicinal products that contain at least one of the compounds as claimed in claims 1-3.

The present invention also relates to the use of the compounds as claimed in claims 1-7.

25

For use of the compounds according to the invention as medicinal products they are converted to the form of a pharmaceutical preparation, which contains, in addition to the active substance, pharmaceutical, organic or inorganic inert vehicles that are suitable for enteral or parenteral application, for example
30 water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols etc. The pharmaceutical preparations can be in solid form, for example as tablets, dragées, suppositories, or capsules, or in liquid form, for example as solutions, suspensions or emulsions. If necessary they

21

also contain excipients, such as preservatives, stabilizers, wetting agents or emulsifiers; salts for altering osmotic pressure or buffers. These pharmaceutical preparations are also the object of the present invention.

- 5 Injection solutions or suspensions, especially aqueous solutions of the active compounds in polyhydroxyethoxylated castor oil, are particularly suitable for parenteral application.

10 Surface-active excipients such as salts of bile acids or animal or vegetable phospholipids, as well as mixtures thereof and liposomes or their constituents, can also be used as carrier systems.

In particular, tablets, dragées or capsules with talc and/or hydrocarbon vehicles or binders, for example lactose, maize starch or potato starch, are suitable for
15 oral application. Application can also be in liquid form, for example as juice, to which a sweetener is added if required. Clathrates are also suitable for oral application of these compounds, and the following may be mentioned as examples: the clathrates with alpha-, beta-, gamma-cyclodextrin or alternatively beta-hydroxypropyl-cyclodextrin.

20

The present invention also relates to enteral, parenteral and oral application.

The dosage of the active substances can vary depending on the route of administration, the patient's age and weight, the nature and severity of the
25 disease to be treated and similar factors. The daily dose is 0.5-1000 mg, preferably 50-200 mg, and the dose can be a single dose that is to be administered once, or can be divided into 2 or more daily doses.

The compounds according to the invention of general Formula I are, among
30 other things, excellent inhibitors of soluble adenylate cyclase. Inhibitors of soluble adenylate cyclase lead to depression of the cAMP signal. The cAMP level is decisive for control of the processes that play an important role in cell proliferation, cell differentiation and apoptosis. Diseases, e.g. cancer, in which

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depression of the cAMP level is decisive, can be modulated by inhibitors of soluble adenylate cyclase. This modulation can have prophylactic and therapeutic effects for patients suffering such a disease. At the present time diseases which are, like cancer, associated with increased cell proliferation, are treated for example by radiotherapy and chemotherapy. These methods are nonspecific and have a high potential for side-effects. The provision of new substances, which act directly on particular target sites, is therefore advantageous. The present invention relates to substances that modulate cAMP production by the inhibition of soluble adenylate cyclase. For example, abnormal cell proliferation can be reduced or prevented by regulation or inhibition of cAMP production. Soluble adenylate cyclase can be inhibited by the use of the substances according to the invention, with a consequent reduction in cell proliferation. The present invention relates to medicinal products for the treatment of diseases that contain at least one compound according to general Formula I, and medicinal products with suitable vehicles and excipients. The diseases are characterized in that they are caused by disturbances of metabolism of the second messenger cAMP.

Lowering of the cAMP concentration by inhibition of soluble adenylate cyclase can provide a means of modulation of sperm capacitation. The present invention relates to the use of the substances according to the invention for the lowering and/or inhibition of male gamete fertility, mediated by the reduction or inhibition of soluble adenylate cyclase activity and accordingly of sperm capacitation.

Fertilization of the ovum can be prevented by administering an effective amount of a substance that leads to inhibition of cAMP production. The present invention also relates to the use of the compound of general Formula I for the production of a medicinal product for non-hormonal contraception.

If the production of the starting compounds is not described, these are known or can be produced similarly to known compounds or methods described here. It is

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also possible to carry out all the reactions described here in parallel reactors or using combinatorial techniques.

5 The mixtures of isomers can be separated into the enantiomers or E/Z isomers by usual methods, for example crystallization, chromatography or salt formation.

10 The salts are produced in the usual manner, by adding the equivalent amount or an excess of a base or acid, which is in solution if necessary, to a solution of the compound of Formula I, separating the precipitate or processing the solution in the usual way.

Production of the compounds according to the invention

15 The following examples explain the production of the compounds of general Formula I according to the invention, without limiting the scope of the claimed compounds to these examples.

The compounds of general Formula I according to the invention can be produced as described below.

20 **Step 1: Amide coupling:**

Dissolve a carboxylic acid (1.0 equivalent) in N,N-dimethylformamide (DMF) (10 ml/1 mmol), and add N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminiumhexafluorophosphate- N-oxide (HATU) (1.1 equivalent) and the amine for coupling (1.0 equivalent). Then add
25 ethyldiisopropylamine (1.1 equivalent) at 0°C and stir the mixture for 22 hours at room temperature. Then add ice water to the mixture (35 ml/1 mmol carboxylic acid), and stir for 30 min at room temperature. Filter the precipitated crystals with suction and dry in air. Use the product in the next stage either without further purification or purified chromatographically. If no crystals form, after
30 removing the DMF extract the aqueous phase with ethyl acetate or dichloromethane, combine the organic phases and dry over sodium sulfate. After removing the solvent, carry out chromatographic purification of the residue.

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Step 2: Reduction of the nitro group:

- Place the nitro compound (1.0 equivalent) in methanol (10 ml/1 mmol) and water (0.03 ml/1 mmol), add ammonium formate (5 equivalent) and catalytic amounts of palladium on carbon (10%) and heat for 3 hours at 90°C under reflux. Then filter through Celite with suction and rinse with boiling methanol. After removing the solvent, add water to the residue (7 ml/1 mmol amide) and filter off the precipitated crystals with suction. If no crystals form, extract the aqueous phase with ethyl acetate or dichloromethane. Wash the combined organic phases with saturated sodium chloride solution and dry over sodium sulfate. Then remove the solvent under reduced pressure.

Step 3: Coupling with arylsulfonyl chlorides:

- Dissolve the resulting amine (1.0 equivalent) in DMF (10 ml/1 mmol), add, at 0°C, ethyldiisopropylamine (1.5 equivalent) and arylsulfonyl chloride (1.0 equivalent) and stir for one hour at room temperature. Remove the solvent under reduced pressure and purify the residue chromatographically.

Step 4: Bromination:

- Dissolve the compound to be brominated (1.0 equivalent) in tetrahydrofuran (5 ml/1 mmol) and add N-bromosuccinimide (1.0 equivalent). After 30 min add water, and 20 min later filter off the precipitated crystals with suction. If no crystals form, extract the aqueous phase with ethyl acetate and dry the combined organic phases over sodium sulfate. After removing the solvent, carry out chromatographic purification of the residue.

Step 5: Saponification:

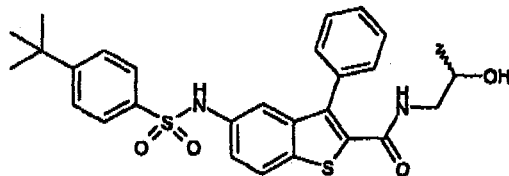
- Add 19 equivalent of a 1M sodium hydroxide solution in ethanol/water (1/1) to the ester compounds (1.0 equivalent). After 6 hours at room temperature, remove the ethanol under reduced pressure, dilute with water and adjust to pH 2 with 10% aqueous sulfuric acid. Then filter off the precipitated crystals with suction.

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Step 6: Coupling with arylboronic acids:

Suspend the bromine compound obtained after Step 4 (1.0 equivalent) with an arylboronic acid (1.5 equivalent) in toluene/ethanol 1:1 (40 ml/1 mmol ester) and add 1M sodium carbonate solution (2.5 equivalent) and lithium chloride (2.8 equivalent). After adding tetrakis(triphenylphosphine)-palladium (0.08 equivalent), reflux the reaction mixture for 8 hours. After cooling to room temperature, dilute with ethyl acetate (70 ml/1 mmol ester) and, 10 min later, filter through Celite with suction. Wash the filtrate with saturated sodium hydrogen carbonate/saturated sodium chloride solution and dry over sodium sulfate. After removing the solvent, carry out chromatographic purification of the residue.

Example 1: (+/-)-5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(2-hydroxypropyl)amide

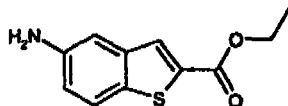


According to Step 1 after reaction of 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid (155 mg, 0.33 mmol) with 1-amino-2-propanol (0.027 mL, 0.35 mmol) and subsequent chromatographic purification (silica gel, dichloromethane/methanol (0-10% methanol)), the desired compound is obtained at 17% yield (29 mg).

NMR (300 MHz, DMSO-d₆): δ 0.93 (d, 3H), 1.25 (s, 9H), 3.00-3.13 (m, 2H), 3.62-3.70 (m, 1H), 4.65 (d, 1H), 6.90 (d, 2H), 7.24-7.38 (m, 6H), 7.43 (d, 2H), 7.50 (s, 1H), 7.91 (d, 1H), 8.70 (t, 1H), 9.30 (s, 1H).

The starting material for the title compound above is prepared as follows:

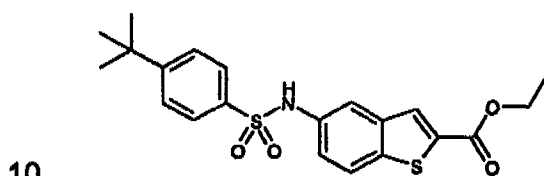
1a) 5-amino-1-benzothiophene-2-carboxylic acid ethyl ester



According to Step 2, after reaction of 5-nitro-1-benzothiophene-2-carboxylic acid-ethyl ester (5.0 g, 19.9 mmol) with ammonium formate (6.28 g, 99.5 mmol) in the presence of palladium on carbon (500 mg), the desired compound is obtained at 89% yield (3.92 g).

- 5 NMR (300 MHz, DMSO-d₆): δ 1.25 (t, 3H), 4.30 (q, 2H), 5.25 (s, 2H), 6.85 (dd, 1H), 7.00 (d, 1H), 7.60 (d, 1H), 7.90 (s, 1H).

1b) 5-(4-tert-Butylbenzenesulfonylamino)-1-benzothiophene-2-carboxylic acid ethyl ester

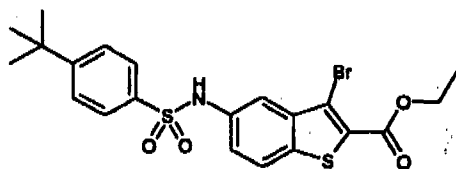


- According to Step 3, after reaction of 5-amino-1-benzothiophene-2-carboxylic acid ethyl ester (3.92 g, 17.72 mmol) from Example 1a) with 4-tert-Butylbenzenesulfonyl chloride (4.12 g, 17.72 mmol) and diisopropylethylamine (6.9 mL, 26.9 mmol) followed by chromatographic purification (silica gel, 15 hexane/ethyl acetate (0-100% ethyl acetate)), the desired compound is obtained at 72% yield (5.34 g).

NMR (300 MHz, DMSO-d₆): δ 1.20 (s, 9H), 1.25 (t, 3H), 4.30 (q, 2H), 7.25 (dd, 1H), 7.52 (d, 2H), 7.68 (d, 2H), 7.72 (d, 1H), 7.88 (d, 1H), 8.10 (s, 1H), 10.45 (s, 1H).

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1c) 3-Bromo-5-(4-tert-butylbenzenesulfonylamino)-1-benzothiophene-2-carboxylic acid ethyl ester

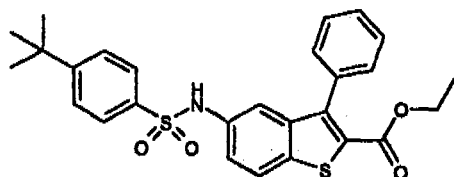


- According to Step 4, after reaction of 5-(4-tert-Butylbenzenesulfonylamino)-1-benzothiophene-2-carboxylic acid ethyl ester (5.34 mg, 12.79 mmol) from Example 1b) with N-bromosuccinimide (2.30 g, 12.79 mmol) followed by chromatographic purification (silica gel, hexane/ethyl acetate (0-70% ethyl acetate)), the desired compound is obtained at 94% yield (5.98 g).
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NMR (600 MHz, DMSO-d₆): δ 1.25 (s, 9H), 1.32 (t, 3H), 4.35 (q, 2H), 7.30 (d, 1H), 7.55 (d, 2H), 7.64 (d, 2H), 7.92 (s, 1H), 8.05 (d, 1H), 10.10 (s, 1H).

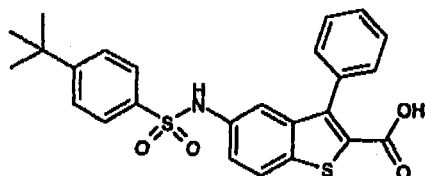
1d) 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-ethyl ester



According to Step 6, after reaction of 3-Bromo-5-(4-tert-butylbenzenesulfonylamino)-1-benzothiophene-2-carboxylic acid ethyl ester (496 mg, 1.0 mmol) from Example 1c) with phenylboronic acid (176 mg, 1.44 mmol) followed by chromatographic purification (silica gel, hexane/ethyl acetate (0-100% ethyl acetate) and ethyl acetate/methanol (0-15%)), the desired compound is obtained at 61% yield (300 mg).

NMR (300 MHz, DMSO-d₆): δ 1.22 (t, 3H), 1.30 (s, 9H), 4.33 (q, 2H), 6.90 (d, 2H), 7.30-7.32 (m, 3H), 7.35-7.40 (m, 4H), 7.43 (d, 2H), 8.02 (d, 1H), 9.45 (s, 1H).

1e) 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid

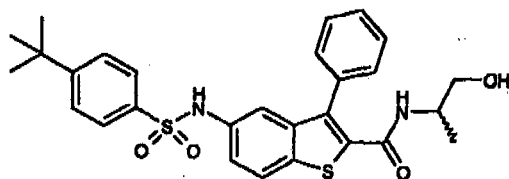


According to Step 5, after reaction of 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid ethyl ester (1.24 g, 2.5 mmol) from Example 1d) with 1M sodium hydroxide solution in ethanol/water (2:1, 49 mL), the desired compound is obtained at quantitative yield (1.18 g).

NMR (300 MHz, DMSO-d₆): δ 1.30 (s, 9H), 6.92 (d, 2H), 7.30-7.42 (m, 7H), 7.50 (d, 2H), 8.03 (d, 1H), 9.45 (s, 1H).

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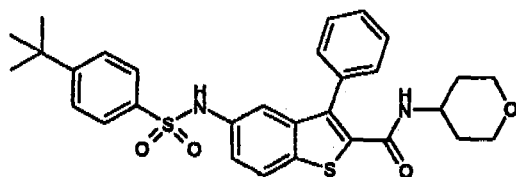
Example 2: (+/-)-5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(2-hydroxy-1-methylethyl)amide



- 5 According to Step 1, after reaction of 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid (155 mg, 0.33 mmol) with 2-amino-1-propanol (0.027 mL, 0.35 mmol) followed by chromatographic purification (silica gel, dichloromethane/methanol (0-10% methanol)) and recrystallization from ethyl acetate/hexane, the desired compound is obtained at 29% yield (51 mg).

NMR (300 MHz, DMSO-d₆): δ 1.03 (d, 3H), 1.25 (s, 9H), 3.15-3.40 (m, 2H), 3.82-3.92 (m, 1H); 4.65 (t, 1H), 6.92 (d, 2H), 7.25-7.38 (m, 6H), 7.42 (d, 2H), 7.50 (s, 1H), 7.92 (d, 1H), 8.40 (d, 1H), 9.25 (s, 1H).

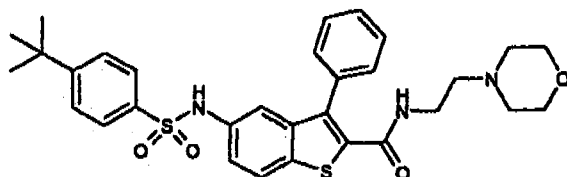
- 15 **Example 3:** 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(tetrahydropyran-4-yl)amide



- 20 According to Step 1, after reaction of 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid (155 mg, 0.33 mmol) with 4-aminotetrahydropyran (22 mg, 0.35 mmol), the desired compound is obtained at 50% yield (92 mg).

- NMR (300 MHz, DMSO-d₆): δ 1.25 (s, 9H), 1.40-1.52 (m, 2H), 1.62-1.70 (m, 2H), 3.20-3.40 (m, 2H and water), 3.75-3.82 (m, 2H), 3.84-3.93 (m, 1H), 6.92 (d, 2H), 7.26-7.38 (m, 6H), 7.43 (d, 2H), 7.48 (s, 1H), 7.92 (d, 1H), 8.55 (d, 1H), 9.25 (s, 1H).

Example 4: 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(2-morpholin-4-ylethyl)amide



- According to Step 1, after reaction of 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid (155 mg, 0.33 mmol) with N-(2-aminoethyl)-morpholine (0.046 mL, 0.35 mmol) followed by chromatographic purification (silica gel, dichloromethane/methanol (0-10% methanol)) and recrystallization from ethyl acetate/hexane, the desired compound is obtained at 14% yield (27 mg).
- 10 NMR (300 MHz, DMSO-d₆): δ 1.26 (s, 9H), 2.25-2.38 (m, 6H), 3.20-3.30 (m, 2H), 3.45-3.52 (m, 4H), 6.92 (d, 2H), 7.22-7.40 (m, 6H), 7.42-7.48 (m, 3H), 7.92 (d, 1H), 8.65 (t, 1H), 9.32 (s, 1H).

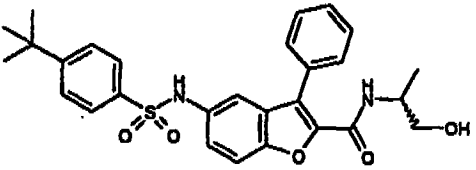
- 15 The following compounds were produced by analogy:

#	Designation	Structure
5	5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(tetrahydropyran-4-yl)amide	
6	5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(2-morpholin-4-ylethyl)amide	
7	5-(4-tert-Butylphenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(3-morpholin-4-yl-propyl)-amide	

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#	Designation	Structure
8	5-(4-tert-Butyl-phenylsulfonylamino)-3-phenylbenzo[b]thiophene-2-carboxylic acid-cyclopentyl-amide	
9	5-(4-tert-Butyl-phenylsulfonylamino)-3-phenylbenzo[b]thiophene-2-carboxylic acid-(4-pyridyl)-amide	
10	5-(4-tert-Butyl-phenylsulfonylamino)-3-phenylbenzo[b]thiophene-2-carboxylic acid-(2-methoxy-ethyl)-amide	
11	5-(4-tert-Butyl-phenylsulfonylamino)-3-phenylbenzo[b]thiophene-2-carboxylic acid-cyclohexyl-amide	
12	5-(4-tert-Butyl-phenylsulfonylamino)-3-phenylbenzo[b]thiophene-2-carboxylic acid-(2-hydroxy-ethyl)-amide	
13	5-(4-tert-Butyl-phenylsulfonylamino)-3-phenylbenzo[b]thiophene-2-carboxylic acid-(2-propen-1-yl)-amide	
14	5-(4-tert-Butyl-phenylsulfonylamino)-3-phenylbenzo[b]thiophene-2-carboxylic acid-(2-acetylamino-ethyl)-amide	
15	5-(4-tert-Butyl-phenylsulfonylamino)-3-phenylbenzo[b]thiophene-2-carboxylic acid-(5-hydroxy-4,4-dimethyl-pentyl)-amide	
16	(+/-)-5-(4-tert-Butylphenylsulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(2-hydroxypropyl)amide	

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#	Designation	Structure
17	(+/-)-5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(2-hydroxy-1-methylethyl)amide	

Biological examples:

Example 1: sAC assay

- 5 In a suitable buffer system, soluble, sperm-specific adenylate cyclase catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) and pyrophosphate. Free cAMP generated in this way is then used in a competitive detection technique, in which the binding of a europium cryptate Eu[K]-labeled anti-cAMP antibody (anti-cAMP-Eu[K]-AB) to a
- 10 modified allophycocyanine-1 molecule labeled with cAMP molecules (cAMP-XL665) is prevented. In the absence of exogenous cAMP, after excitation at 335 nm there is Fluorescence Resonance Energy Transfer (FRET) between the anti-cAMP-Eu[K]-AB (FRET donor) and the cAMP-XL665 molecule (FRET acceptor). This process is quantified, time-resolved, on the basis of the
- 15 emission of the FRET acceptor XL665 (665nm and 620nm). A decrease in signal (measured as Well Ratio; calculated from the Formula: $[(E_{665nm}/E_{620nm}) \times 10000]$) can be attributed to the presence of cAMP and thus to the activity of sAC. First, 1.5 μ l of the test substance (in 30% DMSO) is placed in each well of a 384-well test plate (polystyrene; 384, NV), and in the
- 20 solvent controls only 30% DMSO. Then 10 μ l of a dilute sAC enzyme solution is applied (enzyme stock solution in 300 mM NaCl, 10% glycerol; pH 7.6; enzyme intermediate and final dilution a) 1:10 and b) 1:2000 in each case in: 1.0 mM MnCl₂; 0.2% BSA; 50 mM Tris pH 7.5 in H₂O). The enzyme reaction is started by adding 5 μ l of the ATP substrate solution (200 μ M ATP in H₂O) and after
- 25 incubation (25 min at room temperature) stopped by adding 5 μ l of the stop solution (200 μ M EDTA in PBS). Finally the whole reaction is adjusted to a total volume of 91.5 μ l by adding 70 μ l PBS.
- Next, 8 μ l of detection solution 1 is placed in a well of the 384-well measuring plate (measuring plate: polystyrene; 384, SV – black; detection solution 1: 50 μ l

cAMP-XL665; 950 µl reconstituted buffer; 2200 µl PBS; cAMP-XL665: prepared by adding 5 ml H₂O to the lyophilized product according to the instructions in Cis bio Kit: #62AMPPEC; storage: in aliquots at -80°C). Next, 3 µl from the 91.5 µl is added to the corresponding well of the test plate. Finally, 8 µl of detection
5 solution 2 is added (detection solution 2: 50 µl anti-cAMP-Eu[K]-AB; 950 µl reconstituted buffer; 2200 µl PBS; anti-cAMP-Eu[K]-AB: prepared according to the instructions in Cis bio Kit: #62AMPPEC; storage: in aliquots at -80°C).
After further incubation for 90 min at room temperature, the HTRF result is measured either on the Packard Discovery or with the RubiStar HTRF
10 measuring instrument (delay: 50 µs; integration time: 400 µs).

Example 2. Isolation of human sperm from ejaculates and capacitation

2.1. Isolation of the sperm

Human sperm from ejaculate are purified in a two-layer gradient system based
15 on colloidal silica particles (trade name: Percoll or ISolate).
Per ejaculate, 2.5 ml of pre-warmed lower layer ("90% ISolate lower layer", from Irvine) is placed in a 15 ml centrifuge tube (conical, plastic) and is carefully covered with 2.5 ml of pre-warmed upper layer ("50% ISolate upper layer", from Irvine) and held at 37°C for < 1h on a water bath. The gradient is carefully
20 covered with max. 3 ml of normal (with respect to sperm count, motility and liquefaction) ejaculate. Sedimentation of the sperm is carried out at 1000 x g for 25 min at room temperature. Using a glass capillary, the two layers are removed by suction to just above the sperm pellet. For elutriation of the ISolate gradients, the sperm pellets, each resuspended in approx. 200 µl, are transferred to a
25 15 ml plastic tube with 12 ml mHTF medium (4 mM NaHCO₃; 0.01% BSA; 37°C) and the sperm are sedimented at 1000 x g for 20 min. The medium is removed by suction to just above the pellet and adjusted with mHTF medium (4 mM NaHCO₃; 0.01% BSA; 37°C) to 1000 µl. The sperm count is determined in a Neubauer counter and for subsequent capacitation is adjusted if necessary to
30 4x10⁶ sperm/150 µl with mHTF medium (4 mM NaHCO₃; 0.01% BSA; 37°C).

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2.2. Capacitation

If the influence of test substances on the acrosome reaction is to be tested, the sperm must be preincubated with the test substances. This preincubation (15 min in a heating cabinet at 37°C) is necessary to permit penetration of the test substances into the sperm before the start of capacitation, i.e. to achieve presaturation of the binding sites in the sperm, especially in the case of substances that do not pass through the membrane easily. It is also necessary because the increase in BSA concentration during capacitation due to the high lipid binding of the BSA could lead to a decrease in the effective concentration of test substance in the sample.

The test substances are dissolved in DMSO and diluted with mHTF medium (4 mM NaHCO₃; 0.01% BSA; 37°C), so that in the final 400-μl capacitation sample the DMSO concentration is 0.5%. In each case 150 μl of sperm suspension is added by pipette to 150 μl of the aforementioned temperature-controlled solution of test substance, followed by preincubation at 37°C for 15 min. Capacitation of the sperm is started by adding 100 μl of mHTF medium (88 mM NaHCO₃; 4% BSA; 37°C). In the final 400-μl capacitation sample, the concentration of sperm is 10x10⁶/ml, the bicarbonate concentration is 4 mM and the BSA concentration is 1%. Capacitation is carried out for 3 hours at 37°C in the heating cabinet.

For stopping capacitation, the samples (each of 400 μl) are each transferred completely to a 15-ml sample tube with 1.5 ml mHTF (4 mM NaHCO₃; 37°C), centrifuged for 5 min at 1000 x g and the supernatant is removed. This step removes both the large amount of protein and the test substances.

Example 3. Flow cytometric determination of the acrosome reaction

3.1. Initiation of the acrosome reaction by treatment with ionophore and simultaneous CD46-FITC staining

The acrosome reaction (AR) of the sperm is triggered by binding of the sperm to the zona pellucida (ZP). This releases enzymes from the acrosome, enabling the sperm to penetrate the ZP and reach the ovum. In the AR, there is partial fusion, at the sperm, of the plasma membrane with the outer acrosomal

membrane (OAM). At the end the sperm head is still restricted by the inner acrosomal membrane (IAM). The CD46 antigen is only detectable at the IAM.

In vitro the acrosome reaction can only be induced with a suitable concentration of the calcium ionophore A23187 on capacitated sperm, but not on uncapacitated sperm or sperm for which capacitation was inhibited by test substances. By means of the FITC-labeled anti-CD46 antibody (from Pharmingen) to the IAM, the acrosome-reacted sperm can be differentiated from the acrosome-intact sperm, in which the IAM is not exposed, in the flow cytometer. With simultaneous staining of the sperm with the DNA stain ethidium homodimer (EhD), which only stains cells that have defective DNA membranes, i.e. are dead, it is possible to distinguish dead sperm from live sperm.

Because the ionophore dilutions for initiating the AR appear to be very unstable and must be mixed with the CD46-FITC solution for simultaneous staining, the solutions cannot be prepared before the start of the test, but must be prepared during processing of the capacitation samples.

The sperm pellets are resuspended in the residue of the supernatant and are diluted with 450 µl mHTF (4 mM NaHCO₃; 0.01% BSA; 37°C) on a water bath (37°C). 100 µl aliquots of the sperm suspensions are transferred by pipette to prepared sample-FACS flow tubes (on the water bath). 150 µl of a solution with ionophore and FITC-labeled anti-CD46 antibody is added by pipette to the sperm. The final concentration is 800 nm ionophore and a 1:125 dilution of the anti-CD46 antibody in mHTF (4 mM NaHCO₃; 0.01% BSA; 37°C). The sperm are incubated therein for 30 min, protected from the light, on a water bath at 37°C.

Incubation is stopped by adding 3.5 ml PBS [0.1% BSA] / sample, followed by centrifugation for 5 min at 700 x g (room temperature) and then removal of the supernatants with suction. After centrifugation, the samples are kept warm on a hot-plate until measurement.

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3.2. EhD staining (for differentiation of the dead/live acrosome-reacted sperm)

500 µl of freshly prepared EhD solution (150 nm EhD in PBS [w/o BSA]; 37°C) is added to each of the sperm pellets after removal by suction. The samples can

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- then be measured in the flow cytometer (BD FACS Calibur). Measurement is performed at a laser excitation wavelength of 488 nm, detecting 10000 sperm per measurement. Acrosome-reacted sperm are measured via CD46-FITC in the FL-1 filter at 530 nm. Dead sperm are measured by means of EhD-DNA staining in the FL-2 filter at 634 nm. The measurement channels are correspondingly compensated relative to one another beforehand.

3.3 Evaluation

- The sperm are selected as a very uniform cell population in an FSC-H (forward scatter) versus SSC-H (sideward scatter) dot-plot. As two-color fluorescence staining is used, evaluation is performed by quadrant analysis in an FL-1 (EhD; X axis) vs. FL-2 (FITC-CD46, Y axis) dot-plot with the selected sperm population from the FSC vs. SSC dot-plot:

	Quadrant in FL-1 vs. FL-2 dot-plot	Staining	Analysis
Q1 = UL	upper left	only EhD	dead, not acrosome-reacted sperm
Q2 = UR	upper right	EhD and FITC-CD46	dead, acrosome-reacted sperm
Q3 = LL	lower left	unstained	live, not acrosome-reacted sperm
Q4 = LR	lower right	only FITC-CD46	live, acrosome-reacted sperm

- To calculate the %-induced acrosome-reacted sperm (= "IAR[%]"), only the live sperm from Q3 and Q4 are taken, and their total count is set equal to 100%. IAR is then calculated as follows:

$$IAR[\%] = \frac{LR \times 100}{LL + LR}$$

- A proportion of the sperm undergo the acrosome reaction spontaneously without addition of ionophore (= "SAR[%]"). Therefore a control measurement is always performed on identically-treated sperm without addition of ionophore. Calculation of SAR is similar to calculation of IAR. The acrosome reaction actually induced by the ionophore (= "ARIC[%]") is calculated as the difference: ARIC = IAR - SAR.

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- For subsequent analysis of the influence of our inhibitors on sAC-mediated capacitation (measured as the capacity of the sperm for the ionophore-induced acrosome reaction), the percentage of acrosome-reacted sperm in the positive capacitation control (= incubation with mHTF medium with 25 mM NaHCO₃; 1% BSA without test substances) is set = 100%. The capacity of the sperm to which the test substances have been added, for the acrosome reaction, is stated relative to this maximum acrosome reaction.

Materials used

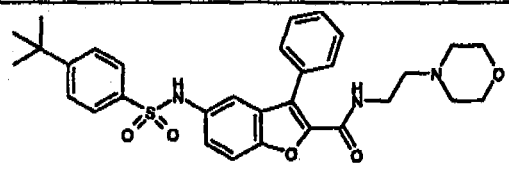
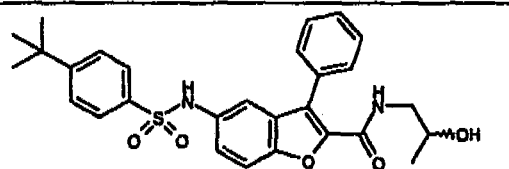
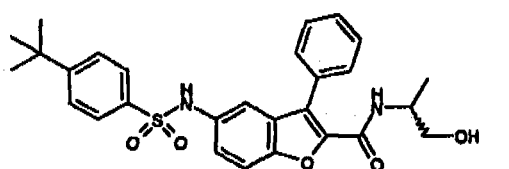
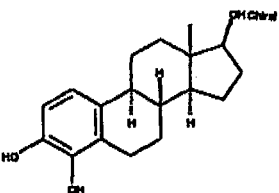
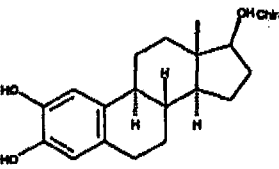
- 10 mHTF = modif. human tubular fluid (from Irvine Scientific), Dulbeccos's Phosphate-Buffered-Saline (from Gibco) (with Ca²⁺, Mg²⁺, 1 g/L D-glucose, 36 mg/L Na-pyruvate, w/o phenol red, w/o NaHCO₃); bovine serum albumin, Fraction V (from Fluka); dimethylsulfoxide (DMSO), anhydrous (from Merck); sodium bicarbonate 7.5% solution (893mM) (from Irvine Scientific); Isolate-
15 Gradient (from Irvine Scientific); Ionophore-A23187 free acid, (from Calbiochem); Ethidium Homodimer (EhD) (from Molecular Probe), Mouse Anti Human CD46:FITC (from Pharmingen).

References:

- 20 J. W. Carver-Ward, Human Reproduction Vol. 11, No. 9, pp: 1923 ff, 1996
High fertilization prediction by flow cytometric analysis of the CD46 antigen on the inner acrosomal membrane of spermatozoa
O. J. D'Cruz, G. G. Haas, Fertility and Sterility Vol. 65, No. 4, pp: 843 ff, 1996
Fluorescence-labeled fucolectins are superior markers for flow cytometric
25 quantitation of the sperm acrosome reaction
E. Nieschlag, H.M. Behre, Andrology, Springer Verlag 1996

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Examples:

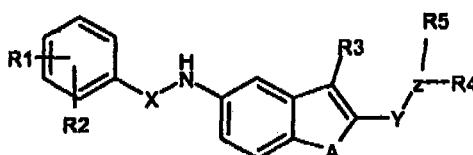
#	R ⁴	Y	IC ₅₀ (μM)
 6	-(CH ₂) ₂ -morpholine	-CO	5.2
 16	-CH ₂ -CH(CH ₃)-OH	-CO	4.3
 17	-CHCH ₃ -CH ₂ -OH	-CO	8.5
 4-OH-estradiol			13
 2-OH-estradiol			11

It can be seen from the table that with respect to the inhibition of soluble adenylate cyclase, expressed by the IC₅₀ value, the compounds according to the invention display greater activity than the known catechol estrogens (OH-estradiols). The catechol estrogens are toxic, therefore the compounds according to the invention are superior to the known compounds.

Patent claims

1. A compound of general Formula 1

5



where the following notation is used

- 10 **R¹** a hydrogen, halogen, CF₃,
 a C₃-C₆-cycloalkyl, which is optionally multiply saturated and
 optionally multiply substituted, or
 the group C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl, C₁-
 C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-C₁-C₆-acyl,
 C₁-C₆-alkyl-C₁-C₆-aryl, C₁-C₆-aryl-C₁-C₆-alkyl or CF₃,
 in which C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-
 15 alkyl, C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-
 acyl-C₁-C₆-acyl, C₁-C₆-alkyl-C₁-C₆-aryl or C₁-C₆-aryl-C₁-C₆-
 alkyl can optionally be interrupted singly or multiply,
 identically or differently by oxygen, sulfur or nitrogen, or
 the group sulfonyl-C₁-C₆-alkyl, sulfonamide, or cyano,
- 20 **R²** a halogen, CF₃, a C₃-C₆-cycloalkyl, which is optionally multiply
 saturated and optionally multiply substituted, or
 the group C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl, C₁-
 C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-C₁-C₆-acyl,
 25 C₁-C₆-alkyl-C₁-C₆-aryl, C₁-C₆-aryl-C₁-C₆-alkyl or CF₃,
 in which C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-
 alkyl, C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-
 acyl-C₁-C₆-acyl, C₁-C₆-alkyl-C₁-C₆-aryl or C₁-C₆-aryl-C₁-C₆-
 alkyl can optionally be interrupted singly or multiply,
 30 identically or differently by oxygen, sulfur or nitrogen, or
 the group sulfonyl-C₁-C₆-alkyl, sulfonamide, or cyano,

49

- R³** a C₆-C₁₂-aryl, which can optionally be substituted singly or multiply, identically or differently with halogen, with C₁-C₆-alkyl or C₁-C₆-acyl,
- 5 which can optionally be singly or multiply substituted, or can be substituted with C₁-C₆-alkoxy, hydroxy, cyano, CO₂-(C₁-C₆-alkyl), N-(C₁-C₆-alkyl)₂, CO-NR⁴R⁵ or with CF₃, a C₅-C₁₂-heteroaryl, which can optionally be substituted singly or multiply, identically or differently with halogen, with C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, hydroxy, cyano, CO₂-(C₁-C₆-alkyl), N-(C₁-C₆-alkyl)₂, CO-NR⁴R⁵ or with CF₃ or
- 10 a C₃-C₆-cycloalkyl, which can optionally be substituted singly or multiply, identically or differently with halogen, CF₃, hydroxy, cyano, CO₂-(C₁-C₆-alkyl), C₁-C₆-alkyl, C₁-C₆-acyl, N-(C₁-C₆-alkyl)₂, CO-NR⁴R⁵ or C₁-C₆-alkoxy,
- 15
- R⁴** a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy or CF₃,
- 20 a C₆-C₁₂-aryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, N-C₁-C₆-alkyl-C₁-C₆-alkyl, CF₃ or cyano, or a C₅-C₁₂-heteroaryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, N-C₁-C₆-alkyl-C₁-C₆-alkyl, CF₃ or cyano, or
- 25 a C₁-C₆-alkyl, which can be substituted arbitrarily,
- R⁵** a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy or CF₃,
- 30 a C₆-C₁₂-aryl, which is optionally substituted singly or multiply, identically or differently with halogen, with C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, N-C₁-C₆-alkyl-C₁-C₆-alkyl, CF₃ or cyano, or

50

a C₅-C₁₂-heteroaryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₆-alkyl, C₁-C₆-acyl, C₁-C₆-alkoxy, N-C₁-C₆-alkyl-C₁-C₆-alkyl, CF₃ or cyano, or a C₁-C₆-alkyl, which can be substituted arbitrarily,

5

R⁴ and R⁵ together form a 5-8-membered ring, which can contain further heteroatoms, and

X the groups sulfonyl, (CH₂)_n or carbonyl,

10

Y a -(CH₂)_n- or carbonyl group,

Z a nitrogen,

15

A an oxygen or sulfur and

n 0 - 4,

as well as their isomers, diastereomers, enantiomers and salts.

20

2. The compound as claimed in claim 1, where the symbols have the following meanings:

25

R¹ a hydrogen, halogen, CF₃,
a C₃-C₆-cycloalkyl, or the group C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-C₁-C₆-acyl, C₁-C₆-alkyl-C₁-C₆-aryl, C₁-C₆-aryl-C₁-C₆-alkyl or CF₃,

30

in which C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-C₁-C₆-acyl, C₁-C₆-alkyl-C₁-C₆-aryl or C₁-C₆-aryl-C₁-C₆-alkyl can optionally be interrupted singly or multiply,

identically or differently by oxygen, sulfur or nitrogen, or

35

the group sulfonyl-C₁-C₆-alkyl, sulfonamide, or cyano,

81

- R²**
- 5 a halogen, CF₃, a C₃-C₆-cycloalkyl,
or the group C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl,
C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-C₁-C₆-
acyl, C₁-C₆-alkyl-C₁-C₆-aryl, C₁-C₆-aryl-C₁-C₆-alkyl or CF₃,
in which C₁-C₆-alkyl, C₁-C₆-aryl, C₁-C₆-acyl, halo-C₁-C₆-alkyl,
C₁-C₆-alkyl-C₁-C₆-alkyl, C₁-C₆-alkyl-C₁-C₆-acyl, C₁-C₆-acyl-
C₁-C₆-acyl, C₁-C₆-alkyl-C₁-C₆-aryl or C₁-C₆-aryl-C₁-C₆-alkyl
10 can optionally be interrupted singly or multiply, identically or
differently by oxygen, sulfur or nitrogen, or
the group sulfonyl-C₁-C₆-alkyl, sulfonamide, or cyano,
- R³**
- 15 a C₆-C₁₂-aryl, which can optionally be substituted singly or multiply,
identically or differently with halogen, with C₁-C₆-alkyl, C₁-C₃-acyl,
C₁-C₃-alkoxy, cyano, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-
NR⁴R⁵ or with CF₃,
a C₅-C₁₂-heteroaryl, which can optionally be substituted singly or
multiply, identically or differently with chlorine and/or fluorine, with
C₁-C₆-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, cyano, hydroxy, N-(CH₃)₂,
20 CO₂-(C₁-C₃-alkyl), CO-NR⁴R⁵ or with CF₃,
a C₃-C₆-cycloalkyl, which can optionally be substituted singly or
multiply, identically or differently with chlorine and/or fluorine, CF₃,
cyano, C₁-C₃-alkyl, C₁-C₃-acyl, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-
alkyl), CO-NR⁴R⁵ or C₁-C₃-alkoxy,
- R⁴**
- 25 a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted
singly or multiply, identically or differently with C₁-C₃-alkyl, C₁-C₃-
acyl, C₁-C₃-alkoxy or CF₃,
a C₆-C₁₂-aryl, which is optionally substituted singly or multiply,
30 identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-
C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or
a C₁-C₆-alkyl, which can be substituted arbitrarily,

52

- R⁵** a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy or CF₃,
a C₆-C₁₂-aryl, which is optionally substituted singly or multiply,
5 identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or
a C₅-C₁₂-heteroaryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or
10 a C₁-C₆-alkyl, which can be substituted arbitrarily,
- R⁴ and R⁵** together form a 5-8-membered ring, which can contain further heteroatoms, and
- 15 **X** the groups sulfonyl, (CH₂)_n or carbonyl,
- Y** a -(CH₂)_n- or carbonyl group,
- Z** a nitrogen,
- 20 **A** an oxygen or sulfur, and
- n** stands for 0 – 2,

25 as well as their isomers, diastereomers, enantiomers and salts.

3. The compound as claimed in claim 1, where the symbols have the following meanings:

30

R¹ a hydrogen,

53

- R²** a C₃-C₆-cycloalkyl, C₁-C₆-alkyl, CF₃, cyano, bromine, or the group -OCF₃, -SO₂-CH₃,
- 5 R³** a C₆-C₁₂-aryl, which can optionally be substituted singly or multiply, identically or differently with halogen, C₁-C₆-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, cyano, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-NR⁴R⁵ or CF₃,
- 10** a C₅-C₁₂-heteroaryl, which can optionally be substituted singly or multiply, identically or differently with chlorine and/or fluorine, with C₁-C₆-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, cyano, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-NR⁴R⁵ or with CF₃,
- 15** a C₃-C₆-cycloalkyl, which can optionally be substituted singly or multiply, identically or differently with chlorine and/or fluorine, CF₃, cyano, C₁-C₃-alkyl, C₁-C₃-acyl, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-NR⁴R⁵ or C₁-C₃-alkoxy,
- 20 R⁴** a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted singly or multiply, identically or differently with C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy or CF₃,
- 25** a C₆-C₁₂-aryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or a C₅-C₁₂-heteroaryl, which is optionally substituted singly or multiply, identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or a C₁-C₆-alkyl, which can be substituted arbitrarily,
- 30 R⁵** a hydrogen,
- 30 X** a sulfonyl or carbonyl group or -(CH₂)_n,
- Y** a -(CH₂)_n- or carbonyl group,

5A

Z a nitrogen,

A an oxygen or sulfur and

5 n 0 - 2,

as well as their isomers, diastereomers, enantiomers and salts.

4. The compound as claimed in claim 1, where the symbols have the following
10 meanings:

R¹ a hydrogen,

15 R² a C₃-C₆-cycloalkyl, C₁-C₆-alkyl, CF₃, cyano, bromine, or the group
-OCF₃, -SO₂-CH₃ in the para-position,

20 R³ a C₆-C₁₂-aryl, which can optionally be substituted singly or doubly,
identically or differently with halogen, C₁-C₃-alkyl, acetyl, methoxy,
ethoxy, cyano, hydroxy, N-(CH₃)₂, CO₂-(C₁-C₃-alkyl), CO-NHR⁵ or
CF₃,

a C₅-C₁₂-heteroaryl, which can optionally be substituted singly or
doubly, identically or differently with chlorine and/or fluorine, with
C₁-C₃-alkyl, acetyl, methoxy, ethoxy, cyano, hydroxy, N-(CH₃)₂,
CO₂-(C₁-C₃-alkyl), CO-NHR⁵ or with CF₃,

25 a C₃-C₆-cycloalkyl,

R⁴ a hydrogen, a C₃-C₆-cycloalkyl, which is optionally substituted
singly or multiply, identically or differently with C₁-C₃-alkyl, C₁-C₃-
acyl, C₁-C₃-alkoxy or CF₃,

30 a C₆-C₁₂-aryl, which is optionally substituted singly or multiply,
identically or differently with halogen, C₁-C₃-alkyl, C₁-C₃-acyl, C₁-
C₃-alkoxy, N-C₁-C₃-alkyl-C₁-C₃-alkyl, CF₃ or cyano, or

59
60

X a sulfonyl or carbonyl group, or $-(CH_2)_n-$

Y a $-(CH_2)_n-$ or carbonyl group,

Z a nitrogen,

A an oxygen or sulfur, and

n 1 - 2.

as well as their isomers, diastereomers, enantiomers and salts.

7. The compound as claimed in claims 1-6, selected from the group comprising the following compounds:

- (+/-)-5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(2-hydroxypropyl)amide
- (+/-)-5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(2-hydroxymethylethyl)amide
- 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(tetrahydropyran-4-yl)amide
- 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzothiophene-2-carboxylic acid-(2-morpholin-4-yl-ethyl)amide
- 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(tetrahydropyran-4-yl)amide
- 5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(2-morpholin-4-yl-ethyl)amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(3-morpholin-4-yl-propyl)-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-cyclopentyl-amide

60

- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(4-pyridyl)-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(2-methoxy-ethyl)-amide
- 5 - 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-cyclohexyl-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(2-hydroxy-ethyl)-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(2-propen-1-yl)-amide
- 10 - 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(2-acetyl-amino-ethyl)-amide
- 5-(4-tert-Butyl-phenylsulfonylamino)-3-phenyl-benzo[b]thiophene-2-carboxylic acid-(5-hydroxy-4,4-dimethyl-pentyl)-amide
- 15 - (+/-)-5-(4-tert-Butylphenylsulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(2-hydroxypropyl)amide
- (+/-)-5-(4-tert-Butylbenzenesulfonylamino)-3-phenyl-1-benzofuran-2-carboxylic acid-(2-hydroxy-1-methylethyl)amide.

20

8. A medicinal product that contains at least one of the compounds as claimed in claims 1-7.

25 9. The medicinal product as claimed in claim 8, which contains the compound of general Formula 1 at an effective dose.

10. The use of the compound of general Formula 1 as claimed in claims 1-9 for the production of medicinal products for the treatment of diseases that are
30 caused by disturbances in cAMP metabolism.

11. The use of the compound of general Formula 1 as claimed in claims 1-9 for the production of medicinal products for contraception.