



No. 06-089826-00003-0000

Fecha: 2008-06-05 16:35:59 Dep. 2020 NUECREACION
Tra 11 PATENTILYI Eve 379 FASENACIONALI
Act. 329 CIOINFORMACION Folios: 8

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

P2006/000162

SOLICITUD DE:

1

☐

Corrección de Error Material.

☒

Modificación a una Solicitud.

2

SOLICITANTE
(71)

Nombre: PFIZER PRODUCTS INC

Dirección: Eastern Point Road, Groton,
Connecticut 06340, E.U.A.

Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: Estados Unidos de
América

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

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

Teléfono: 601-7700 **Fax:** 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747 Bta
TP 74.295

4

Número de expediente:
06-089.826

5

Descripción de la corrección o modificación solicitada VER PAGINA ADJUNTA

6

Comprobante de pago No. 08-44.026

Fecha 4 de Junio de 2008

7

Anexos

☒

Comprobante de pago de la tasa.

☐

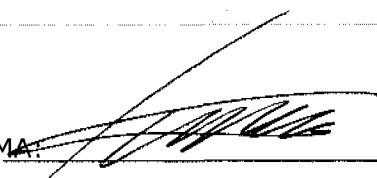
Poderes, si fuere el caso. Documento que soporta la cesión de Derechos.

☐

Documento que acredita la existencia y representación legal de las partes; cuando sean personas jurídicas.

8

NOMBRE: CARLOS R. OLARTE

FIRMA: 

C.C. 79.782.747 Bta T.P. 74.295

346
344

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-089826- -00003-0000

Fecha: 2008-06-05 16:35:59 Dep. 2020 NUECLACIONI
Tra. 11 PATENTEIYII Lve. 379 FASL NACIONALII
Act. 329 CTOINFORMACION Folios: 8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176099-2

RECIBO OFICIAL DE CAJA : 08 - 44.026
FECHA : JUNIO 4 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	NO. PAGO	FECHA PGO	MON. PAGO
CLARTE RAISREX	CONSIGNACION	BANCO DE BOGOTA	002754387	338833	03/06/2008	4,557,000.00

***** D E N O T A C I O N *****

CANT. REENTISTADO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	103,000.00
	TOTAL :	103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

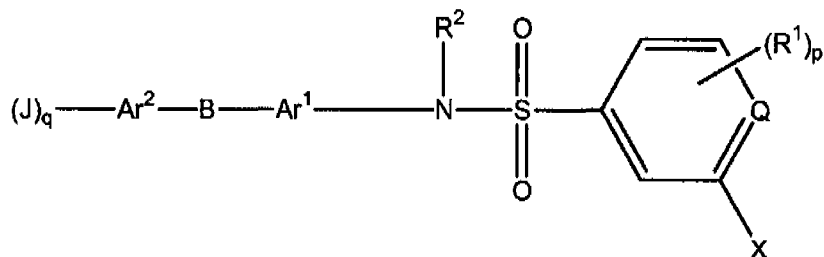
ANEXO EXPLICATIVO DE LAS MODIFICACIONES

El presente Capítulo Reivindicatorio reemplaza en su totalidad al Capítulo Modificado presentado con fecha 17 de octubre de 2006 y que contenía algunos errores involuntarios.

En el presente Capítulo Reivindicatorio se eliminó la definición de los sustituyentes R^3 y R^5 de la nueva Reivindicación 1 y se incorporaron las nuevas Reivindicaciones 11 y 12 dirigidas a una modalidad específica de los compuestos de Fórmula I.

CAPÍTULO REIVINDICATORIO MODIFICADO

1. Un compuesto que tiene Fórmula I



Fórmula I

o una sal farmacéuticamente aceptable de dicho compuesto, en el que

Q es carbono;

cada R^1 es independientemente hidrógeno, halo, alquilo (C_1 - C_5) opcionalmente sustituido con uno o más halo o con alcoxi (C_1 - C_3), alcoxi (C_1 - C_5) opcionalmente sustituido con uno a once halo, alquiltio (C_1 - C_5) opcionalmente sustituido con uno o más halo, o R^1 junto con los dos átomos de carbono adyacentes forma un anillo carbocíclico C_5 - C_6 de cinco o seis miembros condensado, totalmente saturado, parcialmente insaturado o totalmente insaturado en el que cada carbono en la cadena de carbono puede reemplazarse opcionalmente por un heteroátomo seleccionado entre oxígeno y azufre;

R^2 es hidrógeno o alquilo (C_1 - C_5) opcionalmente sustituido con alcoxi C_1 - C_3 ;

X es $-COOR^4$;

R^4 es H, alquilo (C_1 - C_4); bencilo o *p*-nitrobencilo;

Ar^1 es fenilo o fenilo condensado a un miembro seleccionado entre tiazolilo, oxazolilo, donde Ar^1 está opcionalmente mono- o di-sustituido independientemente con: halo, alquilo (C_1 - C_3) opcionalmente sustituido con uno a nueve halo o alcoxi (C_1 - C_3) opcionalmente sustituido con uno a nueve halo o alquiltio (C_1 - C_3) opcionalmente sustituido con uno a nueve halo;

B es un enlace, $-L-(CY_2)_n-$ o $-(CY_2)_n-L-$ y L es O o S, cada Y es independientemente hidrógeno o alquilo (C_1 - C_3) y n es 0, 1 o 2;

Ar^2 es fenilo o fenilo condensado a un anillo seleccionado entre el grupo compuesto por: fenilo, piridinilo, tienilo, tiazolilo, oxazolilo, e imidazolilo.

cada J es independientemente hidrógeno, hidroxi, halo, alquilo (C_1-C_8) opcionalmente sustituido con de uno a once halo, alcoxi (C_1-C_8) opcionalmente sustituido con uno a once halo, alquiltio (C_1-C_8) opcionalmente sustituido con uno a once halo, cicloalquilo (C_3-C_7), cicloalcoxi (C_3-C_7), cicloalquiltio (C_3-C_7) o fenilo opcionalmente sustituido con uno a cuatro sustituyentes seleccionados entre el grupo compuesto por: halo, alquilo (C_1-C_3) opcionalmente sustituido con uno a cinco halo, alcoxi (C_1-C_3) opcionalmente sustituido con uno a cinco halo, alquiltio (C_1-C_3) opcionalmente sustituido con uno a cinco halo;

p y q son cada uno independientemente 0, 1, 2 ó 3; y

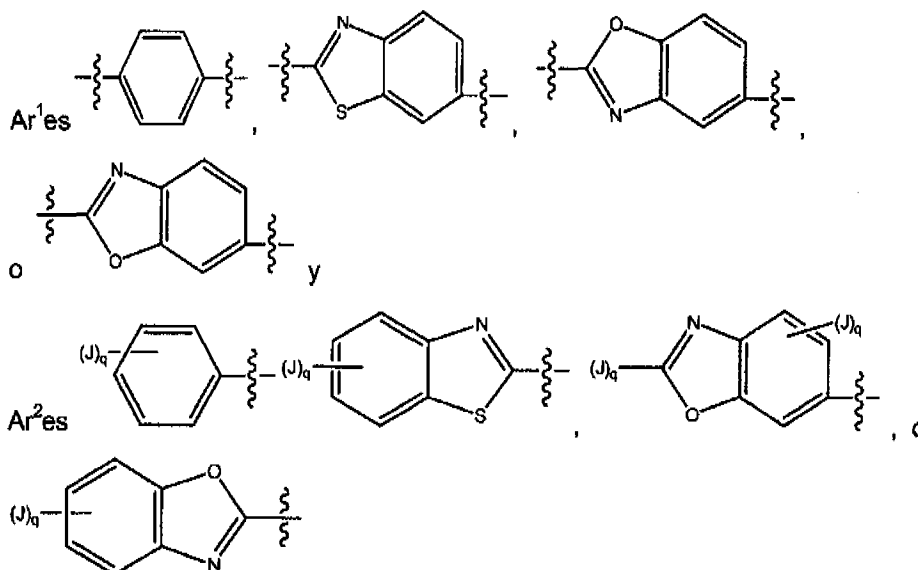
con las condiciones:

a) si Ar^1 es fenilo, B es un enlace, Ar^2 es un enlace o fenilo y X es $-COOH$, entonces q es diferente de 0 y J es diferente de hidrógeno, halo, alquilo (C_1-C_8) o fenilo no sustituido;

b) si Ar^1 es fenilo, B no es un enlace, Ar^2 es fenilo y X es $-COOR^4$ entonces B se une a Ar^1 en posición para a NR^2 ; y

c) si B es O, S, SO, NH, CO, CH_2 o SO_2 entonces R^1 no es H.

2. Un compuesto de acuerdo con la reivindicación 1, en el que



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3. Un compuesto de acuerdo con la reivindicación 2, en el que q es 1 ó 2 y cada J es independientemente halo, alquilo (C_1-C_3) opcionalmente sustituido con uno a tres halo, o alcoxi (C_1-C_3) opcionalmente sustituido con uno a tres halo.
4. Un compuesto de acuerdo con la reivindicación 3 en el que p es 1 y R^4 es H o alquilo (C_1-C_3).
5. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-4, en el que L es S, n es 1, y halo es fluoro.
6. El compuesto Ácido 5-[4-(4-etil-bencilsulfanil)-fenilsulfamoi]l]-2-metil-benzoico, o una sal farmacéuticamente aceptable de dicho compuesto.
7. Un compuesto de cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de dicho compuesto, para tratar dislipidemia, obesidad, afección por sobrepeso, hipertrigliceridemia, hiperlipidemia, hipoalfalipoproteinemia, síndrome metabólico, diabetes mellitus (Tipo I y/o Tipo II), hiperinsulinemia, tolerancia alterada a la glucosa, resistencia a insulina, complicaciones diabéticas, aterosclerosis, hipertensión, enfermedad cardíaca coronaria, hipercolesterolemia, inflamación, osteoporosis, trombosis, enfermedad vascular periférica, disfunción cognitiva o insuficiencia cardíaca congestiva en un mamífero.
8. Un compuesto de cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable de dicho compuesto, para tratar el balance energético negativo en rumiantes.
9. Una combinación farmacéutica que comprende: una cantidad terapéuticamente eficaz de una composición que comprende:

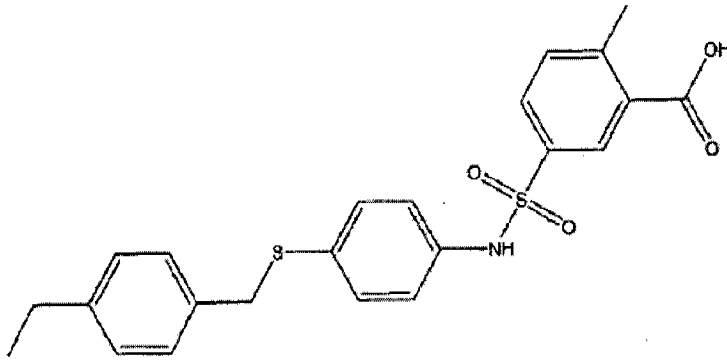
un primer compuesto, siendo dicho primer compuesto un compuesto de cualquiera de las reivindicaciones 1-6, o una sal farmacéuticamente aceptable de dicho compuesto;

un segundo compuesto, siendo dicho segundo compuesto un inhibidor de lipasa, un inhibidor de HMG-CoA reductasa, un inhibidor de HMG-CoA sintasa, un inhibidor de expresión génica de HMG-CoA reductasa, un inhibidor de expresión génica de HMG-CoA sintasa, un inhibidor de la secreción de MTP/Apo B, un inhibidor de CETP, un inhibidor de la absorción de ácidos biliares, un inhibidor de la absorción de colesterol, un inhibidor de la síntesis de colesterol, un inhibidor de escualeno sintetasa, un inhibidor de escualeno epoxidasa, un inhibidor de escualeno ciclasa, un inhibidor de escualeno epoxidasa/escualeno ciclasa combinadas, un fibrato, niacina, una combinación de niacina y lovastatina, una resina de intercambio iónico, un antioxidante, un inhibidor de ACAT, un secuestrador de ácidos biliares, o un profármaco de dicho compuesto o una sal farmacéuticamente aceptable de dicho compuesto o profarmaco; y un portador, vehículo o diluyente farmacéuticamente aceptable.

10. La composición de combinación de la reivindicación 9, en la que el segundo compuesto es rosuvastatina, rivastatina, pitavastatina, lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina, cerivastatina o éster etílico del ácido [2R,4S] 4-[(3,5-bis-trifluorometil-bencil)-metoxycarbonil-amino]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolin-1-carboxílico o un profármaco de dicho compuesto o una sal farmacéuticamente aceptable de dicho compuesto o profármaco.

11. Un compuesto libre de ácido de un compuesto que presenta la siguiente estructura:

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o una sal farmacéuticamente aceptable del mismo.

12. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva del compuesto de las Reivindicaciones 6 u 11 y un portador, vehículo o diluyente farmacéuticamente aceptable.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
SISTEMA DE TRAMITES-CONSULTA DE TRÁMITES*

Viernes 21 de Agosto de 2009



Datos del Trámite (PENDIENTE)

Radicación: Año: 2006 Número: 89826 Ctrl: Cons Rad: 2 Secto Even: 0

Tipo Trámite: 11 PAT- PATENTE DE INVENCION CAPITULOS I Y II

Tipo Evento: 379. FASE NACIONAL INCLUIDO CAPITULO II

Tipo Actuación: 638. PETICION DE EXAMEN

Dependencia Origen: 2020. DIVISION DE NUEVAS CREACIONES

Solicitante/Destinatario: CARLOS REYNALDO OLARTE GARCIA Tipo: Contenido

Identificación: CC. CEDULA DE CIUDADANIA Número: 79782747.0

Dirección: AVENIDA 22 NO 10-62 PISO 6 BOGOTA D.C. COLOMBIA

Tipo de Radicación: EN ENTRADA

Fecha de Radicación: Día: 13 Mes: Febrero Año: 2007 17:43:30

Quié: fecha

Observaciones:

Fotos: 2

Entrega: VENTANILLA

Otros Datos
[Documentos] [Recibos] [Ver Documento]

Nueva Consulta

Salir

Registro: 3 / 4

Información adicional en la Oficina de Sistemas

Debe quedar el original?

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
SISTEMA DE TRAMITES-CONSULTA DE RECIBOS

Viernes 21 de Agosto de 2009

Recibos de pago del Expediente Año: 6 Número: 89826 Ctrl: Cons Rad: 2

Salir

Numero de Recibo	Fecha	Parasico	Concepto	Tipo	Numero	Cuenta	Cantidad	Valor	Estado
7	10645	06/02/2007	SOLICITUDES	PTC CAP-II EXAMEN DE PATENTIBILIDAD DE INVENCION	67477377	050-00110-6	1	202000.0	U

Información adicional en la Oficina de Sistemas

354
351

355 352

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

202012

Bogotá, D.C., 24-nov-2009

Apoderado: Carlos Reinaldo Olarte García.

ASUNTO	Radicación	06-89826
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	22-13910
	Folios	

Patente de Invención ☒

Vía PCT (fase nacional) ☒ Cap.I ☐ Cap. II ☒

No. Sol. Internacional	PCT/IB2005/000526
Fecha de Presentación Internal.	28-feb-2005

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:

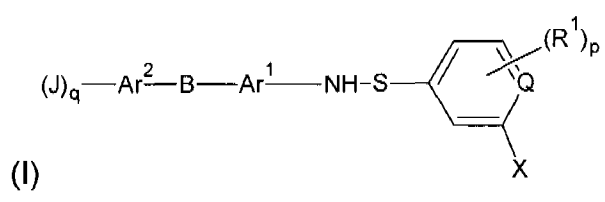
1. Documentos estudiados

- | | | | |
|------|--------------------------|---|--|
| 1.1. | <u>Descripción:</u> | Folios: 92 a 303 | Como se radicó inicialmente. |
| 1.2. | <u>Reivindicaciones:</u> | Folios 304 a 312
Folios 346 a 349 | Como se radicó inicialmente.
Modificaciones realizadas en la fase nacional. |
| 1.3. | <u>Dibujos:</u> | Folios 314 | Como se radicó inicialmente. |
| 1.4. | <u>Prioridad:</u> | Folio 1: US 60/552.114; 10-mar-2004
US 11/012.139; 16-dic-2004 | |

2. Objeto de la invención

Título de la solicitud: COMPUESTOS DE HETEROARIL- Y FENILSIFAMOILO SUSTITUIDOS.

El objeto de la invención se refiere a los derivados de aril- aril/heteroaril sulfamoil, de fórmula (I) que presentan actividad como agonistas del receptor activador del proliferador de peroxisoma:



Reivindicaciones 1-8: un compuesto de la fórmula (I);
Reivindicación 9-10: combinación
Reivindicación 11: Compuesto
Reivindicación 12: Composición que comprende los compuestos.

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.):
C07D311/21, 323/49,311/44, C07D213/75, 231/12, 271/06, 285/00, 263/54,
277/62, 235/18, 333/58, 307/79, 215/12, A61K31/18,31/33; A61P7/00,9/00.

3. De la solicitud de Patente:

3.1. Reivindicaciones (artículo 30 D 486 de la C.A.N.)

- Las reivindicaciones 7 y 8 no son claras, porque el encabezado no es consecuente con el texto de la reivindicación, se encabeza como compuesto y el texto de la reivindicación no contiene ninguna característica de compuesto, se hace referencia es a método terapéutico.
- La reivindicación 9 hace referencia a combinación la cual no está definida, el segundo componente esta denominado solamente como un efecto que se desea tenga cualquier compuesto.
- La reivindicación 10 hace referencia a un profármaco de un segundo componente que no existe tal profármaco, ni en la descripción ni en el estado de la técnica, por lo tanto esa extrapolación es puramente especulativa y no tiene sustento en la descripción.

Por lo tanto las reivindicaciones no cumplen con el requisito de definición, claridad, concisión y sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica es la fecha de presentación de la solicitud de la cual se reclama prioridad,10-mar-2004

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la materia reclamada en la solicitud encontrándose los siguientes documentos más relevantes:

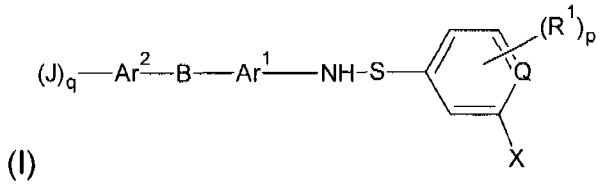
Nº	Documento	Título	Fecha de publicación*
D1	CH558789	Verfahren zur herstellung der neuen 5-(2-aminophenyl-sulfamoyl)-4-chlor-N-furfurylanthranilsäure und ihrer salze.	14-feb-1975

D2	US3.658.990	Diuretic Compositions	25-abr-1972
D3	US3.806.542	5-Arylsulphamoil-antranilic acids	23-abr-1974
D4	US3.812.104	5-Arylsulphamoil-antranilic acids	21-may-1974
D5	US3.992.441	Sulfaoilbenzoic acids	16-nov-1976
D6	EP0068408	Antiviral compositions and a method for treating virus diseases	05-ene-1983
D7	US5.413.892	Electrstatic image developing toner	09-may-1995
D8	GB2090136	Antiviral compositions containing sulphonamide derivatives	07-jul-1982
D9	EP0068407	Aminosulphonylbenzoic acid derivatives	05-ene-1983
D10	WO0174786	Heterobiarylsulphonamides and their use as PDE 7 inhibitors	11-oct-2001
D11	GB2378179	Aromatic sulphonamides and their use in treating bacterial diaseases	05-feb-2003
D12	US20030187001	4-aminopyrrolopyrimidines as kinase inhibitors	02-oct-2003

5. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

5.1 Novedad (artículo 16 D486 de la C.A.N.)

La solicitud de patente de invención se refiere a los derivados de aril- aril/heteroaril sulfamoil, de fórmula (I):



-D1 enseña derivados fenilsulfamoil-aril sustituidos que caen bajo el alcance de los compuestos reclamados por la presente solicitud con la formula Markush (I), véase toda la anterioridad [pag 1,2,3]

-Las anterioridades D2-D4 enseñan derivados de fenilsulfamoil-acido benzoico y formulaciones que los comprenden, que caen dentro del alcance de la materia que se reclama en la solicitud. (ver D1 todo el documento, especialmente ejemplos 1,3,5,6,14,15,23,27; D3, todo el documento especialmente los ejemplos 1,4,5,6,8,14,15,27, las reivindicaciones 3,6; D4 todo el documento especialmente los ejemplos 1,3,5,6,8,14,15,27,37).

-D5 describe compuestos derivados del ácido sulfamoilbenzoico, que caen bajo el alcance de los compuestos reclamados en la solicitud en estudio con la formula genérica (I). (vér especialmente los ejemplos 38,51,53,56 y la reivindicación 8).

-D6 describe compuestos derivados de arilsulfamoil esteres, que caen bajo el alcance de los compuestos reclamados en la solicitud en estudio con la formula genérica (I). (ver especialmente ejemplos 22 y 23, junto con las tablas 2 y 10).

- En D7 se encuentra descrito el compuesto #23 que cae bajo el alcance de los compuestos reclamados en la solicitud en estudio con la formula genérica (I).
- D8 describe derivados de fenilsulfonamidas que caen bajo el alcance de los compuestos reclamados en la solicitud en estudio con la formula genérica (I). (ver especialmente los ejemplos 13, 25,26; tabla 3).
- D9 describe compuestos derivados de arilsulfamoil esteress, que caen bajo el alcance de los compuestos reclamados en la solicitud en estudio con la formula genérica (I). (ver especialmente ejemplos 3 y 15).
- D10 Describe compuestos derivados de heterobiarilsulfonamides que caen bajo el alcance de los compuestos reclamados en la solicitud en estudio con la formula genérica (I). (ver especialmente ejemplos 1,2,3,5,6,8,10).
- D11describe compuestos derivados de arylsulamidass-aril sustituidass, que caen bajo el alcance de los compuestos reclamados en la solicitud en estudio con la formula genérica (I). (ver especialmente pags. 1, 12-18,20-22, 28-30,33-49, 52, 54, 55, 59, 61, 62].
- D12 describe compuestos derivados de 4-aminopirrolopirimidines, que caen bajo el alcance de los compuestos reclamados en la solicitud en estudio con la formula genérica (I). (ver especialmente pags 64-66).
- El elemento característico de las reivindicaciones composiciones es la estructura N-[4-(aril)fenil]benzensulfonamida con los sustituyentes como se reclama genéricamente, ya era conocido en D1-D12; por lo cual los compuestos las composiciones de las reivindicaciones no pueden considerarse nuevas, no cumplen con el requisito exigido en el artículo 16 D486 de la C.A.N.

5. Conclusión:

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

Una solicitud que no posee novedad obviamente no va a presentar nivel inventivo.

Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	1-12	Novedad
D2	1-12	Novedad
D3	1-12	Novedad
D4	1-12	Novedad
D5	1-12	Novedad
D6	1-12	Novedad
D7	1-12	Novedad
D8	1-12	Novedad
D9	1-12	Novedad
D10	1-12	Novedad
D11	1-12	Novedad
D12	1-12	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados

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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

CONCEPTO TÉCNICO No. 4104 | EXAMINADOR TÉCNICO Cód. N°202012



(19)

CH PATENTSCHRIFT



558 789

- (21) Gesuchsnummer: 6797/74
- (61) Zusatz zu:
- (62) Teilgesuch von: 12215/71
- (22) Anmeldungsdatum: 19. 8. 1971, 17 h
- (13) (32) (31) Priorität:

Patent erteilt: 31. 12. 1974

- (45) Patentschrift veröffentlicht: 14. 2. 1975

- (54) Titel: **Verfahren zur Herstellung der neuen 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure und ihrer Salze**

- (73) Inhaber: CIBA-GEIGY AG, Basel

- (74) Vertreter:

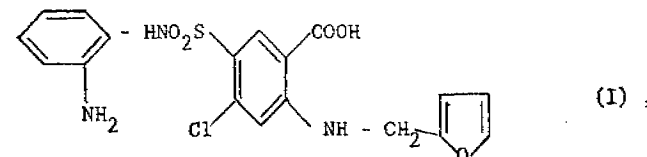
- (72) Erfinder: Lincoln Harvey Werner, Summit (N. J., USA)

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Die vorliegende Erfindung betrifft ein Verfahren zur Herstellung der neuen 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure der Formel



sowie von Salzen, z. B. pharmazeutisch verwendbaren Salzen, wie entsprechenden Metallsalzen, z. B. Alkalimetall- oder Erdalkalimetall-, Ammoniumsalzen oder Säureadditionssalzen davon.

Salze sind insbesondere die Natrium-, Kalium-, Magnesium- oder Calciumsalze, oder Ammoniumsalze mit Ammoniak oder Aminen, wie Mono-, Di- oder Triniederalkylaminen, z. B. Mono-, Di- oder Trimethylamin oder Mono-, Di- oder Triäthylamin. Säureadditionssalze sind solche mit anorganischen oder organischen Säuren, wie Mineralsäuren, z. B. Chlorwasserstoff-, Bromwasserstoff-, Schwefel-, Phosphor-, Salpeter- oder Perchlorsäure, oder aliphatischen, aromatischen oder araliphatischen Carbon- oder Sulfonsäuren, z. B. Ameisen-, Essig-, Propion-, Bernstein-, Glykol-, Milch-, Apfel-, Wein-, Zitronen-, Ascorbin-, Malein-, Hydroxymalein-, Brenztrauben-, Phenyllessig-, Benzoe-, 4-Aminobenzoe-, Anthranil-, 4-Hydroxybenzoe-, Salicyl-, 4-Aminosalicyl-, Embon-, Nicotin-, Methansulfon-, Äthansulfon-, Hydroxyäthansulfon-, 1,2-Äthandisulfon-, Halogenbenzolsulfon-, Toluolsulfon-, Naphthalinsulfon- oder Sulfanilsäure.

Die Verbindung der vorliegenden Erfindung und ihre Salze weisen wertvolle pharmazeutische Eigenschaften auf. In erster Linie zeigen sie diuretische, natriuretische und chloruretische Wirkungen mit raschem Wirkungseintritt und hohen Urin-, aber niedriger Kaliumausscheidungsraten. Diese Wirkung kann an Testtieren nachgewiesen werden, wobei man Säugetiere, z. B. Ratten oder Hunde, als Testobjekte verwendet. Die Versuche können z. B. so durchgeführt werden, dass man die Testsubstanz in Gelatine-Kapseln Hunden oder in Form von wässrigen Lösungen oder Suspensionen mittels Magensonde an Ratten verabreicht, wobei man Dosen von etwa 0,0001 bis etwa 0,1 g/kg pro Tag, vorzugsweise von etwa 0,0003 bis etwa 0,05 g/kg pro Tag und in erster Linie von etwa 0,001 bis etwa 0,005 g/kg pro Tag verwendet. Gleichzeitig können die Testtiere enteral oder parenteral verschiedene Salzlösungen erhalten, wobei man z. B. verschiedene Mengen, einem Hund mittlerer Grösse z. B. 100 ml, einer 0,9%igen physiologischen Natriumchloridlösung subkutan verabreicht. Der Urin wird mit oder ohne Katheter, z. B. in zweistündigen Intervallen, gesammelt und sein Volumen sowie der Natrium-, Kalium- oder Chloridgehalt gemessen und mit dem Urin von unbehandelten oder mit einer Salzlösung behandelten Tieren verglichen. Aufgrund der Testresultate erweisen sich die Verbindung der vorliegenden Erfindung und ihre Salze als quantitativ stärker wirksam als die 4-Chlor-N-furfuryl-5-sulfamoyl-anthranilsäure. Ferner sind sie lang wirksame Diuretika und erhöhen die Kaliumexkretion nur in einem sehr niedrigen und engen Dosenbereich. Die neue Verbindung und ihre Salze sind starke diuretische, natriuretische und chloruretische Verbindungen, die zur Behandlung von Ödemen und Hypertonie verwendet werden können.

Die Verbindung und ihre Salze werden erfindungsgemäss hergestellt, indem man in einer 4-Chlor-N-furfuryl-5-(2-acylamino-phenyl-sulfamoyl)-anthranilsäure oder in einem

Ester oder Salz davon die Acylaminogruppe durch Hydrolyse 15 oder Alkoholyse in die primäre Aminogruppe überführt und einen gegebenenfalls erhaltenen Ester hydrolysiert. Wenn erwünscht, kann ein erhaltenes Salz in die freie Verbindung der Formel I oder in ein anderes Salz oder die erhaltene freie Verbindung der Formel I in ein Salz übergeführt werden.

20 Ester von Ausgangsstoffen sind Niederalkyl-, z. B. Methyl-, Äthyl-, n-Propyl-, Isopropyl-, n-Butyl- oder tert.-Butyl-, oder Aryl-niederalkyl-, z. B. Benzyl- oder 1- oder 2-Phenyläthyl-ester. Salze sind die oben genannten, insbesondere die Metall- oder Ammoniumsalze.

25 Der Acylrest von Ausgangsstoffen ist insbesondere derjenige von organischen, insbesondere aliphatischen, aromatischen oder araliphatischen Carbonsäuren, wie Niederalkancarbonsäuren, z. B. Essig-, Propion-, Butter- oder Pivalin-, ferner Niederalkencarbon-, z. B. Acryl- oder Methacryl-, oder 30 Benzoe-, Phenyl-niederalkancarbonsäuren oder Phenyl-niederalkencarbon-, z. B. Benzoe-, Phenyllessig- oder Zimtsäuren, ferner von Kohlensäurehalbestern, wie -niederalkylhalbestern. Bevorzugt sind Ausgangsstoffe, in welchen die Acylaminogruppe für Niederalkanoilamino, z. B. Acetylamino, oder 35 Niederalkoxycarbonylamino, z. B. Äthoxycarbonylamino, steht. Diese Acylausgangsstoffe werden durch Hydrolyse oder Alkoholyse in die Verbindung der Formel I übergeführt, wobei man z. B. eine wässrige oder alkoholische Base, wie ein wässriges Alkalimetall-, z. B. Natrium- oder Kaliumhydroxyd 40 oder -carbonat, oder ein quaternäres Ammoniumhydroxyd, z. B. Trimethylbenzylammoniumhydroxyd, in Gegenwart von Wasser, oder ein Alkalimetallniederalkoxyd, z. B. Natrium- oder Kaliummethoxyd, -äthoxyd, -isopropoxyd oder -tert.-butoxyd, in Gegenwart eines Niederalkanols, z. B. Methanol, 45 Äthanol, Isopropanol oder tert.-Butanol, als geeignete Reagentien verwendet.

Verfahrensgemäss erhältliche Ester werden in üblicher Weise hydrolysiert, wobei man z. B. basische Mittel, wie wässrige Alkalimetall- oder Erdalkalimetallhydroxyde oder quaternäre Ammoniumhydroxyde, vorzugsweise die oben erwähnten, verwendet.

Die Verbindung der vorliegenden Erfindung kann je nach den Bedingungen ihrer Herstellung in freier Form oder in Form ihrer Salze erhalten werden; die Salze werden von der vorliegenden Erfindung ebenfalls umfasst. Erhaltene Salze 55 können nach an sich bekannten Methoden in die freie Verbindung übergeführt werden, Säureadditionssalze z. B. durch Behandeln mit alkalischen Mitteln, wie Alkalimetallhydroxyden oder -carbonaten, oder Anionenaustauschern, und Metall- oder Ammoniumsalze durch Behandeln mit Säuren oder Kationenaustauschern. Die freie Verbindung kann aus ihren Salzen in einem pH-Bereich von etwa 4 bis etwa 7 isoliert werden. Im Hinblick auf die obigen engen Beziehungen zwischen der Verbindung in freier Form und in Form ihrer Salze sind 60 im Vorausgegangenen und nachfolgend unter freien Verbindungen und Salzen sinn- und zweckgemäss gegebenenfalls auch die entsprechenden Salze bzw. freien Verbindungen zu verstehen.

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Die oben beschriebenen Reaktionen werden nach an sich bekannten Methoden, in Ab- oder Anwesenheit von Verdünnungsmitteln, vorzugsweise solchen, die gegenüber den Reaktionsteilnehmern inert sind und diese zu lösen vermögen, von Katalysatoren und/oder, wenn notwendig, in Inertgas, z. B. Stickstoffatmosphären, bei tiefen Temperaturen unter Kühlen, bei Raumtemperaturen oder vorzugsweise bei erhöhten Temperaturen unter Erwärmen und/oder unter atmosphärischem oder erhöhtem Druck durchgeführt.

Das Verfahren umfasst auch diejenigen Ausführungsformen, wonach ein Ausgangsstoff in Form eines unter den Reaktionsbedingungen erhältlichen rohen Reaktionsgemisches oder in Form eines der genannten funktionellen Derivate verwendet wird.

Die Ausgangsstoffe können in an sich bekannter Weise hergestellt werden. So kann man, z. B. eine 4-Chlor-2-halogenbenzoesäure mit Chlorsulfonsäure umsetzen, wobei man die entsprechende 4-Chlor-5-chlorsulfonyl-2-halogenbenzoesäure erhält. Diese oder ein Ester davon wird dann mit einem N-Monosulfonyl-derivat des o-Phenylendiamins umgesetzt. Einen Ester kann man aus der entsprechenden Säure nach an sich bekannten Methoden bilden. Die erhaltene 5-(2-Acetylaminophenyl-sulfamoyl)-4-chlor-2-halogenbenzoesäure oder ein Ester davon kann man mit Furfurylamin umsetzen und so das gewünschte Ausgangsmaterial erhalten.

Die pharmakologisch verwendbaren Verbindungen der vorliegenden Erfindung können z. B. zur Herstellung von pharmazeutischen Präparaten verwendet werden, welche eine wirksame Menge der Aktivsubstanz zusammen oder im Gemisch mit anorganischen oder organischen, festen oder flüssigen, pharmazeutisch verwendbaren Trägerstoffen enthalten, die sich zur enteralen oder parenteralen Verabreichung eignen.

Die Temperaturen sind in den folgenden Beispielen in Celsiusgraden angegeben.

Beispiel 1

Ein Gemisch von 15 g 5-(2-Acetylaminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure und 90 ml einer 2-n. wässrigen Natriumhydroxyd-Lösung wird während 2½ Stunden unter einer Stickstoffatmosphäre am Rückfluss gekocht, gekühlt und mit Eisessig angesäuert. Das feste Material wird abfiltriert, mit Wasser gewaschen und aus wässrigem Äthanol umkristallisiert; das erhaltene Gemisch besteht aus gleichen Teilen des Natriumsalzes der 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure und der freien 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure, das bei 246–248° schmilzt.

Das Ausgangsmaterial kann wie folgt hergestellt werden: Eine Lösung von 50 g N-Acetyl-2-aminoanilin in 100 ml Dimethylformamid wird bei 20° portionenweise mit 30 g 2,4-Dichlor-5-chlorsulfonyl-benzoesäure versetzt. Das Reaktionsgemisch wird während 2 Stunden auf 40° erwärmt und dann unter vermindertem Druck eingedampft; der Rückstand wird auf 500 ml Wasser und 7 ml konzentrierte Salzsäure ausgegossen. Das feste Material wird abfiltriert, mit Wasser und verdünnter Salzsäure gewaschen und mit wässrigem Äthanol trituriert. Man erhält so die 5-(2-Acetylaminophenyl-sulfamoyl)-2,4-dichlor-benzoesäure, F. 222–225°.

Ein Gemisch von 30 g 5-(2-Acetylaminophenyl-

sulfamoyl)-2,4-dichlor-Benzoesäure, 30 g Furfurylamin und 75 ml 2-Methoxyäthanol wird während 4 Stunden unter einer Stickstoffatmosphäre am Rückfluss gekocht, dann unter vermindertem Druck auf die Hälfte des Volumens eingeeengt und unter Rühren auf 250 ml 2n Salzsäure ausgegossen. Der erhaltene Niederschlag wird abfiltriert, mit Wasser gewaschen und mit einem 1:1-Gemisch von Äthanol und Wasser bei 70°, dann mit 95%igem Äthanol trituriert; man erhält so die 5-(2-Acetylaminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure, F. 221–225°.

Beispiel 2

Eine warme Lösung von 1 g 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure in 100 ml Essigsäureäthylester wird mit einer Lösung von Chlorwasserstoff in Essigsäureäthylester angesäuert. Der nach dem Abkühlen erhaltene Niederschlag wird abfiltriert und mit Essigsäureäthylester gewaschen und ergibt das 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure-hydrochlorid, F. 208° (mit Zersetzen).

Beispiel 3

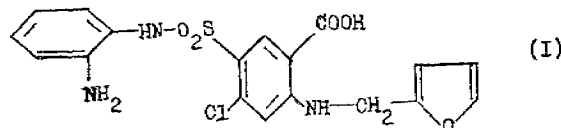
Ein Gemisch von 43,8 g 5-(2-Acetylaminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure, 250 ml einer 2n wässrigen Natriumhydroxyd-Lösung und 4,9 g eines Aktivkohlepräparats wird während 10 Minuten bei 50° und unter einer Stickstoffatmosphäre gerührt, dann filtriert und der Filtrückstand mit 45 ml einer 2n wässrigen Natriumhydroxyd-Lösung gewaschen. Das Filtrat wird während 7 Stunden unter einer Stickstoffatmosphäre am Rückfluss gekocht, während 16 Stunden bei Raumtemperatur gerührt und wiederum zum Rückfluss erhitzt. Man gibt 47,5 ml Eisessig zu, kühlt das Gemisch auf 20° und rührt während einer Stunde. Die entstandene Suspension wird filtriert; der Filtrückstand wird mit 25 ml Wasser gewaschen und während 2½ Stunden in 200 ml Wasser, enthaltend 10 ml Eisessig, gerührt. Das Gemisch wird filtriert; der Filtrückstand wird zweimal mit 25 ml Wasser gewaschen, getrocknet und in 270 ml siedendem Äthanol aufgenommen. Man filtriert die heisse Lösung, kühlt das Filtrat langsam, rührt während 16 Stunden bei 0° und filtriert die entstandene Suspension. Man erhält so die 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure, F. 219–221° (mit Zersetzen).

Beispiel 4

Ein Gemisch von 46 g 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure-hydrochlorid, 110 ml einer 2n wässrigen Natriumhydroxyd-Lösung und 100 ml Wasser wird so lange auf 50–60° erwärmt, bis vollständige Lösung eintritt. Die Lösung wird filtriert und das Filtrat konzentriert, gekühlt und mit einigen Kristallen des vorher hergestellten Produkts angeimpft. Man lässt bei etwa 4° stehen, filtriert den Niederschlag ab, wäscht mit einer kleinen Menge Eiswasser und Isopropanol und erhält so das Natriumsalz der 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure, F. 190° (mit Zersetzen).

PATENTANSPRUCH

Verfahren zur Herstellung von 5-(2-Aminophenyl-sulfamoyl)-4-chlor-N-furfuryl-anthranilsäure der Formel



oder Salzen davon, dadurch gekennzeichnet, dass man in einer 4-Chlor-N-furfuryl-5-(2-Acylamino-phenyl-sulfamoyl)-anthranilsäure oder in einem Ester oder Salz davon die Acylaminogruppe durch Hydrolyse oder Alkoholyse in die primäre Aminogruppe überführt, und einen gegebenenfalls erhaltenen Ester hydrolysiert.

UNTERANSPRÜCHE

1. Verfahren nach Patentanspruch, dadurch gekennzeichnet, dass man ein erhaltenes Salz in die freie Verbindung der Formel I oder in ein anderes Salz oder die erhaltene freie Verbindung der Formel I in ein Salz überführt.

2. Verfahren nach Patentanspruch, dadurch gekennzeichnet, dass man Ausgangsstoffe, worin der Acylrest der primären Aminogruppe den Acylrest einer aliphatischen, aromatischen oder araliphatischen Carbonsäure oder eines Kohlen-säurehalbesters darstellt, verwendet.

3. Verfahren nach Patentanspruch, dadurch gekennzeichnet, dass man die Hydrolyse oder Alkoholyse durch Behandeln mit einer wässrigen oder alkoholischen Base durchführt.

4. Verfahren nach Patentanspruch oder einem der Unter-ansprüche 1–3, dadurch gekennzeichnet, dass man Ausgangsstoffe in Form eines unter den Reaktionsbedingungen erhältlichen rohen Reaktionsgemisches einsetzt.

Anmerkung des Eidg. Amtes für geistiges Eigentum:

Sollten Teile der Beschreibung mit der im Patentanspruch gegebenen Definition der Erfindung nicht in Einklang stehen, so sei daran erinnert, dass gemäss Art. 51 des Patentgesetzes der Patentanspruch für den sachlichen Geltungsbereich des Patentes massgebend ist.

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DIURETIC COMPOSITIONS

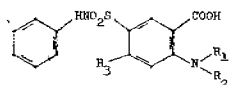
Lincoln Harvey Werner, Summit, N.J., assignor to Ciba-Geigy Corporation, Ardsley, N.Y.
No Drawing. Continuation-in-part of application Ser. No. 675,330, Oct. 16, 1967, which is a continuation-in-part of application Ser. No. 598,980, Dec. 5, 1966. This application June 10, 1969, Ser. No. 832,029
Int. Cl. A61k 27/00

U.S. Cl. 424-228

3 Claims

ABSTRACT OF THE DISCLOSURE

5-arylsulfamyl-4-halo-anthranilic acids, e.g. those of the formula



R₁=aliphatic or araliphatic radical

R₂=H or R₃

R₃=Cl or Br

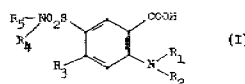
and functional derivatives thereof, exhibit diuretic effects.

CROSS-REFERENCES TO RELATED APPLICATIONS

This is a continuation-in-part of application Ser. No. 675,330, filed Oct. 16, 1967, which in turn is a continuation-in-part of application Ser. No. 598,980, filed Dec. 5, 1966, both are now abandoned.

SUMMARY OF THE INVENTION

The present invention concerns and has for its object the provision of new 5-arylsulfamyl-4-halo-anthranilic acids and their therapeutically acceptable derivatives, more particularly those of Formula I,



in which each of R₁, R₂ and R₃ stands for an aliphatic or araliphatic radical, R₂ and R₃ also for hydrogen, R₃ for chloro or bromo and R₂ for a carbocyclic or heterocyclic aryl radical, esters, amides, acyl derivatives and/or salts thereof, as well as of corresponding pharmaceutical compositions, new starting materials and methods for the preparation and application of these products. Said compositions are primarily useful as orally applicable diuretic, natri- and chloruretic agents in order to relieve excessive water and/or salt retention, for example, in connection with heart and kidney diseases, and in the adjunctive management of hypertension.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The aliphatic or araliphatic radicals mentioned for R₁, R₂ and R₃ are hydrocarbon radicals, which may be substituted by functional groups and/or interrupted by heteroatoms, such as nitrogen, oxygen and/or sulfur atoms. Such radicals are, for example, lower alkyl, e.g. methyl, ethyl, n- or i-propyl, n-, i-, or sec. butyl, n- or i-pentyl, neopentyl, n-hexyl or n-heptyl, lower alkenyl, e.g. vinyl, allyl, methallyl or 2-butenyl, lower alkynyl, e.g. propargyl, mono- or bicyclic cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl with

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preferably 5 to 7 ring-carbon atoms, 1 to 4 chain carbon atoms and optional, e.g. up to 4, lower alkyl groups, e.g. cyclopropyl, 2,3-dimethyl-cyclopropyl, cyclobutyl, cyclopentyl, 2- or 3-methyl-cyclopentyl, 2,5- or 3,4-dimethyl-cyclopentyl, cyclohexyl, 2-, 3- or 4-methyl-cyclohexyl, 2-, 3-, 2,4- or 3,5-dimethyl-cyclohexyl, 2,4,6-trimethyl-cyclohexyl, cycloheptyl, cyclooctyl, 2- or 7-norbornanyl, 1- or 2-decahydronaphthyl; 1- or 2-cyclopentenyl, 2,4-cyclopentadienyl, 2- or 3-methyl-2-cyclopentenyl, 4,5-dimethyl-2-cyclopentenyl, 1-, 2- or 3-cyclohexenyl, 2,5-cyclohexadienyl, 2-, 3- or 4-methyl-1- or 2-cyclohexenyl, 2,4- or 3,5-dimethyl-1- or 2-cyclohexenyl, 2,4,6-trimethyl-2,5-cyclohexadienyl, 1-, 2- or 3-cycloheptenyl, 2,6-cycloheptadienyl, 2-cyclooctenyl or 2-norborn-5-enyl, as well as the corresponding cycloalkyl- or cycloalkenyl-lower alkyl groups in which the chain especially represents methyl, but also ethyl n- or i-propyl, n-, i- or sec. butyl; it contains in any of the positions available for substitution one of the specific cycloalkyl or cycloalkenyl groups listed above.

The term "lower," referred to above and hereinafter in connection with organic radicals or compounds respectively, defines such with up to 7, preferably up to 4, carbon atoms. Aliphatic radicals that are substituted, e.g. by free or functionally converted hydroxy, mercapto or carboxy groups and/or interrupted by heteroatoms, e.g. one oxygen, sulfur and/or nitrogen atom, are represented, for example, by lower haloalkyl, e.g. 2-(chloro, bromo or iodo)-ethyl, 3,3-difluoro- or -dichloropropyl, 3,3,3-trichloropropyl, 3- or 4-chlorobutyl, 4,4- or 3,4-dichlorobutyl or 4,4,4-trifluorobutyl; unsubstituted or halogenated lower alkoxy- or alkylmercapto-lower alkyl, such as 2-ethoxyethyl, 3-methoxy-propyl, 2-ethylmercapto-ethyl, 2-(2,2-dichloroethoxy)-ethyl, 2-(2-chloroethoxy)-ethyl, 2-(2,2,2-trifluoroethoxymercapto)-ethyl or 2-(2,2-dichloroethoxymercapto)-ethyl; carbamyl-lower alkyl or N,N-dilower alkylcarbamyl-lower alkyl, such as carbamyl-methyl, N,N-dimethylcarbamyl-methyl, 2-carbamyl-ethyl or 2-N,N-diethylcarbamyl-ethyl; sec. or tert. amino-lower alkyl, such as mono- or di-lower alkylamino-lower alkyl, lower alkyleneimino-lower alkyl, lower monoaza-, -oxa- or -thiaalkyleneimino-lower alkyl or N-lower alkyl-lower monoazaalkyleneimino-lower alkyl, e.g. 2-ethylamino-ethyl, 2-dimethylamino-ethyl, 3-diethylamino-propyl, 2-pyrrolidino-ethyl, 2-piperidino-ethyl, 2-(4-methyl-piperazino)-ethyl or 2-morpholino-ethyl, 5 to 7 ring-membered oxa-cycloalkyl or -cycloalkenyl, oxacycloalkyl or -cycloalkenyl-lower alkyl, such as 3-tetrahydrofuryl, tetrahydrofuryl-2-methyl, (2-methyl-tetrahydrofuryl-2)-methyl, 2,3-dihydro- or tetrahydropranyl-2-methyl.

R₁ and R₂ when taken together, may also represent lower alkylene or alkenylene, e.g. 1,2-ethylene, 1,3-propylene, 1,4-butylenes, 1,4- or 1,5-pentylene, 1,5-, 2,5- or 1,6-hexylene or 2,6-heptylene; 1,4-but-2-enylene, 1,4- or 1,5-pent-2-enylene, 1,5-hex-2-enylene, 1,6-hex-3-enylene or 2,6-hept-3-enylene; lower monoaza-, -oxa- or -thiaalkylene or N-lower alkyl-monoaza-lower alkylene, e.g. 3-aza-, 3-oxa- or 3-thia-pentylene-(1,5), 3-methyl- or 3-ethyl-3-aza-pentylene-(1,5), 3-aza-hexylene-(1,6) or 4-aza- or oxa-heptylene-(2,6). In the aliphatically substituted group



two heteroatoms, e.g. nitrogen, oxygen and/or sulfur atoms, are separated by at least 2 carbon atoms.

An araliphatic radical R₁, R₂ and R₃ preferably stands for mono- or bicyclic carbocyclic aryl-lower alkyl or aryl-lower alkenyl, especially (mono- or di-R₂-phenyl)-lower alkyl or -alkenyl, but also for mono- or bicyclic heterocyclic, especially monoaza-, -oxa- or -thiacyclic aryl-lower alkyl or aryl-lower alkenyl in which the alkyl or

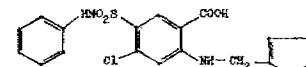
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The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions containing an effective amount thereof in conjunction or admixture with excipients suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredients together with (a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, (b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol, for tablets also (c) binders, e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, if desired, (d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, enzymes of the binders or effervescent mixtures and/or (e) adsorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously fatty emulsions or suspensions. They may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. They may also contain other therapeutically valuable substances. Said pharmaceutical compositions are prepared according to conventional mixing, granulating or coating methods respectively and contain about 0.1 to 75%, preferably about 1 to 50% of the active ingredient.

The following examples illustrating the invention are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade and all parts wherever given are parts by weight.

EXAMPLE 1

The mixture of 2.4 g., 2,4-dichloro-5-phenylsulfamylbenzoic acid, 10 ml. 2-ethoxy-ethanol and 2.7 g. furfurylamine is refluxed for 4 hours under nitrogen. After cooling to room temperature it is poured into 50 ml. 2 N-hydrochloric acid. The supernatant liquid is decanted off and the residue dissolved in 50 ml. 2 N aqueous sodium hydroxide. The solution is extracted twice with diethyl ether and acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from ethanol to yield the N-furfuryl-5-phenylsulfamyl-4-chloroanthranilic acid of the formula



melting at 210-212° (dec.).

The starting material is prepared as follows: To 250 g. chlorosulfonic acid 50 g. 2,4-dichloro-benzoic acid are added portion-wise at room temperature while stirring. The solution obtained is heated to about 180° and stirred for 3 hours. After cooling to room temperature, it is poured into ice, the mixture filtered, the residue washed with water, and dissolved in 400 ml. ethyl acetate. The solution is dried, filtered, evaporated, and the residue triturated with hexane, to yield the 2,4-dichloro-5-chlorosulfonylbenzoic acid.

The mixture of 5.8 g. thereof, 7.5 g. aniline and 50 ml. ethyl acetate is stirred for 4 hours at room temperature. It is then filtered and the residue washed with ethyl acetate. The filtrate is evaporated in vacuo and the residue triturated with 2 N hydrochloric acid. The aqueous solution is decanted off and the precipitate dissolved in 100 ml. 10% aqueous potassium carbonate. The solution is filtered to yield residue A. The filtrate is extracted with diethyl ether and the aqueous layer acidified with hydrochloric acid. The precipitate formed is filtered off, washed with water and recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-phenylsulfamylbenzoic acid melting at 211-213°. Residue A is also recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-phenylsulfamylbenzoic acid phenylamide melting at 173-175°.

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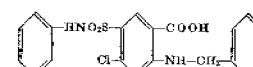
EXAMPLE 2

The mixture of 3.0 g. N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid phenylamide, 30 ml. 2 N-aqueous sodium hydroxide, 10 ml. water and 10 ml. 2-methoxy-ethanol is refluxed for 3 hours under nitrogen and allowed to stand at room temperature overnight. It is poured into 60 ml. 2 N-hydrochloric acid, the precipitate formed filtered off, washed with water and dissolved in 35 ml. 10% aqueous potassium carbonate. The solution is extracted with ethyl acetate, the aqueous layer separated and acidified with hydrochloric acid. The precipitate formed is filtered off, recrystallized from aqueous ethanol to yield the N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid melting at 212-214° with decomposition; it is identical with the compound obtained according to Example 1.

The starting material is prepared as follows: The mixture of 6.0 g. 2,4-dichloro-5-phenylsulfamylbenzoic acid phenylamide, 5.6 g. furfurylamine and 20 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and allowed to stand overnight at room temperature. It is poured into 100 ml. 2 N-hydrochloric acid, the precipitate formed filtered off and the residue dissolved in diethyl ether. The solution is washed with 0.5 N hydrochloric acid, with 10% aqueous potassium carbonate and water, dried, filtered and evaporated in vacuo, to yield the N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid phenylamide melting at 114-117°.

EXAMPLE 3

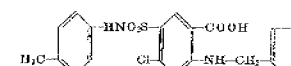
Substituting in Example 1 the furfurylamine by the equivalent amount of benzylamine and performing the reaction as shown therein, the N-benzyl-5-phenylsulfamyl-4-chloroanthranilic acid of the formula



is obtained, M.P. 226-228° (from aqueous ethanol).

EXAMPLE 4

The mixture of 3.1 g. 2,4-dichloro-5-(4-methyl-phenyl)sulfamylbenzoic acid, 3.4 g. furfurylamine and 10 ml. 2-methoxyethanol is refluxed for 4 hours under nitrogen. After cooling to room temperature, it is treated with 2 N-hydrochloric acid, the precipitate formed separated and dissolved in 2 N-aqueous sodium hydroxide. The solution is extracted with diethyl ether, the aqueous layer separated and acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol to yield the N-furfuryl-4-chloro-5-(4-methyl-phenyl)sulfamyl-anthranilic acid of the formula



melting at 218-220°.

The starting material is prepared as follows: To the solution of 5.8 g. 2,4-dichloro-5-chlorosulfonylbenzoic acid in 50 ml. ethyl acetate, 8.6 g. p-toluidine are added while stirring, followed by 100 ml. ethyl acetate. The mixture is stirred at room temperature for 2 hours and refluxed for 2 hours while stirring. After cooling it is filtered, the residue washed with ethyl acetate and the filtrate evaporated in vacuo. The residue is treated with 10 ml. concentrated hydrochloric acid and extracted with ethyl acetate. The organic layer is separated, extracted with 10% aqueous potassium carbonate and the aqueous solution acidified with hydrochloric acid. The precipitate formed is filtered off, washed with water and recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-(4-methyl-phenyl)sulfamylbenzoic acid melting at 202-204°.

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EXAMPLE 5

According to the method shown in the previous examples the compounds of Formula I, $R_1 = \text{furfuryl}$,



$R_3 = Cl$, and listed below, are prepared from equivalent amounts of the corresponding starting materials of Formula II, $R_3 = X = Cl$:

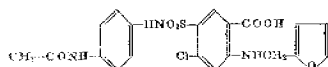
Number	R_1	Yield, percent	Melting point, degrees
1.	4-Cl-5-O-C ₆ H ₄	1268-269	224-225
2.	4-F-5-O-C ₆ H ₄	1207-208	221-223
3.	2-Cl-5-O-C ₆ H ₄	1201-203	169-170
4.	2-Cl-5-O-C ₆ H ₄	1216-218	190-192
5.	4-Cl-5-O-C ₆ H ₄	1218-223	228-240
6.	4-F-5-O-C ₆ H ₄	1230-232	214-216
7.	2-Cl-5-O-C ₆ H ₄	1223	238-239
8.	4-NO ₂ -5-O-C ₆ H ₄	1225	269-271
9.	2-Cl-5-O-C ₆ H ₄	1288-189	176-178

¹ Dec.

All compounds were recrystallized from aqueous ethanol.

EXAMPLE 6

The mixture of 4.0 g. 2,4-dichloro-5-(4-acetylamino-phenylsulfamyl)-benzoic acid, 3.9 g. furfurylamine and 10 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling it is treated with 2 N-hydrochloric acid, the residue formed separated and dissolved in 2 N-aqueous sodium hydroxide. The solution is extracted with diethyl ether, the aqueous layer separated, acidified with hydrochloric acid and the precipitate formed recrystallized from aqueous ethanol to yield the N-furfuryl-4-chloro-5-(4-acetylamino-phenylsulfamyl)-anthranilic acid of the formula

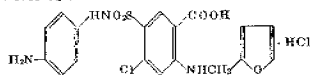


melting at 248° with decomposition.

The starting material is prepared as follows: To the solution of 5.8 g. 2,4-dichloro-5-chlorosulfamoyl-benzoic acid in 50 ml. ethyl acetate, 12.0 g. 4-amino-acetanilide are added, followed by 50 ml. ethyl acetate. The mixture is stirred for 2 hours at room temperature and refluxed for 2 hours while stirring. After cooling to room temperature it is filtered, the residue (A) washed with ethyl acetate and the filtrate evaporated in vacuo. The residue (B) is triturated with water and 10 ml. concentrated hydrochloric acid, filtered off, washed with water and dried. The combined residues (A) and (B) are dissolved in 60 ml. 10% aqueous potassium carbonate, the solution washed with diethyl ether, acidified with hydrochloric acid, the precipitate formed filtered off and washed with water to yield the 2,4-dichloro-5-(4-acetylamino-phenylsulfamyl)-benzoic acid melting at about 150°.

EXAMPLE 7

The mixture of 5.3 g. 2,4-dichloro-5-(4-amino-phenylsulfamyl)-benzoic acid hydrochloride, 5.4 g. furfurylamine and 15 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and evaporated in vacuo. To the residue 50 ml. 2 N-hydrochloric acid are added and the precipitate formed filtered off. It is triturated with 40 ml. water at room temperature, filtered off, washed with a small amount of ice cold water and diethyl ether and recrystallized from aqueous ethanol to yield the N-furfuryl-4-chloro-5-(4-amino-phenylsulfamyl)-anthranilic acid hydrochloride of the formula



melting at about 230°.

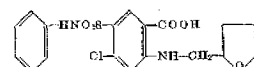
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The starting material is prepared as follows: The mixture of 7.1 g. 2,4-dichloro-5-(4-acetylamino-phenylsulfamyl)-benzoic acid (of Example 6) and 60 ml. 2 N-aqueous sodium hydroxide is refluxed for 90 minutes.

After cooling to room temperature it is acidified with concentrated hydrochloric acid, the precipitate formed filtered off, the residue taken up in ethanol, the solution filtered and evaporated in vacuo, to yield the 2,4-dichloro-5-(4-amino-phenylsulfamyl)-benzoic acid hydrochloride, melting at 185° with decomposition.

EXAMPLE 8

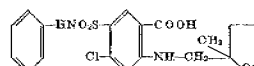
The mixture of 6.5 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 4.6 g. (2-methyl-tetrahydrofuryl-2)-methyl-30 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling to room temperature, it is poured into 180 ml. 2 N-hydrochloric acid, the precipitate separated, ground in a mortar, filtered, washed with water and recrystallized several times from aqueous ethanol to yield the N-(tetrahydrofuryl-2-methyl)-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 238-239°.

EXAMPLE 9

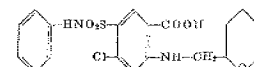
The mixture of 3.5 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 4.6 g. (2-methyl-tetrahydrofuryl-2)-methylamine and 10 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and stirred overnight at room temperature. Hereupon it is poured into 80 ml. 2 N-hydrochloric acid, the residue separated and dissolved in 2 N-aqueous sodium hydroxide. The solution is washed with diethyl ether, filtered and acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-(2-methyl-tetrahydrofuryl-2-methyl)-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 207-208°.

EXAMPLE 10

The mixture of 6.5 g. 2-dichloro-5-phenylsulfamyl-benzoic acid, 9.05 g. 2,3-dihydro-pyran-2-ylmethylamine and 30 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling to room temperature it is poured into 180 ml. 2 N-hydrochloric acid, the precipitate formed filtered off, washed with water and recrystallized from aqueous ethanol, to yield the N-(2,3-dihydro-pyran-2-ylmethyl)-4-chloro-5-phenylsulfamyl-benzoic acid of the formula



melting at 115-117° with decomposition.

EXAMPLE 11

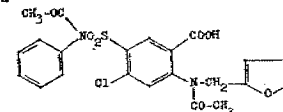
The mixture of 81.4 g. N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid (Example 1), 110 ml. 2 N-aqueous sodium hydroxide and 100 ml. water is heated to about 50 to 60° until dissolution occurs. The solution is filtered, the filtrate cooled, seeded with a few crystals of previously prepared sodium salt, and allowed to stand in the refrigerator. The precipitate formed is filtered off, washed with a small amount of ice water and dissolved in 100 ml. isopropanol at 60°. The solution obtained is

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slowly cooled and finally kept in the refrigerator. The precipitate formed is filtered off, triturated with 75 ml. cold isopropanol, filtered again and dried to yield the sodium salt of the N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid, melting at 244 to 246° with decomposition.

EXAMPLE 12

The mixture of 2.0 g. N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid, 2 ml. acetic acid anhydride and 8 ml. pyridine is heated at the steam bath for 1 hour, cooled and poured into water. The mixture is slightly acidified with concentrated hydrochloric acid, the precipitate formed filtered off and dissolved in ethanol. To the solution, water and a few drops hydrochloric acid are added, the precipitate formed filtered off and again recrystallized from aqueous ethanol to yield the N,N'-bisacetyl-N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 206-208°.

EXAMPLE 13

The mixture of 113.3 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 500 ml. 2-methoxy-ethanol and 126.0 g. furfurylamine is stirred and refluxed under nitrogen for 4 hours. The cold mixture is then slowly poured into 2.5 liters 2 N hydrochloric acid while stirring. The precipitate formed is filtered off, washed with water and dissolved in 1 liter 2 N aqueous sodium hydroxide. The dark solution obtained is extracted three times with 125 ml. methylene chloride each and the aqueous layer carefully acidified with concentrated hydrochloric acid. The precipitate formed is filtered off, dissolved in 1 liter ethanol, the solution decolorized with charcoal, filtered hot, the filtrate combined with 1 liter hot water and, upon cooling to 15°, the N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid (Example 1) crystallizes. It is filtered off and dried; it melts at about 206°, which melting point can be raised to 208-210° by another recrystallization.

The starting material is prepared as follows: The mixture of 150 g. 2,4-dichloro-benzoic acid and 600 g. chlorosulfonic acid is heated to 150-155° for 3 hours while stirring. Thereupon, 223 g. chlorosulfonic acid are distilled off in vacuo and the cold residue poured into a mixture of 1.65 kg. ice and 125 ml. water. The precipitate formed is filtered off, washed with cold water, dissolved in 800 ml. ethyl acetate, the solution dried, filtered, and the filtrate diluted with 600 ml. ethyl acetate. To the solution obtained (containing the 2,4-dichloro-5-chlorosulfamoyl-benzoic acid), cooled in a water bath, the mixture of 216 g. aniline and 220 ml. ethyl acetate is added at such rate that the temperature stays below 30°. The mixture is stirred for 4 hours at 25-30°, whereupon 4 g. charcoal are added. It is then filtered, the residue washed with 125 ml. ethyl acetate, the filtrate washed first with 450 ml. 3 N hydrochloric acid, then with 550 ml. water, and finally extracted with 700 ml. 7% aqueous sodium carbonate. The aqueous extract is separated, carefully acidified with concentrated hydrochloric acid and the precipitate formed filtered off and dried at 75° in vacuo, to yield the 2,4-dichloro-5-phenylsulfamyl-benzoic acid melting at 212-216°.

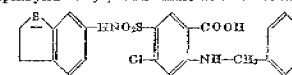
EXAMPLE 14

The mixture of equivalent amounts of 2,4-dichloro-5-(2,3-dihydro-6-thianaphthylsulfamyl)-benzoic acid and 0.5 ml. benzylamine in 1 ml. 2-methoxy-ethanol is heated for 4 hours to 130°. After cooling, 5 ml. 2 N hydrochloric acid and 5 ml. water are added, the precipitate formed

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filtered off, washed with water and triturated with 2 N aqueous sodium hydroxide. The alkaline solution is filtered, the filtrate acidified with hydrochloric acid, the precipitate formed filtered off, washed with water and dried, to yield the N-benzyl-4-chloro-5-(2,3-dihydro-6-thianaphthylsulfamyl)-anthranilic acid of the formula

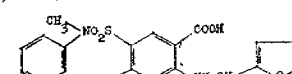


melting at 150° with decomposition.

The starting material is prepared as follows: To the solution of 1.9 g. 6-amino-2,3-dihydro-thianaphthene in 25 ml. ethyl acetate and 3 ml. pyridine, 2.9 g. 2,4-dichloro-5-chlorosulfamoyl-benzoic acid are added slowly while stirring. The mixture is stirred for 3 hours at room temperature and allowed to stand overnight. It is made strongly acidic with hydrochloric acid, extracted with ethyl acetate, the extract washed with water, dried and evaporated in vacuo. The residue is taken up in 1 N aqueous sodium hydroxide, the solution filtered and the filtrate acidified. The precipitate formed is filtered off and recrystallized first from aqueous ethanol and finally from methanol, to yield the 2,4-dichloro-5-(2,3-dihydro-6-thianaphthylsulfamyl)-benzoic acid.

EXAMPLE 15

The mixture of 3.6 g. 2,4-dichloro-5-(N-methyl-N-phenylsulfamyl)-benzoic acid, 3.9 g. furfurylamine and 10 ml. 2-methoxyethanol is refluxed for 4 hours under nitrogen. After cooling, it is poured into 50 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and heated with 50 ml. 2 N aqueous sodium hydroxide. To the suspension obtained, water and diethyl ether are added until 2 clear layers are formed. The aqueous layer is separated, washed with diethyl ether and acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid of the formula



melting at 171-172°.

In the analogous manner, the N-benzyl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid is obtained; M.P. 164-166°.

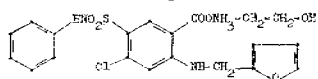
The starting material is prepared as follows: To the solution of 11.6 g. 2,4-dichloro-5-chlorosulfamoyl-benzoic acid in 100 ml. ethyl acetate, 17.1 g. N-methyl-aniline are added slowly, and the mixture is stirred at room temperature for 4 hours. It is then filtered, the filtrate evaporated in vacuo and the residue taken up in water and 20 ml. concentrated hydrochloric acid. The mixture is extracted with ethyl acetate, the extract washed with water and shaken with 10% aqueous potassium carbonate. The aqueous layer is separated, acidified with concentrated hydrochloric acid, the precipitate formed filtered off and recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-(N-methyl-N-phenylsulfamyl)-benzoic acid, melting at 170-171°.

EXAMPLE 16

The mixture of 3 g. N-benzyl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid (Example 15), 12 ml. pyridine and 3 ml. acetic acid anhydride is heated at the steam bath for 1 hour while stirring. After cooling, it is poured into 120 ml. water, the mixture acidified with concentrated hydrochloric acid, the precipitate collected and recrystallized from aqueous methanol to yield the N-acetyl-N-benzyl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid of the formula

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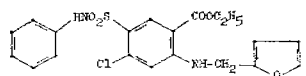
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melting at 90°.

EXAMPLE 23

The mixture of 13.1 g. ethyl 2,4-dichloro-5-phenylsulfamylbenzoate and 20.4 g. furfurylamine is heated for 1 hour to 110°. After cooling, it is poured into 210 ml. water, the mixture acidified with glacial acetic acid to pH 4.5 while keeping the temperature below 20°. The precipitate formed is filtered off, washed with water and suspended in 250 ml. 0.5 N sodium hydroxide while stirring at room temperature. It is filtered, the residue suspended in water and the mixture acidified with hydrochloric acid to pH 2 while stirring. It is again filtered and the residue recrystallized several times from aqueous ethanol and finally from anhydrous ethanol, to yield the ethyl N-furfuryl-5-sulfamyl-4-chloroanthranilate of the formula

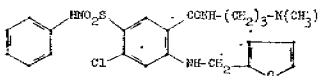


melting at 157-159°.

The starting material is prepared as follows: The mixture of 15 g. 2,4-dichloro-5-phenylsulfamylbenzoic acid and 150 ml. 6 N ethanolic hydrochloric acid is refluxed for 90 minutes and allowed to stand in the cold. The precipitate formed is filtered off, and recrystallized from aqueous ethanol, to yield the ethyl 2,4-dichloro-5-phenylsulfamylbenzoate melting at 132-133°.

EXAMPLE 24

The mixture of 6.6 g. 2,4-dichloro-5-phenylsulfamylbenzoic acid 3-dimethylamino-propylamide, 5.8 g. furfurylamine and 15 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and evaporated in vacuo. The residue is taken up in 100 ml. 2 N aqueous sodium hydroxide and the mixture extracted with ethyl acetate. The organic layer is dried, filtered and evaporated. The residue is triturated with hydrogen chloride in ethyl acetate, the precipitate formed filtered off and taken up in water. The solution is washed with ethyl acetate, filtered and made basic with 2 N aqueous sodium hydroxide. The mixture is extracted with ethyl acetate, the extract dried, filtered and evaporated, to yield the amorphous N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid 3-dimethylaminopropylamide of the formula



showing in the thin layer chromatogram on silica gel in chloroform, methanol and diethylamine (85:5:10) an $R_{F_{CH_2Cl_2}}$ = 7.5.

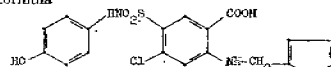
The starting material is prepared as follows: To the mixture of 17.7 g. 2,4-dichloro-5-phenylsulfamylbenzoic acid and 90 ml. 1,2-dimethoxyethane, 24 ml. thionyl chloride are added dropwise during 25 minutes while stirring, the whole is refluxed for 90 minutes and evaporated in vacuo. 18.6 g. of the resulting acid chloride is taken up in 300 ml. ethyl acetate and the solution added dropwise to the mixture of 11.8 g. 3-dimethylaminopropylamine and 450 ml. ethyl acetate while stirring, and stirring is continued overnight at room temperature. The mixture is filtered, the filtrate acidified with hydrogen chloride in ethyl acetate and the precipitate formed filtered off. It is taken up in water, the solution washed with ethyl acetate and made alkaline with 10% potassium carbonate. The mixture is extracted with ethyl acetate, the mixture dried,

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filtered and evaporated, to yield the 2,4-dichloro-5-phenylsulfamylbenzoic acid 3-dimethylamino-propylamide melting between about 80° and 90°.

EXAMPLE 25

The mixture of 3.6 g. 2,4-dichloro-5-(4-hydroxyphenylsulfamyl)-benzoic acid, 10 ml. 2-methoxy-ethanol and 3.9 g. furfurylamine is refluxed for 4 hours under nitrogen. After cooling, it is poured into 50 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered and the filtrate acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(4-hydroxyphenylsulfamyl)-anthranilic acid of the formula



melting at 227° with decomposition.

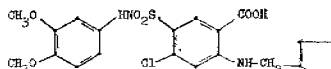
The starting material is prepared as follows: To the mixture of 5.8 g. 2,4-dichloro-5-chlorosulfonylbenzoic acid and 100 ml. ethyl acetate, 8.7 g. 4-hydroxyaniline are added portionwise and the mixture stirred at room temperature for 4 hours. After standing overnight, it is filtered, the residue suspended in 50 ml. water, the mixture acidified with 10 ml. concentrated hydrochloric acid and extracted with ethyl acetate. The extract is filtered, washed with water and shaken with 10% aqueous potassium carbonate. The aqueous solution is filtered, acidified with concentrated hydrochloric acid and the precipitate formed filtered off. It is recrystallized several times from aqueous ethanol, to yield the 2,4-dichloro-5-(4-hydroxyphenylsulfamyl)-benzoic acid melting at 233-235°.

EXAMPLE 26

In the manner described in Example 25, the N-furfuryl-4-chloro-5-(2-hydroxyphenylsulfamyl)-anthranilic acid, M.P. 125° (dec.) and the N-furfuryl-4-chloro-5-(3-hydroxyphenylsulfamyl)-anthranilic acid, M.P. 202° (dec.) are prepared from the same amounts of the corresponding isomeric starting materials, which melt at 187-189° and 192-194° respectively.

EXAMPLE 27

The mixture of 3.9 g. 2,4-dichloro-5-(3,4-dimethoxyphenylsulfamyl)-benzoic acid, 10 ml. 2-methoxyethanol and 3.7 g. furfurylamine is refluxed for 4 hours under nitrogen. After cooling, it is poured into 50 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered, the filtrate acidified with concentrated hydrochloric acid, the precipitate formed collected and recrystallized two times from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(3,4-dimethoxyphenylsulfamyl)-anthranilic acid of the formula



melting at 123°.

The starting material is prepared as follows: To the solution of 12.3 g. 3,4-dimethoxyaniline and 50 ml. ethyl acetate, 5.8 g. 2,4-dichloro-5-chlorosulfonylbenzoic acid are added while stirring, and the mixture stirred for 4 hours at room temperature. It is filtered, the residue washed with ethyl acetate and the filtrate combined with 10 ml. water and concentrated hydrochloric acid each and diluted with ethyl acetate. The organic layer is separated, extracted with 10% aqueous potassium carbonate and the extract acidified with concentrated hydrochloric

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5-ARYLSULFAMYL-ANTHRANILIC ACIDS

Lincoln Harvey Werner, Summit, N.J., assignor to Ciba-Geigy Corporation, Ardsley, N.Y.

No Drawing. Continuation-in-part of application Ser. No. 832,029, June 10, 1969, which is a continuation-in-part of abandoned application Ser. No. 675,330, Oct. 16, 1967, which in turn is a continuation-in-part of abandoned application Ser. No. 598,980, Dec. 5, 1966. This application Nov. 19, 1970, Ser. No. 91,224

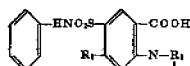
Int. Cl. C07C 143/80

U.S. Cl. 260-518 A

6 Claims

ABSTRACT OF THE DISCLOSURE

5-arylsulfamyl-4-halo-anthranilic acids, e.g. those of the formula



R₁=aliphatic or araliphatic radical

R₂=H or R₁

R₃=Cl or Br

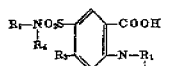
and functional derivatives thereof, exhibit diuretic effects.

CROSS-REFERENCES TO RELATED APPLICATIONS

This is a continuation-in-part of application Ser. No. 832,029, filed June 10, 1969 (now Pat. No. 3,658,990), which in turn is a continuation-in-part of application Ser. No. 675,330, filed Oct. 16, 1967 (now abandoned), which in turn is a continuation-in-part of application Ser. No. 598,980, filed Dec. 5, 1966 (now abandoned).

SUMMARY OF THE INVENTION

The present invention concerns and has for its object the provision of new 5-arylsulfamyl-4-halo-anthranilic acids and their therapeutically acceptable derivatives, more particularly those of Formula I,



in which each of R₁, R₂ and R₃ stands for an aliphatic or araliphatic radical, R₂ and R₃ also for hydrogen, R₁ for chloro or bromo and R₃ for a carbocyclic or heterocyclic aryl radical, esters, amides, acyl derivatives and/or salts thereof, as well as of corresponding pharmaceutical compositions, new starting materials and methods for the preparation and application of these products. Said compositions are primarily useful as orally applicable diuretic, natri- and chloruretic agents in order to relieve excessive water and/or salt retention, for example, in connection with heart and kidney diseases, and in the adjunctive management of hypertension.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The aliphatic or araliphatic radicals mentioned for R₁, R₂ and R₃ are hydrocarbon radicals, which may be substituted by functional groups and/or interrupted by heteroatoms, such as nitrogen, oxygen and/or sulfur atoms. Such radicals are, for example, lower alkyl, e.g. methyl, ethyl, n- or i-propyl, n-, i- or sec-butyl, n- or i-pentyl, neopentyl, n-hexyl or n-heptyl, lower alkenyl, e.g. vinyl, allyl, methallyl or 2-butenyl, lower alkynyl, e.g. propargyl, mono- or bicyclic cycloalkyl, cycloalkenyl, cyclo-

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alkyl-lower alkyl or cycloalkenyl-lower alkyl with preferably 5 to 7 ring-carbon atoms, 1 to 4 chain carbon atoms and optional, e.g. up to 4, lower alkyl groups, e.g. cyclopropyl, 2,3-dimethyl-cyclopropyl, cyclobutyl, cyclopentyl, 2- or 3-methyl-cyclopentyl, 2,5- or 3,4-dimethyl-cyclopentyl, cyclohexyl, 2-, 3- or 4-methyl-cyclohexyl, 2,3-, 2,4- or 3,5-dimethyl-cyclohexyl, 2,4,6-trimethyl-cyclohexyl, cycloheptyl, cyclooctyl, 2- or 7-norbornyl, 1- or 2-decalhydronaphthyl, 1- or 2-cyclopentyl, 2,4-cyclopentadienyl, 2- or 3-methyl-2-cyclopentyl, 4,5-dimethyl-2-cyclopentyl, 1-, 2- or 3-cyclohexenyl, 2,5-cyclohexadienyl, 2-, 3- or 4-methyl-1- or 2-cyclohexenyl, 2,4- or 3,5-dimethyl-1- or 2-cyclohexenyl, 2,4,6-trimethyl-2,5-cyclohexadienyl, 1-, 2- or 3-cycloheptenyl, 2,6-cycloheptadienyl, 2-cyclooctenyl or 2-norborn-5-enyl, as well as the corresponding cycloalkyl- or cycloalkenyl-lower alkyl groups in which the chain especially represents methyl, but also ethyl n- or i-propyl, n-, i- or sec. butyl; it contains in any of the positions available for substitution one of the specific cycloalkyl or cycloalkenyl groups listed above. The term "lower," referred to above and hereinafter in connection with organic radicals or compounds respectively, defines such with up to 7, preferably up to 4, carbon atoms. Aliphatic radicals that are substituted, e.g. by free or functionally converted hydroxy, mercapto or carboxy groups and/or interrupted by heteroatoms, e.g. one oxygen, sulfur and/or nitrogen atom, are represented, for example, by lower haloalkyl, e.g. 2-(chloro, bromo or iodo)-ethyl, 3,3-difluoro- or -dichloropropyl, 3,3,3-trichloropropyl, 3- or 4-chlorobutyl, 4,4- or 3,4-dichlorobutyl or 4,4,4-trifluorobutyl, unsubstituted or halogenated lower alkoxy- or alkylmercapto-lower alkyl, such as 2-ethoxyethyl, 3-methoxypropyl, 2-ethylmercapto-ethyl, 2-(2,2-dichloroethoxy)-ethyl, 2-(2-chloroethoxy)-ethyl, 2-(2,2,2-trifluoroethoxy)-ethyl, carbamyl-lower alkyl or N,N-di-lower alkylcarbamyl-lower alkyl, such as carbamyl-methyl, N,N-dimethylcarbamyl-methyl, 2-carbamyl-ethyl or 2-N,N-diethylcarbamyl-ethyl; sec. or tert. amino-lower alkyl, such as mono- or di-lower alkylamino-lower alkyl, lower alkylencimino-lower alkyl, lower monoaza-, oxo- or -thiaalkylencimino-lower alkyl or N-lower alkyl-lower monoazaalkylencimino-lower alkyl, e.g. 2-ethylamino-ethyl, 2-dimethylamino-ethyl, 3-diethylamino-propyl, 2-pyrrolidino-ethyl, 2-piperidino-ethyl, 2-(4-methyl-piperidino)-ethyl or 2-morpholino-ethyl, 5 to 7 ring-membered oxo-cycloalkyl or -cycloalkenyl, oxo-cycloalkyl- or -cycloalkenyl-lower alkyl, such as 3-tetrahydrofuryl, tetrahydrofuryl-2-methyl, (2-methyl-tetrahydrofuryl-2)-methyl, 2,3-dihydro- or tetrahydropranyl-2-methyl.

R₁ and R₂ when taken together, may also represent lower alkylene or alkenylene, e.g. 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,4- or 1,5-pentylene, 1,5, 2,5- or 1,6-hexylene or 2,6-heptylene; 1,4-but-2-enylene, 1,4- or 1,5-pent-2-enylene, 1,5-hex-2-enylene, 1,6-hex-3-enylene or 2,6-hept-3-enylene; lower monoaza-, oxo- or -thiaalkylene or N-lower alkyl-monoaza-lower alkylene, e.g. 3-aza-, 3-oxa- or 3-thia-pentylene-(1,5), 3-methyl- or 3-ethyl-3-aza-pentylene-(1,5), 3-aza-hexylene-(1,6) or 4-aza- or oxa-heptylene-(2,6). In the aliphatically substituted group



two heteroatoms, e.g. nitrogen, oxygen and/or sulfur atoms, are separated by at least 2 carbon atoms.

An araliphatic radical R₁, R₂ and R₃ preferably stands for mono- or bicyclic carbocyclic aryl-lower alkyl or aryl-lower alkenyl, especially (mono- or di-R₆-phenyl)-lower alkyl or -alkenyl, but also for mono- or bicyclic heterocyclic, especially monoaza-, oxo- or -thiacyclic aryl-lower alkyl or aryl-lower alkenyl in which the alkyl or alkenyl

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moiety preferably has up to 4 chain carbon atoms, and the aromatic portion is unsubstituted or substituted by one or more than one, preferably 1 or 2, substituents selected, for example, from lower alkyl, e.g. that mentioned above, phenyl, free or functionally converted hydroxy or mercapto, such as lower alkoxy, lower alkylene-dioxy, lower alkylmercapto or halogeno, e.g. methoxy, ethoxy, n- or i-propoxy or -butoxy, methylenedioxy, 1,1- or 1,2-ethylenedioxy, methyl- or ethylmercapto, fluoro, chloro or bromo; (hydroxy or halogeno)-lower alkyl or -alkoxy, e.g. 2-hydroxyethyl, trifluoromethyl or 2-hydroxyethoxy, nitro, amino, especially di-lower alkylamino, e.g. dimethylamino or diethylamino, sulfamoyl, or free or functionally converted carboxy, e.g. lower carbalkoxy, carbamoyl or cyano. Preferred aryl-substituents R₆ are hydrogen, lower alkyl, hydroxy-lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkylmercapto, hydroxy-lower alkoxy, halogeno, trifluoromethyl, nitro, amino, di-lower alkylamino, carboxy and/or lower carbalkoxy. Unsubstituted carbocyclic aralkyl or aralkenyl radicals are exemplified by benzyl, 1- or 2-phenylethyl, 1-, 2- or 3-phenyl-propyl, 2-phenyl-2-propyl, 1-, 2-, 3- or 4-phenyl-butyl, 1- or 2-phenyl-2-butyl, styryl or cinnamyl. In the corresponding heterocyclic aralkyl or aralkenyl radicals aryl is preferably monocyclic monoaza-, -oxa- or -thiacyclic aryl, e.g. 2-, 3- or 4-pyridyl, 2- or 3-furyl or -thienyl, but also 5-(1,2-oxazolyl), 2-(1-oxazolyl), 2-(1,3-thiazolyl), 6-thianaphthyl or 2-benzimidazolyl. Araliphatic radicals are also partially hydrogenated, preferably bi- or tri-cyclic aryl radicals, bound at the aliphatic portion, such as 1- or 2-indolyl, 1- or 2-(1,2,3,4-tetrahydronaphthyl) or 9-fluorenyl.

The radical R₆ preferably stands for mono- or bicyclic carbocyclic or heterocyclic aryl, e.g. that mentioned for the above araliphatic radicals. It especially represents mono- or di-R₆-phenyl, in which R₆ has the meaning given above.

Esters and amides of the compounds of Formula I are particularly lower alkyl esters, the amide, mono- or di-loweralkyl-amides (hydroxy or lower alkoxy)-lower alkyl esters or amides (amino, mono- or di-loweralkylamino)-lower alkyl esters or amides, wherein two heteroatoms are separated by at least 2, preferably 2 or 3, carbon atoms, e.g. the methyl, ethyl, n- or i-propyl or -butyl ester, the amide, mono- or dimethylamide, diethylamide or i-propylamide, the 2-(hydroxy or methoxy)-ethyl ester or amide, 2-(amino, mono- or dimethylamino)-ethyl ester or amide or 3-dimethyl-amino-propyl ester or amide, or aralkyl esters, such as (R₆-phenyl)-lower alkyl, e.g. benzyl, 1- or 2-phenylethyl esters.

The acyl derivatives are preferably those of lower alkanolic acids, such as acetic, propionic, butyric or pivalic acid, but also of lower alkenolic acids, such as acrylic or methacrylic acid, or of R₆-phenyl-lower alkanolic or -alkenolic acids, such as benzoic, phenylacetic or cinnamic acid. The acyl group therein is preferably attached to a primary, but also a secondary amino group and/or a free hydroxy or mercapto group.

The compounds of the invention exhibit valuable pharmacological properties. Primarily they show diuretic, natri- and chloruretic activity with rapid onset of action, high urine but low potassium excretion levels. This can be demonstrated in animal tests using, for example mammals, e.g. rats or dogs, as test objects. Such tests can be performed, for example, by administering the compounds of the invention within a gelatin capsule to dogs, or in the form of aqueous solutions or suspensions by stomach tube to rats, in an oral dosage range between about 0.1 and 100 mg./kg./day, preferably between about 0.3 and 50 mg./kg./day, advantageously between about 1 and 5 mg./kg./day. Simultaneously the test animals may receive various salt loads enterally or parenterally, for example, various amounts of subcutaneously applied 0.9% saline, e.g. 100 ml. thereof per medium-sized dog (beagle). Urine is then collected, e.g. at 2 hour intervals, with or without

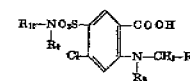
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catheterization, and its volume, sodium, potassium and chloride content estimated and compared with that of the same untreated or saline-treated animals. Besides the above-mentioned utility, the compounds of the invention can also be used as intermediates in the preparation of other valuable products, primarily of pharmacologically active compounds.

Preferred are those compounds of Formula I in which R₁ is lower alkyl, lower alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenyl-alkyl, oxo-cycloalkyl or -cycloalkenyl, oxocycloalkyl- or -cycloalkenyl-lower alkyl, with 5 to 7 ring-carbon and 1 to 4 chain carbon atoms, lower fluoro- or chloroalkyl, lower alkoxy- or alkylmercapto-lower alkyl, di-lower alkylamino- or lower-alkylene-imino-lower alkyl, R₂ and R₃ are hydrogen, lower alkyl or (mono- or di-R₆-phenyl)-alkyl with 1 to 4 chain carbon atoms, R₆ is chloro and R₃ is mono- or di-R₆-phenyl or unsubstituted or lower alkyl-substituted monocyclic monoaza-, -oxa- or -thiacyclic aryl, preferably pyridyl, furyl or thienyl, or especially those compounds of Formula I, in which R₂-R₆ have the meaning given in this paragraph and R₃ is (mono- or di-R₆-phenyl)-alkyl or unsubstituted or lower alkyl-substituted monocyclic monoaza-, -oxa- or -thiacyclic arylalkyl with 1 to 4 chain carbon atoms, or lower alkanoyl derivatives of compounds containing a primary or secondary amino group, or lower alkyl esters, the amide, mono- or di-lower-alkylamides (hydroxy or lower alkoxy)-lower alkyl esters or amides (amino, mono- or di-lower-alkylamino)-lower alkyl esters or amides, wherein two heteroatoms are separated by at least 2 carbon atoms, the alkali metal, alkaline earth metal or ammonium salts of said anthranilic acids, or acid addition salts of basic compounds.

Especially valuable are the compounds of Formula II



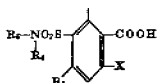
(II)

in which each of R₁, R₂ and R₃ is phenyl, mono- or di-lower alkylphenyl, lower hydroxyalkylphenyl, mono- or dihydroxyphenyl, lower alkylhydroxyphenyl, mono- or dimercapto-phenyl, mono- or di-lower alkoxy-phenyl, lower alkoxy-hydroxyphenyl, lower hydroxyalkoxyphenyl, mono- or di-lower alkylmercapto-phenyl, mono- or di-halogeno-phenyl, trifluoromethylphenyl, nitrophenyl, mono- or diaminophenyl, di-lower alkylaminophenyl, lower alkanoylaminophenyl, carbonylphenyl, lower carbalkoxyphenyl, pyridyl, lower alkylpyridyl, furyl, lower alkylfuryl, thienyl, lower alkylthienyl, tetrahydrofuryl, lower alkyltetrahydrofuryl, dihydropranyl or lower alkylidihydropranyl, and each of R₁ and R₃ is hydrogen or lower alkanoyl, the lower alkyl esters, the amide, mono- or di-loweralkylamides (hydroxy or lower alkoxy)-lower alkyl esters or amides, (amino mono- or di-lower alkylamino)-lower alkyl esters or amides, wherein two heteroatoms are separated by at least 2 carbon atoms, the alkali metal, alkaline earth metal, ammonium or acid addition salts thereof.

Outstanding are the compounds of Formula II, in which R₁ is phenyl, 2-furyl, 2-thienyl, 2-tetrahydrofuryl, 2-methyl-2-tetrahydrofuryl or 2,3-dihydro-2-pyranyl, each of R₂ and R₃ is hydrogen or acetyl and R₃ is phenyl, mono- or dimethylphenyl, 2-hydroxyethylphenyl, mono- or dihydroxyphenyl, methyl-hydroxyphenyl, mercapto-phenyl, mono- or dimethoxyphenyl, methoxy-hydroxyphenyl, 2-hydroxyethoxyphenyl, fluoro-phenyl, chlorophenyl, trifluoromethylphenyl, nitrophenyl, mono- or diamino-phenyl, dimethylaminophenyl, acetylaminophenyl, carbonylphenyl, carbomethoxyphenyl or carbethoxyphenyl, the methyl or ethyl ester, 3-dimethylaminopropylamide, the sodium potassium or 2-hydroxyethylammonium salts of the carboxylic acids or the hydrochlorides of the mono- or diamino or dimethylamino compounds.

Most preferred are the N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid and the N-furfuryl-5-(4-hydroxy-, methoxy- or amino-phenylsulfamyl)-4-chloro-anthranilic acid and their sodium or 2-ethanolammonium carboxylic acid salts or the hydrochloride of the 4-amino-phenyl compound which, when given to dogs at oral doses between about 1 and 5 mg./kg./day, exhibit high diuretic, natri- and chloriuretic effects.

The compounds of the invention are prepared according to methods in themselves known. Advantageously they are obtained by converting in a compound of the Formula III



in which X stands for a group capable of being converted into the amino group



an ester, halide, amide, hydrazide, acyl derivative or salt thereof, X into



and hydrolyzing any resulting amide or hydrazide different from such defined above and, if desired, converting any resulting compound into another compound of the invention.

Any ester, amide, hydrazide or acyl derivative used as starting material may be such as described above for the final products. Generally, the amides or hydrazides used as starting material may be N-unsubstituted or N-substituted, for example, by one or more than one aliphatic, araliphatic or aromatic radical, e.g. any of those described above.

The group X, capable of being converted into



is preferably a halogen atom, advantageously fluoro or chloro, but also primary amino or an imino group, forming after reduction (of the corresponding Schiff's base) the group R_1-NH-R_2 . The starting material, in which X stands for halogeno, is reacted with the amine



that in which X stands for NH_2 , is reacted with a reactive ester of the alcohol R_1-OH , e.g. such of a hydrohalic or sulfonic acid, e.g. hydrochloric, hydrobromic, hydriodic, methane-, ethane-, benzene- or p-toluenesulfonic acid, whereas that starting material, in which X stands for said amino group, is subjected to hydrogenation, for example, with the use of catalytically activated or nascent hydrogen.

The above process is carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing agents and/or inert atmospheres, at low temperatures, room temperature or advantageously elevated temperatures, at atmospheric or superatmospheric pressures.

In the above reaction the amine reagent is advantageously used in excess, in order to neutralize any generated acid. It may however, also be used in equivalent amounts and in the presence of other condensing agents such as inorganic or organic bases, e.g. alkali metal carbonates or bicarbonates or tertiary nitrogen bases, for example tri-lower alkylamines, N,N-dimethyl-aniline or pyridine.

Any resulting amide or hydrazide can be hydrolyzed in the usual manner, for example, with the use of a base, e.g. an aqueous alkali or alkaline earth metal hydroxide, or a quaternary ammonium hydroxide. The compounds of the invention so obtained may be converted into each other

according to known methods. For example, resulting compounds in which R_2 and/or R_3 stands for hydrogen, may be reacted with a reactive ester of a corresponding alcohol, for example that of a hydrohalic or sulfonic acid. Resulting compounds with a hydroxy, prim. or sec. amino group may be acylated, for example, with a reactive functional derivative of a corresponding acid, such as a halide or anhydride thereof, e.g. thionyl or acetyl chloride or acetic anhydride, resulting acyl derivatives or esters may be hydrolyzed, for example with the use of acidic or alkaline hydrolyzing agents, resulting esters may be transesterified or reacted with corresponding amines or resulting acids esterified or amidated in known manner.

The compounds of the invention are obtained in the free form or in the form of their salts, depending on the conditions under which the process is carried out, the salts are also included in the present invention. These are particularly derived from the free acids and therapeutically useful inorganic or organic bases, primarily the alkali metal, alkaline earth metal, e.g. sodium, potassium, magnesium or calcium salts, or ammonium salts derived from ammonia or amines, such as those corresponding to the amino group



e.g. mono-, di- or tri-lower alkylamines, cycloalkylamines, cycloalkyl-lower alkylamines or -aralkylamines, mixed amines or tertiary nitrogen bases, such as pyridine, collidine or lutidine. Resulting compounds that contain basic groups, e.g. amino groups, may also form acid addition salts, preferably such of therapeutically useful acids, such as mineral acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric, nitric or perchloric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, embonic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogen-benzenesulfonic, toluenesulfonic, naphthalenesulfonic and sulfanilic acid; methionine, tryptophane, lysine and arginine.

The invention further includes any variant of the present process in which an intermediate product obtainable at any stage of the process is used as starting material and any remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions, or in which the reaction components are used in the form of their salts. Mainly those starting materials should be used in the reactions of the invention that lead to the formation of those compounds indicated above as being especially valuable.

The starting material is new and, therefore, a further object of the present invention. It can be prepared according to known methods, for example, a corresponding 2,4-dihalo-benzoic acid is reacted with chlorosulfonic acid in order to yield the 2,4-dihalo-5-chlorosulfonyl-benzoic acid. The latter, or a functional derivative thereof, is then reacted with the amine R_1-NH-R_2 in order to obtain the compounds of Formula III in which X stands for halogeno, or functional derivatives thereof. The latter, e.g. the esters, halides, amides or hydrazides, may also be prepared from the acids of Formula III by conventional methods. The resulting 2,4-dihalo-5-sulfonyl-benzoic acids may be reacted with ammonia in order to obtain the starting material in which X represents NH_2 , which further may be reacted with a corresponding aldehyde or ketone, in order to obtain the starting material in which X stands for an imino group.

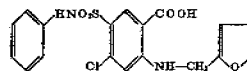
The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions containing an effective amount thereof in conjunction or admixture with excipients suitable for either enteral or parenteral application. Preferred are tablets and

gelatin capsules comprising the active ingredient together with (a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, (b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol, for tablets also (c) binders, e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, if desired, (d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, enzymes of the binders or effervescent mixtures and/or (e) adsorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously fatty emulsions or suspensions. They may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. They may also contain other therapeutically valuable substances. Said pharmaceutical compositions are prepared according to conventional mixing, granulating or coating methods respectively and contain about 0.1 to 75%, preferably about 1 to 50% of the active ingredient.

The following examples illustrating the invention are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade and all parts wherever given are parts by weight.

EXAMPLE 1

The mixture of 2.4 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 10 ml. 2-ethoxy-ethanol and 2.7 g. furfurylamine is refluxed for 4 hours under nitrogen. After cooling to room temperature it is poured into 50 ml. 2 N-hydrochloric acid. The supernatant liquid is decanted off and the residue dissolved in 50 ml. 2 N aqueous sodium hydroxide. The solution is extracted twice with diethyl ether and acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from ethanol to yield the N-furfuryl-5-phenylsulfamyl-4-chloroanthranilic acid of the formula



melting at 210-212° (dec.).

The starting material is prepared as follows: To 250 g. chlorosulfonic acid 50 g. 2,4-dichloro-benzoic acid are added portion-wise at room temperature while stirring. The solution obtained is heated to about 180° and stirred for 3 hours. After cooling to room temperature, it is poured into ice, the mixture filtered, the residue washed with water, and dissolved in 400 ml. ethyl acetate. The solution is dried, filtered, evaporated, and the residue triturated with hexane, to yield the 2,4-dichloro-5-chlorosulfonyl-benzoic acid.

The mixture of 5.8 g. thereof, 7.5 g. aniline and 50 ml. ethyl acetate is stirred for 4 hours at room temperature. It is then filtered and the residue washed with ethyl acetate. The filtrate is evaporated in vacuo and the residue triturated with 2 N hydrochloric acid. The aqueous solution is decanted off and the precipitate dissolved in 100 ml. 10% aqueous potassium carbonate. The solution is filtered to yield residue A. The filtrate is extracted with diethyl ether and the aqueous layer acidified with hydrochloric acid. The precipitate formed is filtered off, washed with water and recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-phenylsulfamyl-benzoic acid melting at 211-213°. Residue A is also recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-phenylsulfamyl-benzoic acid phenylamide melting at 173-175°.

EXAMPLE 2

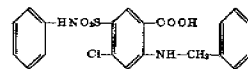
The mixture of 3.0 g. N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid phenylamide, 30 ml. 2 N aqueous sodium hydroxide, 10 ml. water and 10 ml. 2-methoxy-

ethanol is refluxed for 3 hours under nitrogen and allowed to stand at room temperature overnight. It is poured into 60 ml. 2 N - hydrochloric acid, the precipitate formed filtered off, washed with water and dissolved in 35 ml. 10% aqueous potassium carbonate. The solution is extracted with ethyl acetate, the aqueous layer separated and acidified with hydrochloric acid. The precipitate formed is filtered off, recrystallized from aqueous ethanol to yield the N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid melting at 212-214° with decomposition; it is identical with the compound obtained according to Example 1.

The starting material is prepared as follows: The mixture of 6.0 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid phenylamide, 5.6 g. furfurylamine and 20 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and allowed to stand overnight at room temperature. It is poured into 100 ml. 2 N-hydrochloric acid, the precipitate formed filtered off and the residue dissolved in diethyl ether. The solution is washed with 0.5 N hydrochloric acid, with 10% aqueous potassium carbonate and water, dried, filtered and evaporated in vacuo, to yield the N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid phenylamide melting at 114-117°.

EXAMPLE 3

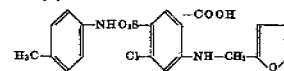
Substituting in Example 1 the furfurylamine by the equivalent amount of benzylamine and performing the reaction as shown therein, the N-benzyl-5-phenylsulfamyl-4-chloroanthranilic acid of the formula



is obtained, M.P. 226-228° (from aqueous ethanol).

EXAMPLE 4

The mixture of 3.1 g. 2,4-dichloro-5-(4-methyl-phenylsulfamyl)-benzoic acid, 3.4 g. furfurylamine and 10 ml. 2-methoxyethanol is refluxed for 4 hours under nitrogen. After cooling to room temperature, it is treated with 2 N-hydrochloric acid, the precipitate formed separated and dissolved in 2 N aqueous sodium hydroxide. The solution is extracted with diethyl ether, the aqueous layer separated and acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol to yield the N-furfuryl-4-chloro-5-(4-methyl-phenylsulfamyl)-anthranilic acid of the formula



melting at 218-220°.

The starting material is prepared as follows: To the solution of 5.8 g. 2,4-dichloro-5-chlorosulfonyl-benzoic acid in 50 ml. ethyl acetate, 8.6 g. p-toluidine are added while stirring, followed by 100 ml. ethyl acetate. The mixture is stirred at room temperature for 2 hours and refluxed for 2 hours while stirring. After cooling it is filtered, the residue washed with ethyl acetate and the filtrate evaporated in vacuo. The residue is treated with 10 ml. concentrated hydrochloric acid and extracted with ethyl acetate. The organic layer is separated, extracted with 10% aqueous potassium carbonate and the aqueous solution acidified with hydrochloric acid. The precipitate formed is filtered off, washed with water and recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-(4-methyl-phenylsulfamyl)-benzoic acid melting at 202-204°.

EXAMPLE 5

According to the method shown in the previous examples the compounds of Formula I, R_2 =furfuryl, R_3 =H, R_4 =Cl, and listed below, are prepared from

equivalent amounts of the corresponding starting materials of Formula III, $R_1 = X = Cl$:

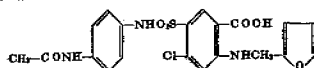
Number	R_1	M.P. anal product	M.P. starting material
1	$4-CH_3O-C_6H_4$	206-208°	224-225°
2	$4-F-C_6H_4$	207-208°	224-225°
3	$2-O-C_6H_4$	207-208°	188-179°
4	$2-Cl-C_6H_4$	225-226°	190-192°
5	$4-Cl-C_6H_4$	225-226°	228-240°
6	$2-OP-C_6H_4$	226-228°	224-226°
7	$4-CP-C_6H_4$	222°	228-230°
8	$4-NO_2-C_6H_4$	225°	209-271°
9	$2-CH_3-C_6H_4$	188-189°	175-176°
10	$4-HOCH_2CH_2-C_6H_4$	178-179°	196-198°
11	$4-CH_3N-C_6H_4$	228°	198°
12	$2-HOCH_2CH_2-C_6H_4$	147°	229-231°
13	$2-NH_2-C_6H_4$	180°	178-180°
14	$4-H_2COON-C_6H_4$	228°	245-247°
15	$4-CH_3NE-C_6H_4$	190°	140°

* Decomposition.

NOTE.—All compounds were recrystallized from aqueous ethanol.

EXAMPLE 6

The mixture of 4.0 g. 2,4-dichloro-5-(4-acetylaminophenylsulfamyl)-benzoic acid, 3.9 g. furfurylamine and 10 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling it is treated with 2 N-hydrochloric acid, the residue formed separated and dissolved in 2N-aqueous sodium hydroxide. The solution is extracted with diethyl ether, the aqueous layer separated, acidified with hydrochloric acid and the precipitate formed recrystallized from aqueous ethanol to yield the N-furfuryl-4-chloro-5-(4-acetylaminophenylsulfamyl)-anthranilic acid of the formula

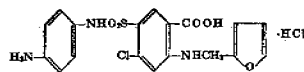


melting at 248° with decomposition.

The starting material is prepared as follows: To the solution of 5.8 g. 2,4-dichloro-5-chlorosulfonyl-benzoic acid in 50 ml. ethyl acetate, 12.0 g. 4-amino-acetanilide are added, followed by 50 ml. ethyl acetate. The mixture is stirred for 2 hours at room temperature and refluxed for 2 hours while stirring. After cooling to room temperature it is filtered, the residue (A) washed with ethyl acetate and the filtrate evaporated in vacuo. The residue (B) is triturated with water and 10 ml. concentrated hydrochloric acid, filtered off, washed with water and dried. The combined residues (A) and (B) are dissolved in 60 ml. 10% aqueous potassium carbonate, the solution washed with diethyl ether, acidified with hydrochloric acid, the precipitate formed filtered off and washed with water to yield the 2,4-dichloro-5-(4-acetylaminophenylsulfamyl)-benzoic acid melting at about 150°.

EXAMPLE 7

The mixture of 5.3 g. 2,4-dichloro-5-(4-amino-phenylsulfamyl)-benzoic acid hydrochloride, 5.4 g. furfurylamine and 15 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and evaporated in vacuo. To the residue 30 ml. 2 N-hydrochloric acid are added and the precipitate formed filtered off. It is triturated with 40 ml. water at room temperature, filtered off, washed with a small amount of ice cold water and diethyl ether and recrystallized from aqueous ethanol to yield the N-furfuryl-4-chloro-5-(4-aminophenylsulfamyl)-anthranilic acid hydrochloride of the formula

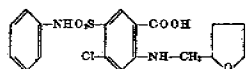


melting at about 230°.

The starting material is prepared as follows: The mixture of 7.1 2,4-dichloro-5-(4-acetylaminophenylsulfamyl)-benzoic acid (of Example 6) and 60 ml. 2 N-aqueous sodium hydroxide is refluxed for 90 minutes. After cooling to room temperature it is acidified with concentrated hydrochloric acid, the precipitate formed filtered off, the residue taken up in ethanol, the solution filtered and evaporated in vacuo, to yield the 2,4-dichloro-5-(4-amino-phenylsulfamyl)-benzoic acid hydrochloride, melting at 185° with decomposition.

EXAMPLE 8

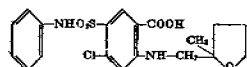
The mixture of 6.5 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 8.0 g. tetrahydrofuryl-2-methylamine and 30 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling to room temperature, it is poured into 180 ml. 2 N-hydrochloric acid, the precipitate separated, ground in a mortar, filtered, washed with water and recrystallized several times from aqueous ethanol to yield the N-(tetrahydrofuryl-2-methyl)-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 238-239°.

EXAMPLE 9

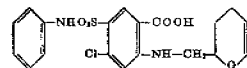
The mixture of 3.5 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 4.6 g. (2-methyl-tetrahydrofuryl-2)-methylamine and 10 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and stirred overnight at room temperature. Hereupon it is poured into 80 ml. 2 N-hydrochloric acid, the residue separated and dissolved in 2 N-aqueous sodium hydroxide. The solution is washed with diethyl ether, filtered and acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-(2-methyl-tetrahydrofuryl-2-methyl)-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 207-208°.

EXAMPLE 10

The mixture of 6.5 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 9.05 g. 2,3-dihydro-pyran-2-methylamine and 30 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling to room temperature it is poured into 180 ml. 2 N-hydrochloric acid, the precipitate formed filtered off, washed with water and recrystallized from aqueous ethanol, to yield the N-(2,3-dihydro-pyran-2-methyl)-4-chloro-5-phenylsulfamyl-benzoic acid of the formula



melting at 115-117° with decomposition.

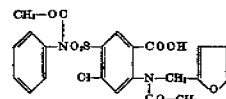
EXAMPLE 11

The mixture of 81.4 g. N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid (Example 1), 110 ml. 2 N aqueous sodium hydroxide and 100 ml. water is heated to about 50 to 60° until dissolution occurs. The solution is filtered, the filtrate cooled, seeded with a few crystals of previously prepared sodium salt, and allowed to stand in the refrigerator. The precipitate formed is filtered off, washed with a small amount of ice water and dissolved in 100 ml. isopropanol at 60°. The solution obtained is slowly cooled and finally kept in the refrigerator. The

precipitate formed is filtered off, triturated with 75 ml. cold isopropanol, filtered again and dried to yield the sodium salt of the N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid, melting at 244 to 246° with decomposition.

EXAMPLE 12

The mixture of 2.0 g. N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid, 2 ml. acetic acid anhydride and 8 ml. pyridine is heated at the steam bath for 1 hour, cooled and poured into water. The mixture is slightly acidified with concentrated hydrochloric acid, the precipitate formed filtered off and dissolved in ethanol. To the solution, water and a few drops hydrochloric acid are added, the precipitate formed filtered off and again recrystallized from aqueous ethanol to yield the N,N'-bisacetyl-N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 206-208°.

EXAMPLE 13

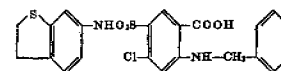
The mixture of 113.3 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 500 ml. 2-methoxy-ethanol and 126.0 g. furfurylamine is stirred and refluxed under nitrogen for 4 hours. The cold mixture is then slowly poured into 2.5 liters 2 N hydrochloric acid while stirring. The precipitate formed is filtered off, washed with water and dissolved in 1 liter 2 N aqueous sodium hydroxide. The dark solution obtained is extracted three times with 135 ml. methylene chloride each and the aqueous layer carefully acidified with concentrated hydrochloric acid. The precipitate formed is filtered off, dissolved in 1 liter ethanol, the solution decolorized with charcoal, filtered hot, the filtrate combined with 1 liter hot water and, upon cooling to 15°, the N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid (Example 1) crystallizes. It is filtered off and dried; it melts at about 206°, which melting point can be raised to 208-210° by another recrystallization.

The starting material is prepared as follows: The mixture of 150 g. 2,4-dichloro-benzoic acid and 600 g. chlorosulfonic acid is heated to 150-155° for 3 hours while stirring. Thereupon, 223 g. chlorosulfonic acid are distilled off in vacuo and the cold residue poured into a mixture of 1.65 kg. ice and 125 ml. water. The precipitate formed is filtered off, washed with cold water, dissolved in 800 ml. ethyl acetate, the solution dried, filtered, and the filtrate diluted with 600 ml. ethyl acetate. To the solution obtained (containing the 2,4-dichloro-5-chlorosulfonyl-benzoic acid), cooled in a water bath, the mixture of 216 g. aniline and 220 ml. ethyl acetate is added at such rate that the temperature stays below 30°. The mixture is stirred for 4 hours at 25-30°, whereupon 4 g. charcoal are added. It is then filtered, the residue washed with 125 ml. ethyl acetate, the filtrate washed first with 450 ml. 3 N hydrochloric acid, then with 550 ml. water, and finally extracted with 700 ml. 7% aqueous sodium carbonate. The aqueous extract is separated, carefully acidified with concentrated hydrochloric acid and the precipitate formed filtered off and dried at 75° in vacuo, to yield the 2,4-dichloro-5-phenylsulfamyl-benzoic acid melting at 212-216°.

EXAMPLE 14

The mixture of equivalent amounts of 2,4-dichloro-5-(2,3-dihydro-6-thianaphthylsulfamyl)-benzoic acid and 0.5 ml. benzylamine in 1 ml. 2-methoxy-ethanol is heated for 4 hours to 130°. After cooling, 5 ml. 2 N hydrochloric acid and 5 ml. water are added, the precipitate formed filtered off, washed with water and triturated with 2 N

aqueous sodium hydroxide. The alkaline solution is filtered, the filtrate acidified with hydrochloric acid, the precipitate formed filtered off, washed with water and dried, to yield the N-benzyl-4-chloro-5-(2,3-dihydro-6-thianaphthylsulfamyl)-anthranilic acid of the formula

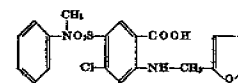


melting at 150° with decomposition.

The starting material is prepared as follows: To the solution of 1.9 g. 6-amino-2,3-dihydro-thianaphthene in 25 ml. ethyl acetate and 3 ml. pyridine, 2.9 g. 2,4-dichloro-5-chlorosulfonylbenzoic acid are added slowly while stirring. The mixture is stirred for 3 hours at room temperature and allowed to stand overnight. It is made strongly acidic with hydrochloric acid, extracted with ethyl acetate, the extract washed with water, dried and evaporated in vacuo. The residue is taken up in 1 N aqueous sodium hydroxide, the solution filtered and the filtrate acidified. The precipitate formed is filtered off and recrystallized first from aqueous ethanol and finally from methanol, to yield the 2,4-dichloro-5-(2,3-dihydro-6-thianaphthylsulfamyl)-benzoic acid.

EXAMPLE 15

The mixture of 3.6 g. 2,4-dichloro-5-(N-methyl-N-phenylsulfamyl)-benzoic acid, 3.9 g. furfurylamine and 10 ml. 2-methoxyethanol is refluxed for 4 hours under nitrogen. After cooling, it is poured into 50 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and heated with 50 ml. 2 N aqueous sodium hydroxide. To the suspension obtained, water and diethyl ether are added until 2 clear layers are formed. The aqueous layer is separated, washed with diethyl ether and acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid of the formula



melting at 171-172°.

In the analogous manner, the N-benzyl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid is obtained; M.P. 164-166°.

The starting material is prepared as follows: To the solution of 11.6 g. 2,4-dichloro-5-chlorosulfonylbenzoic acid in 100 ml. ethyl acetate, 17.1 g. N-methyl-aniline are added slowly, and the mixture is stirred at room temperature for 4 hours. It is then filtered, the filtrate evaporated in vacuo and the residue taken up in water and 20 ml. concentrated hydrochloric acid. The mixture is extracted with ethyl acetate, the extract washed with water and shaken with 10% aqueous potassium carbonate. The aqueous layer is separated, acidified with concentrated hydrochloric acid, the precipitate formed filtered off and recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-(N-methyl-N-phenylsulfamyl)-benzoic acid, melting at 170-171°.

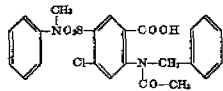
EXAMPLE 16

The mixture of 3 g. N-benzyl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid (Example 15), 12 ml. pyridine and 3 ml. acetic acid anhydride is heated at the steam bath for 1 hour while stirring. After cooling, it is poured into 120 ml. water, the mixture acidified with concentrated hydrochloric acid, the precipitate collected and recrystallized from aqueous methanol to yield the N-

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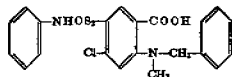
acetyl-N-benzyl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid of the formula



melting at 176-177° with decomposition.

EXAMPLE 17

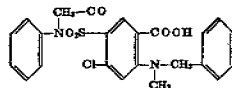
The mixture of equivalent amounts of 2,4-dichloro-5-phenylsulfamyl-benzoic acid and 9.7 g. N-methyl-benzylamine in 20 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling, it is poured into 100 ml. 2 N-hydrochloric acid, the precipitate formed filtered off, washed with water and dissolved in 2 N aqueous sodium hydroxide. The mixture is extracted with diethyl ether, the aqueous layer separated and acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-methyl-N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 183-184° with decomposition.

EXAMPLE 18

The mixture of 3 g. N-methyl-N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid (Example 17), 12 ml. pyridine and 3 ml. acetic acid anhydride is heated at the steam bath for 1 hour while stirring. After cooling, it is poured into 120 ml. water, the mixture acidified with concentrated hydrochloric acid and the precipitate formed filtered off. The residue is dissolved in the minimum amount of hot ethanol, the solution filtered and allowed to cool to room temperature. The precipitate formed is filtered off and washed with aqueous ethanol to yield the N-methyl-N-benzyl-4-chloro-5-(N-acetyl-N-phenylsulfamyl)-anthranilic acid of the formula



melting at 191-192° with decomposition.

EXAMPLE 19

Preparation of 10,000 tablets each containing 50.0 mg. of the active ingredient:

Formula:	G.
Sodium N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilate	500.00
Lactose	1,706.00
Corn starch	90.00
Polyethylene glycol 6,000	90.00
Talcum powder	90.00
Magnesium stearate	24.00
Purified water, q.s.	

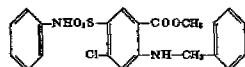
Procedure.—All the powders are passed through a screen with an opening of 0.6 mm. Then the drug substance, lactose, talcum, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 45 ml. water and the suspension added to the boiling solution of the polyethylene glycol in 180 ml. water. The paste formed is added to the powders which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm. openings

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and compressed into tablets using concave punches with 7.1 mm. diameter, uppers bisected.

EXAMPLE 20

The mixture of 2.2 g. methyl 4-chloro-5-phenylsulfamyl-anthranilate and 12 ml. benzaldehyde is heated to 200° C. for 1 hour and evaporated in vacuo. The residue is triturated with 75 ml. ethylacetate, filtered off and the filtrate hydrogenated over 0.3 g. platinum dioxide at room temperature until the hydrogen uptake slows down (½ hour). The mixture is filtered, the filtrate evaporated in vacuo, the residue taken up in chloroform-diethylamine (9:1) and chromatographed on silica gel, to yield as the main eluate the amorphous methyl N-benzyl-4-chloro-5-phenylsulfamyl-anthranilate of the formula



showing in the I.R.-spectrum bands, inter alia at 1750 and 1250 cm.⁻¹.

1.8 g. thereof are dissolved in 20 ml. methanol and 10 ml. 2 N aqueous sodium hydroxide, and the solution is refluxed for 20 minutes. It is then concentrated in vacuo, the aqueous concentrate diluted with water, extracted with diethyl ether and the aqueous layer acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid melting at 226-228°; it is identical with the product obtained according to Example 3.

The starting material is prepared as follows: The mixture of 1.0 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid and 25 ml. concentrated aqueous ammonia is heated in a sealed tube to 120° for 4 hours. Hereupon, it is evaporated in vacuo, the residue taken up in 25 ml. saturated anhydrous methanolic hydrochloric acid and the mixture gently refluxed for 1 hour. It is evaporated in vacuo and the residue recrystallized from methanol, to yield the methyl 4-chloro-5-phenylsulfamyl-anthranilate melting at 183-186°.

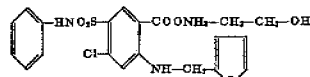
EXAMPLE 21

The mixture of 2.0 g. methyl 4-chloro-5-phenylsulfamyl-anthranilate and 5 ml. benzyl chloride is refluxed for 2 hours and evaporated in vacuo. The residue is triturated with diethyl ether, filtered off and washed with diethyl ether to yield the methyl N-benzyl-4-chloro-5-phenylsulfamyl-anthranilate melting at about 200° (softening at 185°); it is identical with the compound obtained according to Example 20.

The mixture of 1.3 g. thereof, 5 ml. methanol, 5 ml. water and 1.5 ml. 6 N aqueous sodium hydroxide is heated at the steam bath for 30 minutes and allowed to stand at 25° for 1 hour. It is then concentrated in vacuo, the concentrate diluted with water, extracted with diethyl ether and the aqueous layer filtered. The filtrate is acidified with hydrochloric acid to pH 5, the precipitate formed filtered off and recrystallized from aqueous ethanol, to yield the N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid melting at 226°; it is identical with the product obtained according to Example 3.

EXAMPLE 22

To the suspension of 4.07 g. N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid and 50 ml. methanol, 0.61 g. 2-hydroxyethylamine are added while stirring. The resulting yellowish solution is evaporated in vacuo, to yield the 2-hydroxyethylammonium N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilate of the formula



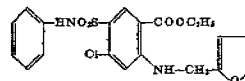
melting at 90°.

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EXAMPLE 23

The mixture of 13.1 g. ethyl 2,4-dichloro-5-phenylsulfamylbenzoate and 20.4 g. furfurylamine is heated for 1 hour to 110°. After cooling, it is poured into 210 ml. water, the mixture acidified with glacial acetic acid to pH 4.5 while keeping the temperature below 20°. The precipitate formed is filtered off, washed with water and suspended in 250 ml. 0.5 N sodium hydroxide while stirring at room temperature. It is filtered, the residue suspended in water and the mixture acidified with hydrochloric acid to pH 2 while stirring. It is again filtered and the residue recrystallized several times from aqueous ethanol and finally from anhydrous ethanol, to yield the ethyl N-furfuryl-5-sulfamyl-4-chloro-anthranilate of the formula

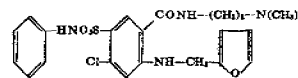


melting at 157-159°.

The starting material is prepared as follows: The mixture of 15 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid and 150 ml. 6 N ethanolic hydrochloric acid is refluxed for 90 minutes and allowed to stand in the cold. The precipitate formed is filtered off, and recrystallized from aqueous ethanol, to yield the ethyl 2,4-dichloro-5-phenylsulfamyl-benzoate melting at 132-133°.

EXAMPLE 24

The mixture of 6.6 g. 2,4-dichloro-5-phenylsulfamylbenzoic acid 3-dimethylamino-propylamide, 5.8 g. furfurylamine and 15 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and evaporated in vacuo. The residue is taken up in 100 ml. 2 N aqueous sodium hydroxide and the mixture extracted with ethyl acetate. The organic layer is dried, filtered and evaporated. The residue is triturated with hydrogen chloride in ethyl acetate, the precipitate formed filtered off and taken up in water. The solution is washed with ethyl acetate, filtered and made basic with 2 N aqueous sodium hydroxide. The mixture is extracted with ethyl acetate, the extract dried, filtered and evaporated, to yield the amorphous N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid 3-dimethylaminopropylamide of the formula



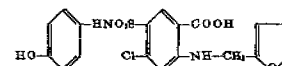
showing in the thin layer chromatogram on silica gel in chloroform, methanol and diethylamine (85:5:10) an R_{fm}=7.5.

The starting material is prepared as follows: To the mixture of 17.7 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid and 90 ml. 1,2-dimethoxyethane, 24 ml. thionyl chloride are added dropwise during 25 minutes while stirring, the whole is refluxed for 90 minutes and evaporated in vacuo. 18.6 g. of the resulting acid chloride is taken up in 300 ml. ethyl acetate and the solution added dropwise to the mixture of 11.8 g. 3-dimethylaminopropylamine and 450 ml. ethyl acetate while stirring, and stirring is continued overnight at room temperature. The mixture is filtered, the filtrate acidified with hydrogen chloride in ethyl acetate and the precipitate formed filtered off. It is taken up in water, the solution washed with ethyl acetate and made alkaline with 10% potassium carbonate. The mixture is extracted with ethyl acetate, the mixture dried, filtered and evaporated, to yield the 2,4-dichloro-5-phenylsulfamyl-benzoic acid 3-dimethylamino-propylamide melting between about 80 and 90°.

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EXAMPLE 25

The mixture of 3.6 g. 2,4-dichloro-5-(4-hydroxyphenylsulfamyl)-benzoic acid, 10 ml. 2-methoxy-ethanol and 3.9 g. furfurylamine is refluxed for 4 hours under nitrogen. After cooling, it is poured into 50 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered and the filtrate acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(4-hydroxyphenylsulfamyl)-anthranilic acid of the formula



melting at 227° with decomposition.

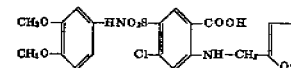
The starting material is prepared as follows: To the mixture of 5.8 g. 2,4-dichloro-5-chlorosulfonylbenzoic acid and 100 ml. ethyl acetate, 8.7 g. 4-hydroxyaniline are added portionwise and the mixture stirred at room temperature for 4 hours. After standing overnight, it is filtered, the residue suspended in 50 ml. water, the mixture acidified with 10 ml. concentrated hydrochloric acid and extracted with ethyl acetate. The extract is filtered, washed with water and shaken with 10% aqueous potassium carbonate. The aqueous solution is filtered, acidified with concentrated hydrochloric acid and the precipitate formed filtered off. It is recrystallized several times from aqueous ethanol, to yield the 2,4-dichloro-5-(4-hydroxyphenylsulfamyl)-benzoic acid melting at 223-235°.

EXAMPLE 26

In the manner described in Example 25, the N-furfuryl-4-chloro-5-(2-hydroxyphenylsulfamyl)-anthranilic acid, M.P. 125° (dec.) and the N-furfuryl-4-chloro-5-(3-hydroxyphenylsulfamyl)-anthranilic acid, M.P. 202° (dec.) are prepared from the same amounts of the corresponding isomeric starting materials, which melt at 187-189° and 192-194° respectively.

EXAMPLE 27

The mixture of 3.9 g. 2,4-dichloro-5-(3,4-dimethoxyphenylsulfamyl)-benzoic acid, 10 ml. 2-methoxyethanol and 3.7 g. furfurylamine is refluxed for 4 hours under nitrogen. After cooling, it is poured into 50 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered, the filtrate acidified with concentrated hydrochloric acid, the precipitate formed collected and recrystallized two times from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(3,4-dimethoxyphenylsulfamyl)-anthranilic acid of the formula



melting at 123°.

The starting material is prepared as follows: To the solution of 12.3 g. 3,4-dimethoxyaniline and 50 ml. ethyl acetate, 5.8 g. 2,4-dichloro-5-chlorosulfonylbenzoic acid are added while stirring, and the mixture stirred for 4 hours at room temperature. It is filtered, the residue washed with ethyl acetate and the filtrate combined with 10 ml. water and concentrated hydrochloric acid each and diluted with ethyl acetate. The organic layer is separated, extracted with 10% aqueous potassium carbonate and the extract acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized two times from aqueous ethanol, to yield the 2,4-dichloro-5-(3,4-dimethoxyphenylsulfamyl)benzoic acid melting at 202-203°.

EXAMPLE 28

In the manner described in Example 27, the N-furfuryl-4-chloro-5-(2,4-dimethoxyphenylsulfamyl)-anthranilic acid, M.P. 103° and the N-furfuryl-4-chloro-5-(2,5-dimethoxyphenylsulfamyl)-anthranilic acid, M.P. 199-202° are prepared from the same amounts of the corresponding isomeric starting materials, which melt at 184-185° and 180-182° respectively.

EXAMPLE 29

Analogous to the procedures illustrated in the previous examples, more particularly according to Example 25, the N-furfuryl-4-chloro-5-(4-mercaptophenyl, 3,4-dihydroxyphenyl, 3-methyl-4-hydroxyphenyl, 3-methoxy-4-hydroxyphenyl, 4-(2-hydroxyethyl)-phenyl, 4-(2-hydroxyethoxy)-phenyl, 4-carboxyphenyl, 4-carbomethoxyphenyl or 4-carbomethoxyphenyl)-sulfamyl-anthranilic acid or, according to Example 7, the N-furfuryl-4-chloro-5-(2- or 3-aminophenyl, 3,5-diaminophenyl, 4-dimethylaminophenyl or 4-diethylaminophenyl)-sulfamyl-anthranilic acid, their sodium, potassium or 2-ethanol-ammonium salts or the hydrochlorides of the aminophenyl compounds, are prepared from equivalent amounts of the corresponding starting materials.

EXAMPLE 30

Preparation of 1,000 capsules, each containing 25 mg. of the active ingredient:

Formula:	
N-furfuryl-4-chloro-5-(4-hydroxyphenylsulfamyl)-anthranilic acid	25.0
Lactose	220.0

Procedure:

The ingredients are intimately mixed in a suitable mixer, passed through a screen with openings of 0.6 mm., remixed and 245 mg. are filled into No. 3 hard shell gelatin capsules.

In the analogous manner, capsules are prepared containing per unit 75 mg. N-furfuryl-4-chloro-5-(4-methoxyphenylsulfamyl)-anthranilic acid or N-furfuryl-4-chloro-5-(4-aminophenylsulfamyl)-anthranilic acid hydrochloride and 170 mg. lactose.

EXAMPLE 31

Preparation of 10,000 tablets, each containing 50 mg. of the active ingredient:

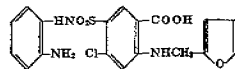
Formula:	
N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid	500.0
Lactose	2,500.0
Microcrystalline cellulose	1,000.0
Corn starch	160.0
Magnesium stearate	40.0
Purified water, q.s.	

Procedure.—All the powders, except the starch and the magnesium stearate, are passed through a screen with 0.6 mm. openings and mixed in a suitable mixer. The starch is suspended in 160 ml. water and the suspension added to 200 ml. boiling water. The paste formed is added to the powders which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm. openings, the magnesium stearate added, mixed well and the granulate compressed into 420 mg. tablets using concave punches with 7.1 mm. diameter, uppers bisected.

EXAMPLE 32

The mixture of 15 g. of N-furfuryl-4-chloro-5-(2-acetylaminophenylsulfamyl)-anthranilic acid and 90 ml. of 2 N aqueous sodium hydroxide are refluxed for 2½ hours in a nitrogen atmosphere, cooled and acidified with glacial acetic acid. The solids formed are collected on a filter, washed with water and recrystallized from aqueous ethanol

to afford the N-furfuryl-4-chloro-5-(2-aminophenylsulfamyl)-anthranilic acid of the formula



melting at 246-248°.

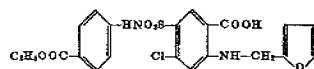
The starting material is prepared as follows:

To the solution of 50 g. of 2-aminoacetanilide and 100 ml. of dimethylformamide are added portionwise 30 g. of 2,4-dichloro-5-chlorosulfonyl-benzoic acid at 20°. The reaction mixture is warmed to 40° for 2 hours, evaporated under reduced pressure and the residue poured into 500 ml. of water and 7 ml. of concentrated hydrochloric acid. The solids formed are collected on a filter, washed with water and dilute aqueous hydrochloric acid, and triturated with aqueous ethanol to give the 2,4-dichloro-5-(2-acetylaminophenylsulfamyl)-benzoic acid melting at 222-225°.

The mixture of 30 g. thereof, 30 g. of furfurylamine and 75 ml. of 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. The mixture is concentrated to half its volume under reduced pressure and is then poured onto 250 ml. of 2 N aqueous hydrochloric acid with stirring. The precipitate formed is filtered, washed with water, triturated with a 1:1 mixture of ethanol and water at 70° and repeated with 95% aqueous methanol to give the N-furfuryl-4-chloro-5-(2-acetylaminophenylsulfamyl)-anthranilic acid melting at 221-225°.

EXAMPLE 33

The mixture of 5.5 g. of 2,4-dichloro-5-(4-carbomethoxyphenylsulfamyl)-benzoic acid, 10 ml. of 2-methoxy-ethanol and 5 g. of furfurylamine is refluxed for 4 hours under nitrogen. After cooling, it is poured onto 50 ml. of 2 N aqueous hydrochloric acid. The precipitate formed is filtered, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered and the filtrate acidified with concentrated hydrochloric acid. The precipitate formed is collected on a filter and recrystallized from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(4-carbomethoxyphenylsulfamyl)-anthranilic acid of the formula



melting at 217° with decomposition.

The starting material is prepared as follows:

To the solution of 16.5 g. of 4-aminobenzoic acid ethyl ester in 100 ml. of ethyl acetate is added portionwise at room temperature 7.2 g. of 2,4-dichloro-5-chlorosulfonyl-benzoic acid. The mixture is allowed to stir for one hour at room temperature, then refluxed for 6 hours. After cooling, the solids are filtered off and washed with ethyl acetate. The filtrate is evaporated under reduced pressure. The residue is treated with water and 15 ml. of concentrated hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate solution is extracted with 3 portions, 50 ml. each, of 10% aqueous potassium carbonate. The carbonate extracts are combined, filtered and acidified with concentrated hydrochloric acid. The precipitate formed is filtered, washed and recrystallized from aqueous ethanol to afford the 2,4-dichloro-5-(4-carbomethoxyphenylsulfamyl)-benzoic acid melting at 226-228°.

EXAMPLE 34

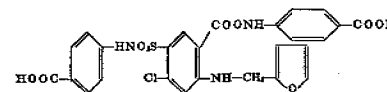
In an analogous manner as in Example 33, 4.7 g. of 2,4-dichloro-5-(4-carboxyphenylsulfamyl)-benzoic acid reacted with 4.7 g. of furfurylamine in 10 ml. of 2-methoxy-ethanol affords on recrystallization from aqueous eth-

anol the N-furfuryl-4-chloro-5-(4-carboxyphenylsulfamyl)-anthranilic acid melting at 264° with decomposition.

The starting material is prepared by the hydrolysis of the 2,4-dichloro-5-(4-carboxyphenylsulfamyl)-benzoic acid (Example 33) and melts at 288° with decomposition.

EXAMPLE 35

The mixture of 5 g. of N-(4-carboxyphenyl)-2,4-dichloro-5-(4-carboxyphenylsulfamyl)-benzamide, 5 g. of furfurylamine and 50 ml. of 2 N aqueous hydrochloric acid. The mixture is stirred for 4 hours under nitrogen. After cooling, it is poured onto 50 ml. of 2 N aqueous hydrochloric acid. The precipitate formed is filtered, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered and the filtrate acidified with concentrated hydrochloric acid to precipitate a syrupy material. The mixture is decanted and the product treated with a 1:1 mixture of ethanol and water. Recrystallization of the solids from a 1:1 ethanol-water mixture gives as a first crop the N-(4-carboxyphenyl)-2-(N-furfurylaminophenyl)-4-chloro-5-(4-carboxyphenylsulfamyl)-anthranilamide of the formula



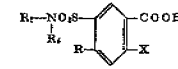
melting at 246° with decomposition. The material obtained on evaporation of the recrystallization solvent corresponds to the product of Example 34.

The starting material is prepared as follows:

The solution of 7.2 g. of 4-aminobenzoic acid in 150 ml. of ethyl acetate is treated with 7.2 g. of 2,4-dichloro-5-chlorosulfonyl-benzoic acid. The mixture is then refluxed for 6 hours. After cooling, the solids are filtered off and washed with ethyl acetate. The filtrate is evaporated under reduced pressure. The residue is treated with water and 15 ml. of concentrated hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate solution is extracted with 3 portions, 50 ml. each, of 10% aqueous potassium carbonate. The carbonate extracts are combined, filtered and acidified with concentrated hydrochloric acid. The crystalline material obtained is ground and treated with a 1:2 ethanol-water mixture, filtered, washed and dried to afford a mixture of N-(4-carboxyphenyl)-2,4-dichloro-5-(4-carboxyphenylsulfamyl)-benzamide and the 2,4-dichloro-5-(4-carboxyphenylsulfamyl)-benzoic acid.

What is claimed is:

1. A 5-arylsulfamyl-2,4-dihalobenzoic acid of the formula



in which X is fluoro or chloro, R1 is chloro or bromo, R2 is hydrogen or lower alkanoyl and R3 is phenyl and phenyl substituted with one or two lower alkyls, hydroxyls, lower alkoxy, halogens or amino, and phenyl substituted with one lower hydroxy-alkyl, lower hydroxyalkoxy, trifluoromethyl, nitro, di-lower alkylamino or lower alkanoylamino, and phenyl substituted with one lower alkyl and one hydroxy, or one lower alkoxy and one hydroxy moiety, or the methyl or ethyl ester, the sodium or potassium salt of the carboxylic acids or the hydrochlorides of the mono- or diamino or di-lower alkylamino compounds.

2. A compound as claimed in claim 1, in which formula each of X and R3 is chloro and R4 and R5 have the meaning given in claim 1.

3. A compound as claimed in claim 1, and being the 2,4-dichloro-5-phenylsulfamyl-benzoic acid.

4. A compound as claimed in claim 1, and being the 2,4-dichloro-5-(4-hydroxy-, methoxy- or aminophenylsulfamyl)-benzoic acid or the sodium or potassium salt thereof or the hydrochloride of the amino compound.

5. A compound as claimed in claim 1 in which formula each of X and R3 is chloro, R4 is hydrogen or acetyl and R5 is phenyl and phenyl substituted with one or two methyls, hydroxyls, methoxies or aminos, and phenyl substituted with one 2-hydroxyethyl, 2-hydroxyethoxy, fluoro, chloro, trifluoromethyl, nitro, dimethylamino or acetyl-amino, and phenyl substituted with one methyl and one hydroxy, or one methoxy and one hydroxy moiety, or the methyl or ethyl ester, the sodium or potassium salt of the carboxylic acids or the hydrochlorides of the mono- or diamino or dimethylamino compounds.

6. A compound as claimed in claim 1, and being the 2,4-dichloro-5-(2-acetylaminophenylsulfamyl)-benzoic acid.

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LORRAINE A. WEINBERGER, Primary Examiner

L. A. THAXTON, Assistant Examiner

U.S. Cl. X.R.

260-239.6, 397.7, 470, 519, 556 B

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3,812,104

5-ARYLSULFAMYL-ANTHRANILIC ACIDS

Inventor: Robert W. Warner, Summit, N.J., assignor to Ciba-Geigy Corporation, Arden, N.Y.

No Drawing. Continuation-in-part of application Ser. No. 157,046, June 25, 1971, which is a continuation-in-part of application Ser. No. 149,027, June 1, 1971, both now abandoned, which is a continuation-in-part of application Ser. No. 91,224, Nov. 19, 1970, which is a continuation-in-part of application Ser. No. 832,029, June 10, 1969, now Patent No. 3,658,990, dated Apr. 25, 1972, which is a continuation-in-part of abandoned application Ser. No. 675,330, Oct. 16, 1967, which in turn is a continuation-in-part of abandoned application Ser. No. 598,980, Dec. 5, 1966. This application July 29, 1971, Ser. No. 167,531.

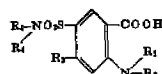
Int. Cl. C07D 5/16

U.S. Cl. 260-239.6

6 Claims

ABSTRACT OF THE DISCLOSURE

5-arylsulfamyl-4-halo-anthranilic acids, e.g. those of the formula



R₁=aliphatic or araliphatic radical

R₂=H or R₁

R₃=Cl or Br

R₄=carbo- or heterocyclic aryl

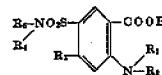
and functional derivatives thereof, exhibit diuretic effects.

CROSS-REFERENCES TO RELATED APPLICATIONS

This is a continuation-in-part of application Ser. No. 157,046, filed June 25, 1971, (now abandoned) which in turn is a continuation-in-part of application Ser. No. 149,027, filed June 1, 1971, (now abandoned) which in turn is a continuation-in-part of application Ser. No. 91,224, filed Nov. 19, 1970, which in turn is a continuation-in-part of application Ser. No. 832,029, filed June 10, 1969, now U.S. Pat. No. 3,658,990 patented Apr. 25, 1972 which in turn is a continuation-in-part of application Ser. No. 675,330, filed Oct. 16, 1967 (now abandoned), which in turn is a continuation-in-part of application Ser. No. 598,980, filed Dec. 5, 1966 (now abandoned).

SUMMARY OF THE INVENTION

The present invention concerns and has for its object the provision of new 5-arylsulfamyl-4-halo-anthranilic acids and their therapeutically acceptable derivatives, more particularly those of Formula I,



in which each of R₁, R₂ and R₄ is an aliphatic or araliphatic radical, R₂ and R₄ are also hydrogen, R₃ is chloro or bromo and R₁ is a carbo- or heterocyclic aryl radical, of esters, amides, acyl derivatives and/or salts thereof, as well as of corresponding pharmaceutical compositions, new starting materials and methods for the preparation and application of these products. Said compositions are primarily useful as orally applicable diuretic, natri- and chloruretic agents in order to relieve excessive water and/or electrolyte retention, for example, in connection with heart and kidney diseases, and in the adjunctive management of hypertension.

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DESCRIPTION OF THE PREFERRED EMBODIMENTS

The aliphatic or araliphatic radicals mentioned for R₁, R₂ and R₄ are hydrocarbon radicals, which may be substituted by functional groups and/or interrupted by heteroatoms, such as nitrogen, oxygen and/or sulfur atoms. Such radicals are, for example, lower alkyl, e.g. methyl, ethyl, n- or i-propyl, n-, i-, or sec. butyl, n- or i-pentyl, neopentyl, n-hexyl or n-heptyl, lower alkenyl, e.g. vinyl, allyl, methallyl or 2-butenyl, lower alkynyl, e.g. propargyl, mono- or bicyclic cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl with preferably 5 to 7 ring-carbon atoms, 1 to 4 chain carbon atoms and optional e.g. up to 4, lower alkyl groups, e.g. cyclopropyl, 2,3-dimethyl-cyclopropyl, cyclobutyl, cyclopentyl, 2- or 3-methyl-cyclopentyl, 2,5- or 3,4- dimethyl-cyclopentyl, cyclohexyl, 2-, 3- or 4-methyl-cyclohexyl, 2,3-, 2,4- or 3,5-dimethyl-cyclohexyl, 2,4,6- trimethyl-cyclohexyl, cycloheptyl, cyclooctyl, 2- or 7-norbornanyl, 1- or 2-decahydro-naphthyl; 1- or 2-cyclopentenyl, 2,4-cyclopentadienyl, 2- or 3-methyl-2-cyclopentenyl, 4,5-dimethyl-2-cyclopentenyl, 1-, 2 or 3-cyclohexenyl, 2,5-cyclohexadienyl, 2-, 3- or 4-methyl-1- or 2-cyclohexenyl, 2,4- or 3,5-dimethyl-1- or 2-cyclohexenyl, 2,4,6-trimethyl-2,5-cyclohexadienyl, 1-, 2- or 3-cycloheptenyl, 2,6-cycloheptadienyl, 2-cyclooctenyl or 2-norborn-5-enyl, as well as the corresponding cycloalkenyl or cycloalkenyl-lower alkyl groups in which the chain especially represents methyl, but also ethyl n-, or i-propyl, n-, i- or sec. butyl; it contains in any of the positions available for substitution one of the specific cycloalkyl or cycloalkenyl groups listed above. The term "lower," referred to above and hereinafter in connection with organic radicals or compounds respectively, defines such with up to 7, preferably up to 4, carbon atoms. Aliphatic radicals that are substituted, e.g. by free or functionally converted hydroxy, mercapto or carboxy groups and/or interrupted by heteroatoms, e.g. one oxygen, sulfur and/or nitrogen atom, are represented, for example, by lower haloalkyl, e.g. 2-(chloro, bromo or iodo)-ethyl, 3,3-difluoro- or -dichloropropyl, 3,3,3-trichloropropyl, 3- or 4-chlorobutyl, 4,4- or 3,4- dichlorobutyl or 4,4,4-trifluorobutyl; unsubstituted or halogenated lower alkoxy- or alkylthio-lower alkyl, such as 2-ethoxyethyl, 3-methoxy-propyl, 2-ethylthio-ethyl, 2- (2,2-dichloroethoxy)-ethyl, 2-(2-chloroethoxy)-ethyl, 2-(2,2,2-trifluoroethylthio)-ethyl or 2-(2,2-dichloroethylthio)-ethyl; carbamyl-lower alkyl or N,N-dilower alkylcarbamyl-lower alkyl, such as carbamyl-methyl, N,N-dimethylcarbamyl-methyl, 2-carbamyl-ethyl or 2-N,N-diethylcarbamyl-ethyl; sec. or tert. amino-lower alkyl, such as mono- or di-lower alkylamino-lower alkyl, lower alkyleneimino-lower alkyl, lower monoazo-, oxo- or -thia-alkyleneimino-lower alkyl or N-lower alkyl-lower mono-azaalkyleneimino-lower alkyl, e.g. 2-ethylaminoethyl, 2-dimethylamino-ethyl, 3- diethylamino-propyl, 2-pyrrolidinoethyl, 2-piperidino-ethyl, 2-(4-methyl-piperazinyl)-ethyl or 2-morpholino-ethyl, 5 to 7 ring-membered oxo-cyclo-alkyl or -cycloalkenyl, oxo-cycloalkyl- or -cycloalkenyl-lower alkyl, such as 3-tetrahydrofuryl, tetrahydrofuryl-2-methyl, (2-methyl-tetrahydrofuryl-2)-methyl, 2,3-dihydro- or tetrahydropyranylyl-2-methyl.

R₁ and R₂ when taken together, may also represent lower alkylene or alkenylene, e.g. 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,4- or 1,5-pentylene, 1,5-, 2,5- or 1,6-hexylene or 2,6- heptylene; 1,4- but - 2- enylene, 1,4- or 1,5- pent - 2- enylene, 1,5- hex - 2- enylene, 1,6-hex - 3- enylene or 2,6- hept - 3- enylene; lower mono-aza-, -oxa- or -thiaalkylene or N-lower alkyl-monoaza-lower alkylene, e.g. 3-aza-, 3-oxa- or 3-thia-pentylene-(1,5), 3-methyl- or 3- ethyl - 3- aza-pentylene-(1,5), 3-aza-hexylene-(1,6) or 4-aza- or -oxa-heptylene-(2,6). In the aliphatically substituted group

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two heteroatoms, e.g. nitrogen, oxygen and/or sulfur atoms, are separated by at least 2 carbon atoms.

An araliphatic radical R₁, R₂ and R₄ preferably stands for mono- or bicyclic carbocyclic aryl-lower alkyl or aryl-lower alkenyl, especially (mono- or di-R₆-phenyl)-lower alkyl or -alkenyl, but also for mono- or bicyclic heterocyclic, especially monoaza-, oxo- or thiacyclic aryl-lower alkyl or aryl-lower alkenyl in which the alkyl or alkenyl moiety preferably has up to 4 chain carbon atoms, and the aromatic portion is unsubstituted or substituted by one or more than one, preferably 1 or 2, substituents selected, for example, from lower alkyl, e.g. that mentioned above, phenyl, free or functionally converted hydroxy or mercapto, such as lower alkoxy, lower alkylthio, lower alkylthio or halogeno, e.g. methoxy, ethoxy, n- or i-propoxy or -butoxy, methylenedioxy, 1,1- or 1,2-ethylene-dioxy, methyl- or ethylthio, fluoro, chloro or bromo; (hydroxy or halogeno)-lower alkyl or -alkoxy, e.g. 2-hydroxyethyl, trifluoromethyl or 2-hydroxyethoxy, nitro, amino, especially di-lower alkylamino, e.g. dimethylamino or diethylamino, sulfamoyl, or free or functionally converted carboxy, e.g. lower carbalkoxy, carbamoyl or cyano. Preferred aryl-substituents R₆ are hydrogen, lower alkyl, hydroxy-lower alkyl, hydroxy, mercapto, lower alkoxy, lower alkylmercapto, hydroxy-lower alkoxy, halogeno, trifluoromethyl, nitro, amino, di-lower alkylamino, carboxy and/or lower carbalkoxy. Unsubstituted carbocyclic aralkyl or aralkenyl radicals are exemplified by benzyl, 1- or 2-phenylethyl, 1-, 2- or 3-phenyl-propyl, 2-phenyl-2-propyl, 1-, 2-, 3- or 4-phenyl-butyl, 1- or 2-phenyl-2-butyl, styryl or cinnamyl. In the corresponding heterocyclic aralkyl or aralkenyl radicals aryl is preferably monocyclic monoaza-, -oxa- or -thiacyclic aryl, e.g. 2-, 3- or 4-pyridyl, 2- or 3-furyl or -thienyl, but also 5-(1,2- oxazolyl), 2- (1,3- oxazolyl), 2- (1,3- thiazolyl), 6-thianaphthyl or 2-benzimidazolyl. Araliphatic radicals are also partially hydrogenated, preferably bi- or tricyclic aryl radicals, bound at the aliphatic portion, such as 1- or 2-indolinyl, 1- or 2-(1,2,3,4-tetrahydronaphthyl) or 9-fluorenyl.

The radical R₄ preferably stands for mono- or bicyclic carbocyclic or heterocyclic aryl, e.g. that mentioned for the above araliphatic radicals. It especially represents mono- or di-R₆-phenyl, in which R₆ has the meaning given above.

Esters and amides of the compounds of Formula I are particularly lower alkyl esters, the amide, mono- or di-loweralkylamides, (hydroxy or lower alkoxy)-lower alkyl esters or amides, (amino, mono- or di-lower alkylamino)-lower alkyl esters or amides, wherein two heteroatoms are separated by at least 2, preferably 2 or 3, carbon atoms, e.g. the methyl, ethyl, n- or i-propyl or -butyl ester, the amide, mono- or dimethylamide, diethylamide or i-propylamide, the 2- (hydroxy or methoxy)-ethyl ester or amide, 2-(amino, mono- or dimethylamino)-ethyl ester or amide or 3-dimethylamino-propyl ester or amide, or aralkyl esters, such as (R₆-phenyl)-lower alkyl, e.g. benzyl, 1- or 2-phenethyl esters.

The acyl derivatives are preferably those of lower alkanic acids, such as acetic, propionic, butyric or pivalic acid, but also of lower alkenic acids, such as acrylic or methacrylic acid, or of R₆-phenyl-lower alkanic or -alkenic acids, such as benzoic, phenylacetic or cinnamic acid. The acyl group therein is preferably attached to a primary, but also a secondary amino group and/or a free hydroxy or mercapto group.

The compounds of the invention exhibit valuable pharmacological properties. Primarily they show diuretic, natri- and chloruretic activity with rapid onset of action, high urine but low potassium excretion levels. This can be demonstrated in animal tests using, for example mammals, e.g. rats or dogs, as test objects. Such tests can be per-

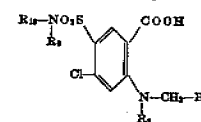
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formed, for example, by administering the compounds of the invention within a gelatin capsule to dogs, or in the form of aqueous solutions or suspensions by stomach tube to rats, in an oral dosage range between about 0.1 and 100 mg./kg./day, preferably between about 0.3 and 50 mg./kg./day, advantageously between about 1 and 5 mg./kg./day. Simultaneously the test animals may receive various salt loads enterally or parenterally, for example, various amounts of subcutaneously applied 0.9% saline, e.g. 100 ml. thereof per medium-sized dog (beagle). Urine is then collected, e.g. at 2 hour intervals, with or without catheterization, and its volume, sodium, potassium and chloride content estimated and compared with that of the same untreated or saline-treated animals. Besides the above-mentioned utility, the compounds of the invention can also be used as intermediates in the preparation of other valuable products, primarily of pharmacologically active compounds.

Preferred are those compounds of Formula I in which R₁ is lower alkyl, lower alkenyl, cycloalkyl, cycloalkenyl, cycloalkyl-alkyl, cycloalkenyl-alkyl, oxo-cycloalkyl or -cycloalkenyl, oxacycloalkyl- or -cycloalkenyl-lower alkyl, with 5 to 7 ring-carbon and 1 to 4 chain carbon atoms, lower fluoro- or chloroalkyl, lower alkoxy- or alkylthio-lower alkyl, lower fluoro- or chloroalkoxy- or -alkylthio-lower alkyl, di-lower alkylamino- or lower alkylene-imino-lower alkyl, R₂ and R₄ are hydrogen, lower alkyl or (mono- or di-R₆-phenyl)-alkyl with 1 to 4 chain carbon atoms, R₃ is chloro and R₆ is mono- or di-R₆-phenyl or unsubstituted or lower alkyl-substituted monocyclic mono-aza-, -oxa- or -thiacyclic aryl, preferably pyridyl, furyl or thienyl, or especially those compounds of Formula I, in which R₂-R₄ have the meaning given in this paragraph and R₁ is (mono- or di-R₆-phenyl)-alkyl or unsubstituted or lower alkyl-substituted monocyclic mono-aza-, -oxa- or -thiacyclic arylalkyl with 1 to 4 chain carbon atoms, or lower alkanoyl derivatives of compounds containing a primary or secondary amino group, or lower alkyl esters, the amide, mono- or di-lower alkylamides, (hydroxy or lower alkoxy)-lower alkyl esters or amides, (amino, mono- or di-lower alkylamino)-lower alkyl esters or amides, wherein two heteroatoms are separated by at least 2 carbon atoms, the alkali metal, alkaline earth metal or ammonium salts of said anthranilic acids, or acid addition salts of basic compounds.

Especially valuable are the compounds of Formula II



(II)

in which each of R₁ and R₁₀ is phenyl, mono- or di-lower alkylphenyl, lower hydroxyalkylphenyl, mono- or dihydroxyphenyl, lower alkylhydroxyphenyl, mono- or dimercaptophenyl, mono- or di-lower alkoxyphenyl, lower alkoxy-hydroxyphenyl, lower hydroxyalkoxyphenyl, mono- or di-lower alkylthiophenyl, mono- or di-halogeno-phenyl, trifluoromethylphenyl, nitrophenyl, mono- or diamino-phenyl, di-lower alkylaminophenyl, lower alkanoylaminophenyl, carboxyphenyl, lower carbalkoxyphenyl, pyridyl, lower alkylpyridyl, furyl, lower alkylfuryl, thienyl, lower alkylthienyl tetrahydrofuryl, lower alkyltetrahydrofuryl, dihydroxypranyl or lower alkylidihydroxypranyl, and each of R₂ and R₄ is hydrogen or lower alkanoyl, the lower alkyl esters, the amide, mono- or di-loweralkylamides, (hydroxy or lower alkoxy)-lower alkyl esters or amides (amino, mono- or di-lower alkylamino)-lower alkyl esters or amides, wherein two heteroatoms are separated by at least 2 carbon atoms, the alkali metal, alkaline earth metal, ammonium or acid addition salts thereof.

Outstanding are the compounds of Formula II, in which R₁ is phenyl, 2-furyl, 2-thienyl, 2-tetrahydrofuryl, 2-meth-

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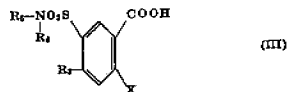
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yl-2-tetrahydrofuryl or 2,3-dihydro-2-pyranyl, each of R_1 and R_2 is hydrogen or acetyl and R_3 is phenyl, mono- or dimethylphenyl, 2-hydroxyethylphenyl, mono- or dihydroxyphenyl, methyl-hydroxyphenyl, mercaptophenyl, mono- or dimethoxyphenyl, methoxy-hydroxyphenyl, 2-hydroxyethoxyphenyl, fluorophenyl, chlorophenyl, trifluoromethylphenyl, nitrophenyl, *meta*- or *diminophenyl*, dimethylaminophenyl, acetylaminophenyl, carboxyphenyl, carbomethoxyphenyl or carbethoxyphenyl, the methyl or ethyl ester, 3-dimethylaminopropylamide, the sodium, potassium or 2-hydroxyethylammonium salts of the carboxylic acids or the hydrochlorides of the mono- or diamino or dimethylamino compounds.

Most preferred are the N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid and the N-furfuryl-5-(hydroxy- or aminophenylsulfamyl)-4-chloro-anthranilic acid and their sodium salts or the hydrochloride of the aminophenyl compounds which, when given to dogs at oral doses between about 0.3 and 5 mg./kg./day, exhibit high diuretic, natri- and chloriuretic effects. Of these compounds the N-furfuryl-5-(2-aminophenylsulfamyl)-4-chloro-anthranilic acid, its sodium salt or hydrochloride, exhibit outstanding diuretic and saluretic effects at an even lower and narrower dosage range.

The compounds of the invention are prepared according to methods in themselves known. Advantageously they are obtained by converting in a compound of the Formula III



in which X stands for a group capable of being converted into the amino group



an ester, halide, amide, hydrazide, acyl derivative or salt thereof, X into



and hydrolyzing any resulting amide or hydrazide different from such defined above and, if desired, converting any resulting compound into another compound of the invention.

Any ester, amide, hydrazide or acyl derivative used as starting material may be such as described above for the final products. Generally, the amides or hydrazides used as starting material may be N-unsubstituted or N-substituted, for example, by one or more than one aliphatic, araliphatic or aromatic radical, e.g., any of those described above.

The group X, capable of being converted into



is preferably a halogen atom, advantageously fluoro or chloro, but also primary amino or an imino group, forming after reduction (of the corresponding Schiff's base) the group R_1-NH-R_2 . The starting material, in which X stands for halogeno, is reacted with the amine



that in which X stands for $-NH_2$, is reacted with a reactive ester of the alcohol R_1-OH , e.g. such of a hydrohalic or sulfonic acid, e.g. hydrochloric, hydrobromic, hydriodic, methane-, ethane-, benzene- or p-toluenesulfonic acid, whereas that starting material, in which X stands for said imino group, is subjected to hydrogenation, for example, with the use of catalytically activated or nascent hydrogen.

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The above process is carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing agents and/or inert atmospheres, at low temperatures, room temperature or advantageously elevated temperatures, at atmospheric or superatmospheric pressure.

In the above reaction the amine reagent is advantageously used in excess, in order to neutralize any generated acid. It may, however, also be used in equivalent amounts and in the presence of other condensing agents such as inorganic or organic bases, e.g. alkali metal carbonates or bicarbonates or tertiary nitrogen bases, for example tri-lower alkylamines, N,N-dimethyl-aniline or pyridine.

Any resulting amide or hydrazide can be hydrolyzed in the usual manner, for example, with the use of a base, e.g. an aqueous alkali or alkaline earth metal hydroxide, or a quaternary ammonium hydroxide. The compounds of the invention so obtained may be converted into each other according to known methods. For example, resulting compounds, in which R_2 and/or R_3 stands for hydrogen, may be reacted with a reactive ester of a corresponding alcohol, for example that of a hydrohalic or sulfonic acid. Resulting compounds with a hydroxy, prim- or sec. amino group may be acylated, for example, with a reactive functional derivative of a corresponding acid, such as a halide or anhydride thereof, e.g., thionyl or acetyl chloride or acetanhydride, resulting acyl derivatives or esters may be hydrolyzed, for example, with the use of acidic or alkaline hydrolyzing agents, resulting esters may be transesterified or reacted with corresponding amines or resulting acids esterified or amidated in known manner.

The compounds of the invention are obtained in the free form or in the form of their salts, depending on the conditions under which the process is carried out, the salts are also included in the present invention. These are particularly derived from the free acids and therapeutically useful inorganic or organic bases, primarily the alkali metal, alkaline earth metal, e.g. sodium, potassium, magnesium or calcium salts, or ammonium salts derived from ammonia or amines, such as those corresponding to the amino group



e.g., mono-, di- or tri-lower alkylamines, cycloalkylamines, -cycloalkyl-lower alkylamines or -aralkylamines, mixed amines or tertiary nitrogen bases, such as pyridine, collidine or lutidine. Resulting compounds that contain basic groups, e.g. amino groups, may also form acid addition salts, preferably such of therapeutically useful acids, such as mineral acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric, nitric or perchloric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxy-benzoic, salicylic, 4-aminosalicylic, embonic, nicotinic, methane-sulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogen-benzenesulfonic, toluenesulfonic, naphthalenesulfonic and sulfanilic acid; methionine, tryptophane, lysine and arginine.

The invention further includes any variant of the present process in which an intermediate product obtainable at any stage of the process is used as starting material and any remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions, or in which the reaction components are used in the form of their salts. Mainly those starting materials should be used in the reactions of the invention that lead

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to the formation of those compounds indicated above as being especially valuable.

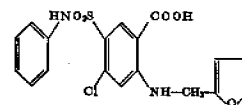
The starting material is new and, therefore, a further object of the present invention. It can be prepared according to known methods, for example, a corresponding 2,4-dihalo-benzoic acid is reacted with chlorosulfonic acid in order to yield the 2,4-dihalo-5-chlorosulfamyl-benzoic acid. The latter, or a functional derivative thereof, is then reacted with the amine R_1-NH-R_2 in order to obtain the compounds of Formula III in which X stands for halogeno, or functional derivatives thereof. The latter, e.g. the esters, halides, amides or hydrazides, may also be prepared from the acids of Formula III by conventional methods. The resulting 2,4-dihalo-5-sulfamyl-benzoic acids may be reacted with ammonia in order to obtain the starting material in which X represents NH_2 , which further may be reacted with a corresponding aldehyde or ketone, in order to obtain the starting material in which X stands for an imino group.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions containing an effective amount thereof in conjunction or admixture with excipients suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with (a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, (b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol, for tablets also (c) binders, e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinyl-pyrrolidone, if desired, (d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, enzymes of the binders or effervescent mixtures and/or (e) adsorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously fatty emulsions or suspensions. They may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. They may also contain other therapeutically valuable substances. Said pharmaceutical compositions are prepared according to conventional mixing, granulating or coating methods respectively and contain about 0.1 to 75%, preferably about 1 to 50% of the active ingredient.

The following examples illustrating the invention are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade and all parts wherever given are parts by weight.

Example 1

The mixture of 2.4 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 10 ml. 2-ethoxy-ethanol and 2.7 g. furfurylamine is refluxed for 4 hours under nitrogen. After cooling to room temperature it is poured into 50 ml. 2 N-hydrochloric acid. The supernatant liquid is decanted off and the residue dissolved in 50 ml. 2 N aqueous sodium hydroxide. The solution is extracted twice with diethyl ether and acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from ethanol to yield the N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid of the formula



melting at 210-212° (dec.).

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The starting material is prepared as follows: To 250 g. chlorosulfonic acid 50 g. 2,4-dichloro-benzoic acid are added portion-wise at room temperature while stirring. The solution obtained is heated to about 180° and stirred for 3 hours. After cooling to room temperature, it is poured onto ice, the mixture filtered, the residue washed with water, and dissolved in 400 ml. ethyl acetate. The solution is dried, filtered, evaporated, and the residue triturated with hexane, to yield the 2,4-dichloro-5-chlorosulfamyl-benzoic acid.

The mixture of 5.8 g. thereof, 7.5 g. aniline and 50 ml. ethyl acetate is stirred for 4 hours at room temperature. It is then filtered and the residue washed with ethyl acetate. The filtrate is evaporated *in vacuo* and the residue triturated with 2 N hydrochloric acid. The aqueous solution is decanted off and the precipitate dissolved in 100 ml. 10% aqueous potassium carbonate. The solution is filtered to yield residue A. The filtrate is extracted with diethyl ether and the aqueous layer acidified with hydrochloric acid. The precipitate formed is filtered off, washed with water and recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-phenylsulfamyl-benzoic acid melting at 211-213°. Residue A is also recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-phenylsulfamyl-benzoic acid phenylamide melting at 173-175°.

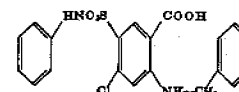
Example 2

The mixture of 3.0 g. N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid phenylamide, 30 ml. 2 N aqueous sodium hydroxide, 10 ml. water and 10 ml. 2-methoxy-ethanol is refluxed for 3 hours under nitrogen and allowed to stand at room temperature overnight. It is poured into 60 ml. 2 N-hydrochloric acid, the precipitate formed filtered off, washed with water and dissolved in 35 ml. 10% aqueous potassium carbonate. The solution is extracted with ethyl acetate, the aqueous layer separated and acidified with hydrochloric acid. The precipitate formed is filtered off, recrystallized from aqueous ethanol to yield the N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid melting at 212-214° with decomposition; it is identical with the compound obtained according to Example 1.

The starting material is prepared as follows: The mixture of 6.0 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid phenylamide, 5.6 g. furfurylamine and 20 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and allowed to stand overnight at room temperature. It is poured into 100 ml. 2 N-hydrochloric acid, the precipitate formed filtered off and the residue dissolved in diethyl ether. The solution is washed with 0.5 N hydrochloric acid, with 10% aqueous potassium carbonate and water, dried, filtered and evaporated *in vacuo*, to yield the N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid phenylamide melting at 114-117°.

Example 3

Substituting in Example 1 the furfurylamine by the equivalent amount of benzylamine and performing the reaction as shown therein, the N-benzyl-5-phenylsulfamyl-4-chloroanthranilic acid of the formula



is obtained, M.P. 226-228° (from aqueous ethanol).

Example 4

The mixture of 3.1 g. 2,4-dichloro-5-(4-methyl-phenylsulfamyl)-benzoic acid, 3.4 g. furfurylamine and 10 ml.

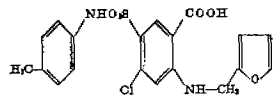
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2-methoxyethanol is refluxed for 4 hours under nitrogen. After cooling to room temperature, it is treated with 2 N-hydrochloric acid, the precipitate formed separated and dissolved in 2 N-aqueous sodium hydroxide. The solution is extracted with diethyl ether, the aqueous layer separated and acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol to yield the N-furfuryl-4-chloro-5-(4-methyl-phenylsulfamyl)-anthranilic acid of the formula



melting at 218-220.

The starting material is prepared as follows: To the solution of 5.8 g. 2,4-dichloro-5-chlorosulfonyl-benzoic acid in 50 ml. ethyl acetate, 8.6 g. p-toluidine are added while stirring, followed by 100 ml. ethyl acetate. The mixture is stirred at room temperature for 2 hours and refluxed for 2 hours while stirring. After cooling it is filtered, the residue washed with ethyl acetate and the filtrate evaporated *in vacuo*. The residue (B) is triturated with water and 10 ml. concentrated hydrochloric acid, filtered off, washed with water and dried. The combined residues (A) and (B) are dissolved in 60 ml. 10% aqueous potassium carbonate, the solution washed with diethyl ether, acidified with hydrochloric acid, the precipitate formed filtered off and washed with water to yield the 2,4-dichloro-5-(4-acetylamino-phenylsulfamyl)-benzoic acid melting at about 150°.

Example 5

According to the method shown in the previous examples the compounds of Formula I, R₁=furfuryl,



R₄=Cl, and listed below, are prepared from equivalent amounts of the corresponding starting materials of Formula III, R₅=X=Cl:

Number	R ₄	M.P., final product, degrees	M.P., starting material, degrees
1	4-CH ₃ O-C ₆ H ₄	196-202	224-226
2	4-F-C ₆ H ₄	197-206	231-233
3	2-Cl-C ₆ H ₄	193-203	168-170
4	3-Cl-C ₆ H ₄	126-213	190-192
5	4-Cl-C ₆ H ₄	218-220	226-240
6	3-CH ₃ -C ₆ H ₄	126-222	214-216
7	4-CH ₃ -C ₆ H ₄	122	226-236
8	4-NH ₂ -C ₆ H ₄	123	268-271
9	2-CH ₃ -C ₆ H ₄	188-190	175-176
10	4-HOCH ₂ CH ₂ -C ₆ H ₄	178-179	155-156
11	4-CH ₂ CH ₂ NH ₂ -C ₆ H ₄	123	153
12	8-CH ₃ COONH-C ₆ H ₄	147	228-241
13	8-NH ₂ -C ₆ H ₄	150	179-188
14	4-CH ₃ COON-C ₆ H ₄	122	246-247
15	4-CH ₃ NH-C ₆ H ₄	199	140

¹ Decomposition.

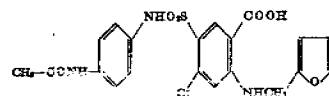
All compounds were recrystallized from aqueous ethanol.

Example 6

The mixture of 4.0 g. 2,4-dichloro-5-(4-acetylamino-phenylsulfamyl)-benzoic acid, 3.9 g. furfurylamine and 10 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling it is treated with 2 N-hydrochloric acid, the residue formed separated and dissolved in 2 N-aqueous sodium hydroxide. The solution is extracted with diethyl ether, the aqueous layer separated, acidified with

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hydrochloric acid and the precipitate formed recrystallized from aqueous ethanol to yield the N-furfuryl-4-chloro-5-(4-acetylamino-phenylsulfamyl)-anthranilic acid of the formula

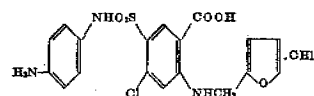


melting at 248° with decomposition.

The starting material is prepared as follows: To the solution of 5.8 g. 2,4-dichloro-5-chlorosulfonyl-benzoic acid in 50 ml. ethyl acetate, 12.0 g. 4-amino-acetanilide are added, followed by 50 ml. ethyl acetate. The mixture is stirred for 2 hours at room temperature and refluxed for 2 hours while stirring. After cooling to room temperature it is filtered, the residue (A) washed with ethyl acetate and the filtrate evaporated *in vacuo*. The residue (B) is triturated with water and 10 ml. concentrated hydrochloric acid, filtered off, washed with water and dried. The combined residues (A) and (B) are dissolved in 60 ml. 10% aqueous potassium carbonate, the solution washed with diethyl ether, acidified with hydrochloric acid, the precipitate formed filtered off and washed with water to yield the 2,4-dichloro-5-(4-acetylamino-phenylsulfamyl)-benzoic acid melting at about 150°.

Example 7

The mixture of 5.3 g. 2,4-dichloro-5-(4-amino-phenylsulfamyl)-benzoic acid hydrochloride, 5.4 g. furfurylamine and 15 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and evaporated *in vacuo*. To the residue 30 ml. 2 N-hydrochloric acid are added and the precipitate formed filtered off. It is triturated with 40 ml. water at room temperature, filtered off, washed with a small amount of ice cold water and diethyl ether and recrystallized from aqueous ethanol to yield the N-furfuryl-4-chloro-5-(4-amino-phenylsulfamyl)-anthranilic acid hydrochloride of the formula



melting at about 230°.

The starting material is prepared as follows: The mixture of 7.1 g. 2,4-dichloro-5-(4-acetylamino-phenylsulfamyl)-benzoic acid (of Example 6) and 60 ml. 2 N-aqueous sodium hydroxide is refluxed for 90 minutes. After cooling to room temperature it is acidified with concentrated hydrochloric acid, the precipitate formed filtered off, the residue taken up in ethanol, the solution filtered and evaporated *in vacuo*, to yield the 2,4-dichloro-5-(4-amino-phenylsulfamyl)-benzoic acid hydrochloride, melting at 185° with decomposition.

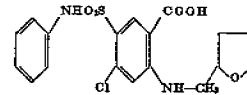
Example 8

The mixture of 6.5 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 8.0 g. tetrahydrofuryl-2-methylamine and 30 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling to room temperature, it is poured into 180 ml. 2 N-hydrochloric acid, the precipitate separated, ground in a mortar, filtered, washed with water and re-

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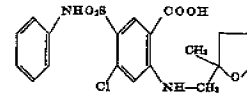
crystallized several times from aqueous ethanol to yield the N-(tetrahydrofuryl-2-methyl)-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 238-239°.

Example 9

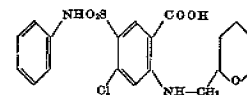
The mixture of 3.5 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 4.6 g. (2-methyl-tetrahydrofuryl-2)-methylamine and 10 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and stirred overnight at room temperature. Hereupon it is poured into 80 ml. 2 N-hydrochloric acid, the residue separated and dissolved in 2 N-aqueous sodium hydroxide. The solution is washed with diethyl ether, filtered and acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-(2-methyl-tetrahydrofuryl-2-methyl)-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 207-208°.

Example 10

The mixture of 6.5 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 9.05 g. 2,3-dihydro-pyran-2-methylamine and 30 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling to room temperature it is poured into 180 ml. 2 N-hydrochloric acid, the precipitate formed filtered off, washed with water and recrystallized from aqueous ethanol, to yield the N-(2,3-dihydro-pyran-2-methyl)-4-chloro-5-phenylsulfamyl-benzoic acid of the formula



melting at 115-117° with decomposition.

Example 11

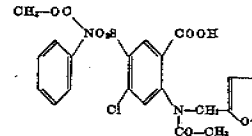
The mixture of 81.4 g. N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid (Example 1), 110 ml. 2 N-aqueous sodium hydroxide and 100 ml. water is heated to about 50 to 60° until dissolution occurs. The solution is filtered, the filtrate cooled, seeded with a few crystals of previously prepared sodium salt, and allowed to stand in the refrigerator. The precipitate formed is filtered off, washed with a small amount of ice water and dissolved in 100 ml. isopropanol at 60°. The solution obtained is slowly cooled and finally kept in the refrigerator. The precipitate formed is filtered off, triturated with 75 ml. cold isopropanol, filtered again and dried to yield the sodium salt of the N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid, melting at 244 to 246° with decomposition.

Example 12

The mixture of 2.0 g. N-benzy-4-chloro-5-phenylsulfamyl-anthranilic acid, 2 ml. acetic acid anhydride and 8 ml. pyridine is heated at the steam bath for 1 hour, cooled and poured into water. The mixture is slightly acidified with concentrated hydrochloric acid, the precipitate formed filtered off and dissolved in ethanol. To the solution, water and a few drops hydrochloric acid are added, the precipitate formed filtered off and again

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recrystallized from aqueous ethanol to yield the N,N-bisacetyl-N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 206-208°.

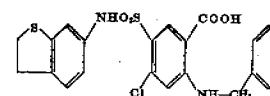
Example 13

The mixture of 113.3 g. 2,4-dichloro-5-phenylsulfamyl-benzoic acid, 500 ml. 2-methoxy-ethanol and 126.0 g. furfurylamine is stirred and refluxed under nitrogen for 4 hours. The cold mixture is then slowly poured into 2.5 liters 2 N hydrochloric acid while stirring. The precipitate formed is filtered off, washed with water and dissolved in 1 liter 2 N aqueous sodium hydroxide. The dark solution obtained is extracted three times with 125 ml. methylene chloride each and the aqueous layer carefully acidified with concentrated hydrochloric acid. The precipitate formed is filtered off, dissolved in 1 liter ethanol, the solution decolorized with charcoal, filtered hot, the filtrate combined with 1 liter hot water and, upon cooling to 15°, the N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid (Example 1) crystallizes. It is filtered off and dried; it melts at about 206°, which melting point can be raised to 208-210° by another recrystallization.

The starting material is prepared as follows: The mixture of 150 g. 2,4-dichloro-benzoic acid and 600 g. chlorosulfonic acid is heated to 150-155° for 3 hours while stirring. Thereupon, 223 g. chlorosulfonic acid are distilled off *in vacuo* and the cold residue poured into a mixture of 1.65 kg. ice and 125 ml. water. The precipitate formed is filtered off, washed with cold water, dissolved in 800 ml. ethyl acetate, the solution dried, filtered, and the filtrate diluted with 600 ml. ethyl acetate. To the solution obtained (containing the 2,4-dichloro-5-chlorosulfonyl-benzoic acid), cooled in a water bath, the mixture of 216 g. aniline and 220 ml. ethyl acetate is added at such rate that the temperature stays below 30°. The mixture is stirred for 4 hours at 25-30°, whereupon 4 g. charcoal are added. It is then filtered, the residue washed with 125 ml. ethyl acetate, the filtrate washed first with 450 ml. 3 N hydrochloric acid, then with 550 ml. water, and finally extracted with 700 ml. 7% aqueous sodium carbonate. The aqueous extract is separated, carefully acidified with concentrated hydrochloric acid and the precipitate formed filtered off and dried at 75° *in vacuo*, to yield the 2,4-dichloro-5-phenylsulfamyl-benzoic acid melting at 212-216°.

Example 14

The mixture of equivalent amounts of 2,4-dichloro-5-(2,3-dihydro-6-thianaphthylsulfamyl)-benzoic acid and 0.5 ml. benzylamine in 1 ml. 2-methoxy-ethanol is heated for 4 hours to 130°. After cooling, 5 ml. 2 N hydrochloric acid and 5 ml. water are added, the precipitate formed filtered off, washed with water and triturated with 2 N aqueous sodium hydroxide. The alkaline solution is filtered, the filtrate acidified with hydrochloric acid, the precipitate formed filtered off, washed with water and dried, to yield the N-benzy-4-chloro-5-(2,3-dihydro-6-thianaphthylsulfamyl)-anthranilic acid of the formula



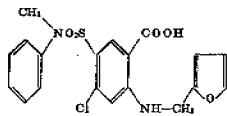
melting at 150° with decomposition.

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The starting material is prepared as follows: To the solution of 1.9 g. 6-amino-2,3-dihydro-thianaphthene in 25 ml. ethyl acetate and 3 ml. pyridine, 2.9 g. 2,4-dichloro-5-chlorosulfamylbenzoic acid are added slowly while stirring. The mixture is stirred for 3 hours at room temperature and allowed to stand overnight. It is made strongly acidic with hydrochloric acid, extracted with ethyl acetate, washed with water, dried and evaporated *in vacuo*. The residue is taken up in 1 N aqueous sodium hydroxide, the solution filtered and the filtrate acidified. The precipitate formed is filtered off and recrystallized first from aqueous ethanol and finally from methanol, to yield the 2,4-dichloro-5-(2,3-dihydro-6-thianaphthylsulfamyl)-benzoic acid.

Example 15

The mixture of 3.6 g. 2,4-dichloro-5-(N-methyl-N-phenylsulfamyl)-benzoic acid, 3.9 g. furfurylamine and 10 ml. 2-methoxyethanol is refluxed for 4 hours under nitrogen. After cooling, it is poured into 50 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and heated with 50 ml. 2 N aqueous sodium hydroxide. To the suspension obtained, water and diethyl ether are added until 2 clear layers are formed. The aqueous layer is separated, washed with diethyl ether and acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid of the formula



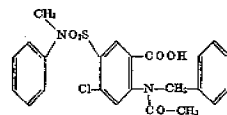
melting at 171-172°.

In the analogous manner, the N-benzyl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid is obtained; M.P. 164-166°.

The starting material is prepared as follows: To the solution of 11.6 g. 2,4-dichloro-5-chlorosulfamylbenzoic acid in 100 ml. ethyl acetate, 17.1 g. N-methyl-aniline are added slowly, and the mixture is stirred at room temperature for 4 hours. It is then filtered, the filtrate evaporated *in vacuo* and the residue taken up in water and 20 ml. concentrated hydrochloric acid. The mixture is extracted with ethyl acetate, the extract washed with water and shaken with 10% aqueous potassium carbonate. The aqueous layer is separated, acidified with concentrated hydrochloric acid, the precipitate formed filtered off and recrystallized from aqueous ethanol to yield the 2,4-dichloro-5-(N-methyl-N-phenylsulfamyl)-benzoic acid, melting at 170-171°.

Example 16

The mixture of 3 g. N-benzyl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid (Example 15), 12 ml. pyridine and 3 ml. acetic acid anhydride is heated at the steam bath for 1 hour while stirring. After cooling, it is poured into 120 ml. water, the mixture acidified with concentrated hydrochloric acid, the precipitate collected and recrystallized from aqueous methanol to yield the N-acetyl-N-benzyl-4-chloro-5-(N-methyl-N-phenylsulfamyl)-anthranilic acid of the formula

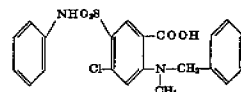


melting at 176-177° with decomposition.

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Example 17

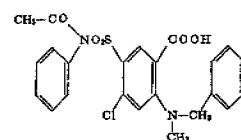
The mixture of equivalent amounts of 2,4-dichloro-5-phenylsulfamylbenzoic acid and 9.7 g. N-methyl-benzylamine in 20 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling, it is poured into 100 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and dissolved in 2 N aqueous sodium hydroxide. The mixture is extracted with diethyl ether, the aqueous layer separated and acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-methyl-N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid of the formula



melting at 183-184° with decomposition.

Example 18

The mixture of 3 g. N-methyl-N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid (Example 17), 12 ml. pyridine and 3 ml. acetic acid anhydride is heated at the steam bath for 1 hour while stirring. After cooling, it is poured into 120 ml. water, the mixture acidified with concentrated hydrochloric acid and the precipitate formed filtered off. The residue is dissolved in the minimum amount of hot ethanol, the solution filtered and allowed to cool to room temperature. The precipitate formed is filtered off and washed with aqueous ethanol to yield the N-methyl-N-benzyl-4-chloro-5-(N-acetyl-N-phenylsulfamyl)-anthranilic acid of the formula



melting at 191-192° with decomposition.

Example 19

Preparation of 10,000 tablets each containing 50.0 mg. of the active ingredient:

Formula:	G.
Sodium N-furfuryl - 4 - chloro-5-phenylsulfamyl-anthranilate	500.00
Lactose	1,706.00
Corn starch	90.00
Polyethylene glycol 6,000	90.00
Talcum powder	90.00
Magnesium stearate	24.00
Purified water q.s.	

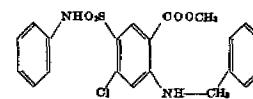
Procedure: All the powders are passed through a screen with an opening of 0.6 mm. Then the drug substance, lactose, talcum, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 45 ml. water and the suspension added to the boiling solution of the polyethylene glycol in 180 ml. water. The paste formed is added to the powders which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm. openings and compressed into tablets using concave punches with 7.1 mm. diameter, uppers bisected.

Example 20

The mixture of 2.2 g. methyl 4-chloro-5-phenylsulfamyl-anthranilate and 12 ml. benzaldehyde is heated to 200° for 1 hour and evaporated *in vacuo*. The residue is trit-

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urated with 75 ml. ethylacetate, filtered off and the filtrate hydrogenated over 0.3 g. platinum dioxide at room temperature until the hydrogen uptake slows down (¼ an hour). The mixture is filtered, the filtrate evaporated *in vacuo*, the residue taken up in chloroform-diethylamine (9:1) and chromatographed on silica gel, to yield as the main eluate the amorphous methyl N-benzyl-4-chloro-5-phenylsulfamylanthranilate of the formula



showing in the IR-spectrum bands, *inter alia* at 1750 and 1250 cm.⁻¹.

1.8 g. thereof are dissolved in 20 ml. methanol and 10 ml. 2 N aqueous sodium hydroxide, and the solution is refluxed for 20 minutes. It is then concentrated *in vacuo*, the aqueous concentrate diluted with water, extracted with diethyl ether and the aqueous layer acidified with hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid melting at 226-228°; it is identical with the product obtained according to Example 3.

The starting material is prepared as follows: The mixture of 1.0 g. 2,4-dichloro-5-phenylsulfamylbenzoic acid and 25 ml. concentrated aqueous ammonia is heated in a sealed tube to 120° for 4 hours. Hereupon, it is evaporated *in vacuo*, the residue taken up in 25 ml. saturated anhydrous methanolic hydrochloric acid and the mixture gently refluxed for 1 hour. It is evaporated *in vacuo* and the residue recrystallized from methanol, to yield the methyl 4-chloro-5-phenylsulfamyl-anthranilate melting at 183-186°.

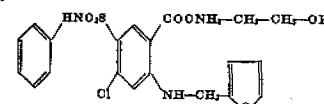
Example 21

The mixture of 2.0 g. methyl 4-chloro-5-phenylsulfamyl-anthranilate and 5 ml. benzyl chloride is refluxed for 2 hours and evaporated *in vacuo*. The residue is triturated with diethyl ether, filtered off and washed with diethyl ether to yield the methyl N-benzyl-4-chloro-5-phenylsulfamyl-anthranilate melting at about 200° (softening at 185°); it is identical with the compound obtained according to Example 20.

The mixture of 1.3 g. thereof, 5 ml. methanol, 5 ml. water and 1.5 ml. 6 N aqueous sodium hydroxide is heated at the steam cone for 30 minutes and allowed to stand at 25° for 1 hour. It is then concentrated *in vacuo*, the concentrate diluted with water, extracted with diethyl ether and the aqueous layer filtered. The filtrate is acidified with hydrochloric acid to pH 5, the precipitate formed filtered off and recrystallized from aqueous ethanol, to yield the N-benzyl-4-chloro-5-phenylsulfamyl-anthranilic acid melting at 226°; it is identical with the product obtained according to Example 3.

Example 22

To the suspension of 4.07 g. N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid and 50 ml. methanol, 0.61 g. 2-hydroxyethylamine are added while stirring. The resulting yellowish solution is evaporated *in vacuo*, to yield the 2-hydroxyethylammonium N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilate of the formula

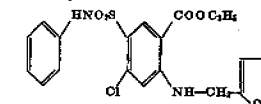


melting at 90°.

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Example 23

The mixture of 13.1 g. ethyl 2,4-dichloro-5-phenylsulfamylbenzoate and 20.4 g. furfurylamine is heated for 1 hour to 110°. After cooling, it is poured into 210 ml. water, the mixture acidified with glacial acetic acid to pH 4.5 while keeping the temperature below 20°. The precipitate formed is filtered off, washed with water and suspended in 250 ml. 0.5 N sodium hydroxide while stirring at room temperature. It is filtered, the residue suspended in water and the mixture acidified with hydrochloric acid to pH 2 while stirring. It is again filtered and the residue recrystallized several times from aqueous ethanol and finally from anhydrous ethanol, to yield the ethyl N-furfuryl-5-sulfamyl-4-chloroanthranilate of the formula

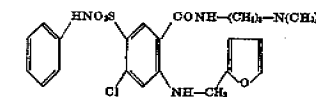


melting at 157-159°.

The starting material is prepared as follows: The mixture of 15 g. 2,4-dichloro-5-phenylsulfamylbenzoic acid and 150 ml. 6 N ethanolic hydrochloric acid is refluxed for 90 minutes and allowed to stand in the cold. The precipitate formed is filtered off, and recrystallized from aqueous ethanol, to yield the ethyl 2,4-dichloro-5-phenylsulfamylbenzoate melting at 132-133°.

Example 24

The mixture of 6.6 g. 2,4-dichloro-5-phenylsulfamylbenzoic acid 3-dimethylamino-propylamide, 5.8 g. furfurylamine and 15 ml. 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and evaporated *in vacuo*. The residue is taken up in 100 ml. 2 N aqueous sodium hydroxide and the mixture extracted with ethyl acetate. The organic layer is dried, filtered and evaporated. The residue is triturated with hydrogen chloride in ethyl acetate, the precipitate formed filtered off and taken up in water. The solution is washed with ethyl acetate, filtered and made basic with 2 N aqueous sodium hydroxide. The mixture is extracted with ethyl acetate, the extract dried, filtered and evaporated, to yield the amorphous N-furfuryl-5-phenylsulfamyl-4-chloro-anthranilic acid 3-dimethylaminopropylamide of the formula



showing in the thin layer chromatogram on silica gel in chloroform, methanol and diethylamine (85:5:10) an R_{f} = 7.5.

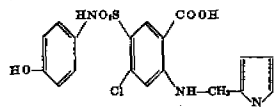
The starting material is prepared as follows: To the mixture of 17.7 g. 2,4-dichloro-5-phenylsulfamylbenzoic acid and 90 ml. 1,2-dimethoxyethane, 24 ml. thionyl chloride are added dropwise during 25 minutes while stirring, the whole is refluxed for 90 minutes and evaporated *in vacuo*. 18.6 g. of the resulting acid chloride is taken up in 300 ml. ethyl acetate and the solution added dropwise to the mixture of 11.8 g. 3-dimethylaminopropylamine and 450 ml. ethyl acetate while stirring, and stirring is continued overnight at room temperature. The mixture is filtered, the filtrate acidified with hydrogen chloride in ethyl acetate and the precipitate formed filtered off. It is taken up in water, the solution washed with ethyl acetate and made alkaline with 10% potassium carbonate. The mixture is extracted with ethyl acetate, the mixture dried, filtered and evaporated, to yield the 2,4-dichloro-5-phenylsulfamylbenzoic acid 3-dimethylamino-propylamide melting between about 80 and 90°.

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Example 25

The mixture of 3.6 g. 2,4-dichloro-5-(4-hydroxyphenylsulfamyl)-benzoic acid, 10 ml. 2-methoxy-ethanol and 3.9 g. furfurylamine is refluxed for 4 hours under nitrogen. After cooling, it is poured into 50 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered and the filtrate acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(4-hydroxyphenylsulfamyl)-anthranilic acid of the formula



melting at 227° with decomposition.

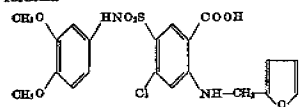
The starting material is prepared as follows: To the mixture of 5.8 g. 2,4-dichloro-5-chlorosulfonyl-benzoic acid and 100 ml. ethyl acetate, 8.7 g. 4-hydroxyaniline are added portionwise and the mixture stirred at room temperature for 4 hours. After standing overnight, it is filtered, the residue suspended in 50 ml. water, the mixture acidified with 10 ml. concentrated hydrochloric acid and extracted with ethyl acetate. The extract is filtered, washed with water and shaken with 10% aqueous potassium carbonate. The aqueous solution is filtered, acidified with concentrated hydrochloric acid and the precipitate formed filtered off. It is recrystallized several times from aqueous ethanol, to yield the 2,4-dichloro-5-(4-hydroxyphenylsulfamyl)-benzoic acid melting at 233-235°.

Example 26

In the manner described in Example 25, the N-furfuryl-4-chloro-5-(2-hydroxyphenylsulfamyl)-anthranilic acid, M.P. 125° (dec.) and the N-furfuryl-4-chloro-5-(3-hydroxyphenylsulfamyl)-anthranilic acid, M.P. 202° (dec.) are prepared from the same amounts of the corresponding isomeric starting materials, which melt at 187-189° and 192-194° respectively.

Example 27

The mixture of 3.9 g. 2,4-dichloro-5-(3,4-dimethoxyphenylsulfamyl)-benzoic acid, 10 ml. 2-methoxyethanol and 3.7 g. furfurylamine is refluxed for 4 hours under nitrogen. After cooling, it is poured into 50 ml. 2 N hydrochloric acid, the precipitate formed filtered off, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered, the filtrate acidified with concentrated hydrochloric acid, the precipitate formed collected and recrystallized two times from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(3,4-dimethoxyphenylsulfamyl)-anthranilic acid of the formula



melting at 123°.

The starting material is prepared as follows: To the solution of 12.3 g. 3,4-dimethoxyaniline and 50 ml. ethyl acetate, 5.8 g. 2,4-dichloro-5-chlorosulfonyl-benzoic acid are added while stirring, and the mixture stirred for 4 hours at room temperature. It is filtered, the residue washed with ethyl acetate and the filtrate combined with 10 ml. water and concentrated hydrochloric acid each and diluted with ethyl acetate. The organic layer is separated, extracted with 10% aqueous potassium carbonate and the extract acidified with concentrated hydrochloric acid. The

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precipitate formed is filtered off and recrystallized two times from aqueous ethanol, to yield the 2,4-dichloro-5-(3,4-dimethoxyphenylsulfamyl)-benzoic acid melting at 202-203°.

Example 28

In the manner described in Example 27, the N-furfuryl-4-chloro-5-(2,4-dimethoxyphenylsulfamyl)-anthranilic acid, M.P. 103° and the N-furfuryl-4-chloro-5-(2,5-dimethoxyphenylsulfamyl)-anthranilic acid, M.P. 199-202° are prepared from the same amounts of the corresponding isomeric starting materials, which melt at 184-185° and 180-182° respectively.

Example 29

Analogous to the procedures illustrated in the previous examples, more particularly according to Example 25, the N-furfuryl-4-chloro-5-[4-mercaptophenyl, 3,4-dihydroxyphenyl, 3-methyl-4-hydroxyphenyl, 3-methoxy-4-hydroxyphenyl, 4-(2-hydroxyethyl)-phenyl, 4-(2-hydroxyethoxy)-phenyl, 4-carboxyphenyl, 4-carbomethoxyphenyl or 4-carbomethoxyphenyl]-sulfamyl-anthranilic acid or, according to Example 7, the N-furfuryl-4-chloro-5-(2- or 3-aminophenyl, 3,5-diaminophenyl, 4-dimethylaminophenyl or 4-diethylaminophenyl)-sulfamyl-anthranilic acid, their sodium, potassium or 2-ethanolammonium salts or the hydrochlorides of the aminophenyl compounds, are prepared from equivalent amounts of the corresponding starting materials.

Example 30

Preparation of 1,000 capsules, each containing 25 mg. of the active ingredient:

Formula:	G.
N-furfuryl-4-chloro-5-(4-hydroxyphenylsulfamyl)-anthranilic acid	25.0
Lactose	220.0

Procedure: The ingredients are intimately mixed in a suitable mixer, passed through a screen with openings of 0.6 mm., re-mixed and 245 mg. are filled into No. 3 hard shell gelatin capsules.

In the analogous manner, capsules are prepared containing per unit 75 mg. N-furfuryl-4-chloro-5-(4-methoxyphenylsulfamyl) anthranilic acid or N-furfuryl-4-chloro-5-(4-aminophenylsulfamyl)-anthranilic acid hydrochloride and 170 mg. lactose.

Example 31

Preparation of 10,000 tablets, each containing 50 mg. of the active ingredient:

Formula:	G.
N-furfuryl-4-chloro-5-phenylsulfamyl-anthranilic acid	500.0
Lactose	2,500.0
Microcrystalline cellulose	1,000.0
Corn starch	160.0
Magnesium stearate	40.0
Purified water q.s.	

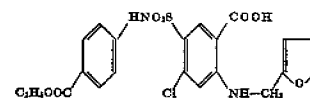
Procedure: All the powders, except the starch and the magnesium stearate, are passed through a screen with 0.5 mm. openings and mixed in a suitable mixer. The starch is suspended in 160 ml. water and the suspension added to 200 ml. boiling water. The paste formed is added to the powders which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm. openings, the magnesium stearate added, mixed well and the granulate compressed into 420 mg. tablets using concave punches with 7.1 mm. diameter, uppers bisected.

Example 32

The mixture of 5.5 g. of 2,4-dichloro-5-(4-carbomethoxyphenylsulfamyl)-benzoic acid, 10 ml. of 2-methoxyethanol and 5 g. of furfurylamine is refluxed for 4 hours under nitrogen. After cooling, it is poured onto 50 ml. of 2 N aqueous hydrochloric acid. The precipitate formed is

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filtered, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered and the filtrate acidified with concentrated hydrochloric acid. The precipitate formed is collected on a filter and recrystallized from aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(4-carbomethoxyphenylsulfamyl)-anthranilic acid of the formula



melting at 217° with decomposition.

The starting material is prepared as follows: To the solution of 16.5 g. of 4-aminobenzoic acid ethyl ester in 100 ml. of ethyl acetate is added portionwise at room temperature 7.2 g. of 2,4-dichloro-5-chlorosulfonyl-benzoic acid. The mixture is allowed to stir for one hour at room temperature, then refluxed for 6 hours. After cooling, the solids are filtered off and washed with ethyl acetate. The filtrate is evaporated under reduced pressure. The residue is treated with water and 15 ml. of concentrated hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate solution is extracted with 3 portions, 50 ml. each, of 10% aqueous potassium carbonate. The carbonate extracts are combined, filtered and acidified with concentrated hydrochloric acid. The precipitate formed is filtered, washed and recrystallized from aqueous ethanol to afford the 2,4-dichloro-5-(4-carbomethoxyphenylsulfamyl)-benzoic acid melting at 226-228°.

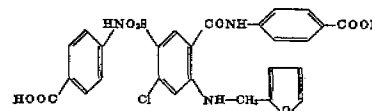
Example 33

In an analogous manner as in Example 33, 4.7 g. of 2,4-dichloro-5-(4-carboxyphenylsulfamyl)-benzoic acid reacted with 4.7 g. of furfurylamine in 10 ml. of 2-methoxy-ethanol affords on recrystallization from aqueous ethanol the N-furfuryl-4-chloro-5-(4-carboxyphenylsulfamyl)-anthranilic acid melting at 264° with decomposition.

The starting material is prepared by the hydrolysis of the 2,4-dichloro-5-(4-carbomethoxyphenylsulfamyl)-benzoic acid (Example 33) and melts at 288° with decomposition.

Example 34

The mixture of 5 g. of N-(4-carboxyphenyl)-2,4-dichloro-5-(4-carboxyphenylsulfamyl)-benzamide, 5 g. of furfurylamine and 10 ml. of 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. After cooling, it is poured onto 50 ml. of 2 N aqueous hydrochloric acid. The precipitate formed is filtered, washed with water and taken up in 2 N aqueous sodium hydroxide. The mixture is washed with diethyl ether, filtered and the filtrate acidified with concentrated hydrochloric acid to precipitate a syrupy material. The mixture is decanted and the product treated with a 1:1 mixture of ethanol and water. Recrystallization of the solids from a 1:1 ethanol-water mixture gives as a first crop the N-(4-carboxyphenyl)-2-(N-furfurylamino)-4-chloro-5-(4-carboxyphenylsulfamyl)-anthranilamide of the formula



melting at 246° with decomposition. The material obtained on evaporation of the recrystallization solvent corresponds to the product of Example 34.

The starting material is prepared as follows: The solution of 7.2 g. of 4-aminobenzoic acid in 150 ml. of ethyl acetate is treated with 7.2 g. of 2,4-dichloro-5-chlorosulfonyl-benzoic acid. The mixture is then refluxed

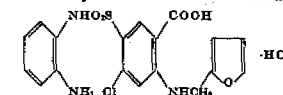
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for 6 hours. After cooling, the solids are filtered off and washed with ethyl acetate. The filtrate is evaporated under reduced pressure. The residue is treated with water and 15 ml. of concentrated hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate solution is extracted with 3 portions, 50 ml. each, of 10% aqueous potassium carbonate. The carbonate extracts are combined, filtered and acidified with concentrated hydrochloric acid. The crystalline material obtained is ground and treated with a 1:2 ethanol-water mixture, filtered, washed and dried to afford a mixture of the N-(4-carboxyphenyl)-2,4-dichloro-5-(4-carboxyphenylsulfamyl)-benzamide and the 2,4-dichloro-5-(4-carboxyphenylsulfamyl)-benzoic acid.

Example 35

The mixture of 5.3 g. of 2,4-dichloro-5-(2-aminophenylsulfamoyl)-benzoic acid hydrochloride, 5.4 g. of furfurylamine and 15 ml. of 2-methoxy-ethanol is refluxed for 4 hours under nitrogen and evaporated under reduced pressure. To the residue 30 ml. of 2 N hydrochloric acid are added, the precipitate formed filtered off and washed with a small amount of ice cold aqueous ethanol, to yield the N-furfuryl-4-chloro-5-(2-aminophenylsulfamoyl)-anthranilic acid hydrochloride of the formula



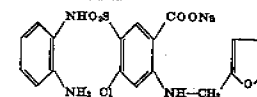
melting at 208° with decomposition.

The starting material is prepared as follows: To the solution of 5.8 g. of 2,4-dichloro-5-chlorosulfonyl-benzoic acid in 50 ml. of ethyl acetate, 12.0 g. of 2-aminoacetanilide are added, followed by 50 ml. of ethyl acetate. The mixture is stirred for 2 hours at room temperature and refluxed for 2 hours while stirring. After cooling to room temperature it is filtered, the residue (A) washed with ethyl acetate and the filtrate evaporated under reduced pressure. The residue (B) is triturated with water and 10 ml. of concentrated hydrochloric acid, filtered off, washed with water and dried. The combined residues (A) and (B) are dissolved in 60 ml. of 10% aqueous potassium carbonate, the solution washed with diethyl ether, acidified with hydrochloric acid, the precipitate formed filtered off and washed with water to yield the 2,4-dichloro-5-(2-aminophenylsulfamoyl)-benzoic acid melting at 222-225°.

The mixture of 7.1 g. thereof and 60 ml. of 2 N aqueous sodium hydroxide is refluxed for 90 minutes. After cooling to room temperature it is acidified with concentrated hydrochloric acid, the precipitate formed filtered off, the residue taken up in ethanol, the solution filtered and evaporated under reduced pressure, to yield the 2,4-dichloro-5-(2-aminophenylsulfamoyl)-benzoic acid hydrochloride.

Example 36

The mixture of 46 g. of N-furfuryl-4-chloro-5-(2-aminophenylsulfamoyl)-anthranilic acid hydrochloride, 110 ml. of 2 N aqueous sodium hydroxide and 100 ml. of water is heated to about 50 to 60° until dissolution occurs. The solution is filtered, the filtrate concentrated, cooled, seeded with a few crystals of previously prepared sodium salt, and allowed to stand in the refrigerator. The precipitate formed is filtered off, washed with a small amount of ice water and isopropanol, to yield the sodium N-furfuryl-4-chloro-5-(2-aminophenylsulfamoyl)-anthranilate of the formula

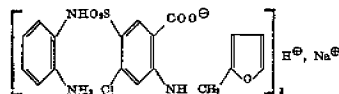


melting at 190° with decomposition.

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Example 37

The mixture of 15 g. of N-furfuryl-4-chloro-5-(2-acetylaminophenylsulfamoyl)-anthranilic acid and 90 ml. of 2 N aqueous sodium hydroxide is refluxed for 2½ hours in a nitrogen atmosphere, cooled and acidified with glacial acetic acid. The solids formed are collected on a filter, washed with water and recrystallized from aqueous ethanol, to afford the monosodium di-[N-furfuryl-4-chloro-5-(2-aminophenylsulfamoyl)-anthranilate] of the formula



melting at 246-248°.

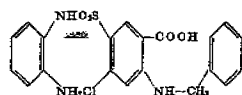
The starting material is prepared as follows:

To the solution of 50 g. of 2-aminoacetanilide and 100 ml. of dimethylformamide are added portionwise 30 g. of 2,4-dichloro-5-chlorosulfonyl-benzoic acid at 20°. The reaction mixture is warmed to 40° for 2 hours, evaporated under reduced pressure and the residue poured into 500 ml. of water and 7 ml. of concentrated hydrochloric acid. The solids formed are collected on a filter, washed with water and dilute aqueous hydrochloric acid, and triturated with aqueous ethanol, to give the 2,4-dichloro-5-(2-acetylaminophenylsulfamoyl)-benzoic acid melting at 222-225°.

The mixture of 30 g. thereof, 30 g. of furfurylamine and 75 ml. of 2-methoxy-ethanol is refluxed for 4 hours under nitrogen. It is concentrated to half its volume under reduced pressure and is then poured onto 250 ml. of 2 N aqueous hydrochloric acid with stirring. The precipitate formed is filtered, washed with water, triturated with a 1:1 mixture of ethanol and water at 70° and repeated with 95% aqueous ethanol, to give the N-furfuryl-4-chloro-5-(2-acetylaminophenylsulfamoyl)-anthranilic acid melting at 221-225°.

Example 38

The mixture of 4 g. of N-benzyl-4-chloro-5-(2-acetylaminophenylsulfamoyl)-anthranilic acid and 24 ml. of 2 N aqueous sodium hydroxide is refluxed for 6 hours under nitrogen and allowed to stand overnight at room temperature. It is combined with 4.5 ml. of glacial acetic acid (pH~5.5), the precipitate formed filtered off, washed with cold water and taken up in 25 ml. of hot water containing 1 ml. of glacial acetic acid. The mixture is stirred, slowly cooled to room temperature, filtered, the residue washed with water, taken up in 70 ml. of hot ethanol and the solution diluted with 70 ml. of water, to yield the N-benzyl-4-chloro-5-(2-aminophenylsulfamoyl)-anthranilic acid of the formula



melting at 227° with decomposition.

The starting material is prepared as follows:

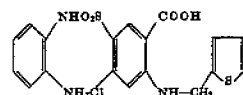
The mixture of 8.1 g. of 2,4-dichloro-5-(2-acetylaminophenylsulfamoyl)-benzoic acid, 20 ml. of 2-methoxy-ethanol and 8.6 g. of benzylamine is refluxed for 4 hours under nitrogen. It is cooled, poured into 100 ml. 2 N hydrochloric acid, the precipitate formed filtered off and washed with water. It is dissolved in 70 ml. of warm 2 N aqueous sodium hydroxide, the solution washed with diethyl ether, filtered and the filtrate acidified with con-

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centrated hydrochloric acid. The precipitate formed is filtered off and twice boiled with 100 ml. of 50% aqueous ethanol, to yield the N-benzyl-4-chloro-5-(2-acetylaminophenylsulfamoyl)-anthranilic acid melting at 240° with decomposition.

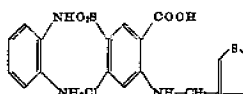
Example 39

The mixture of 3.9 g. of N-(2-thenyl)-4-chloro-5-(2-acetylaminophenylsulfamoyl)-anthranilic acid and 24 ml. of 2 N aqueous sodium hydroxide is refluxed for 6 hours under nitrogen and allowed to stand overnight at room temperature. It is combined with 4.5 ml. of glacial acetic acid, the precipitate formed filtered off, washed with cold water and triturated in 25 ml. water containing 1 ml. of glacial acetic acid. The mixture is filtered, the residue washed with water and recrystallized from 50% aqueous ethanol, to yield the N-(2-thenyl)-4-chloro-5-(2-aminophenylsulfamoyl)-anthranilic acid of the formula



melting at 197° with decomposition.

In the exact analogous manner, the N-(3-thenyl)-4-chloro-5-(2-aminophenylsulfamoyl)-anthranilic acid of the formula



is prepared, M.P. 192° (dec.).

The starting material is prepared as follows: The mixture of 7.8 g. of 2,4-dichloro-5-(2-acetylaminophenylsulfamoyl)-benzoic acid, 20 ml. of 2-methoxy-ethanol and 8.8 g. of 2-thenylamine is refluxed for 4 hours under nitrogen. It is cooled, poured into 100 ml. 2 N hydrochloric acid, the precipitate formed filtered off and washed with water. It is dissolved in 70 ml. of warm 2 N aqueous sodium hydroxide, the solution washed with diethyl ether, filtered and the filtrate acidified with concentrated hydrochloric acid. The precipitate formed is filtered off and recrystallized from 50% aqueous ethanol, to yield the N-(2-thenyl)-4-chloro-5-(2-acetylaminophenylsulfamoyl)-anthranilic acid, melting at 239° with decomposition. The corresponding 3-thenyl isomer melts at 243° (dec.).

Example 40

The mixture of 43.8 g. of N-furfuryl-4-chloro-5-(2-acetylaminophenylsulfamoyl)-anthranilic acid, 250 ml. of 2 N aqueous sodium hydroxide and 4.9 g. of activated charcoal is stirred for 10 minutes at 50° under nitrogen. It is filtered, the residue washed with 45 ml. of 2 N aqueous sodium hydroxide, the filtrate refluxed for 7 hours under nitrogen and stirred overnight at room temperature. It is again heated to reflux, combined with 47.5 ml. of glacial acetic acid, cooled to 20° and stirred for 1 hour. The suspension obtained is filtered, the residue washed with 25 ml. of water, and stirred for 1½ hours in 200 ml. of water containing 10 ml. of glacial acetic acid. The mixture is again filtered, the residue washed twice with 25 ml. of water, dried and taken up in 270 ml. of boiling anhydrous ethanol. The solution is filtered hot, the filtrate slowly cooled, stirred for 16 hours at 0° and the suspension formed filtered, to yield the N-furfuryl-4-

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chloro-5-(2-aminophenylsulfamoyl)-anthranilic acid melting at 219-221° with decomposition.

The starting material is prepared as follows:

To the mixture of 134.3 g. of 2-aminoacetanilide and 400 ml. of dimethylformamide, 130 g. of 2,4-dichloro-5-chlorosulfonylbenzoic acid are added during 10 minutes while stirring and keeping the temperature between 25 and 30°. After ½ hour the mixture is slowly poured into the solution of 62 ml. of concentrated hydrochloric acid in 5.3 l. of water, the suspension stirred for 1 hour at 25°, filtered and the residue washed with 200 ml. of anhydrous ethanol. It is taken up in 160 ml. of dimethylformamide at 80°, 48 ml. of water are added the solution immediately cooled to 15°. The precipitate formed is filtered off, washed twice with 52 ml. of anhydrous ethanol, slurried with 760 ml. of anhydrous ethanol at 50° for 10 minutes, the mixture cooled to 25° and filtered, to yield the 2,4-dichloro-5-(2-acetylaminophenylsulfamoyl)-benzoic acid melting at 225-227°.

The solution of 20 g. thereof in 48 ml. of 2-methoxy-ethanol and 20 g. of furfurylamine is refluxed for 4 hours under nitrogen and concentrated to half of its volume under reduced pressure at about 65°. The concentrate is poured into the mixture of 112 ml. of 2 N hydrochloric acid and 57 ml. of ethanol, the mixture stirred ½ an hour under nitrogen and at 25°. It is filtered, the residue washed with 50 ml. of 50% aqueous ethanol, dried, taken up in 28.6 ml. of water, the precipitate formed filtered off and washed with 50 ml. anhydrous ethanol, to yield the N-furfuryl-4-chloro-5-(2-acetylaminophenylsulfamoyl)-anthranilic acid melting at 224-230° with decomposition.

Example 41

Preparation of 1000 tablets each containing 50 mg. of the active ingredient:

Formula:	G.
N-furfuryl - 4 - chloro-5-(2-aminophenylsulfamoyl)-anthranilic acid	50.0
Lactose	190.0
Corn starch	25.0
Confectioners sugar	6.0
Talcum powder	10.0
Vegetable fat M.P. 60-63°	4.0
Purified water q.s.	

Procedure: All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance, lactose and sugar are mixed in a suitable mixer. The starch is suspended in 45 ml. of water and the suspension added to 180 ml. of boiling water. The paste formed is added to the powders, which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm. openings, combined with the talcum and fat, mixed thoroughly and compressed into tablets using concave punches with 7.1 mm. diameter, uppers bisected.

Example 42

Preparation of 1000 capsules, each containing 50 mg. of the active ingredient:

Formula:	G.
N-furfuryl - 4 - chloro - 5 - (2-aminophenylsulfamoyl)-anthranilic acid	50.0
Lactose	200.0
Talcum powder	25.0
Corn starch	15.0
Vegetable fat M.P. 60-63°	10.0

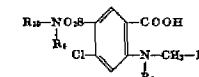
Procedure: All the powders are passed through a screen with openings of 0.6 mm. and mixed until homogenous.

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No. 2 hard gelatine capsules are filled each with 300 mg. of the mixture, using a capsule filling machine.

I claim:

1. A compound having the formula



in which R₂ is phenyl, mono- or di-lower alkylphenyl, lower hydroxyalkylphenyl, mono- or dihydroxyphenyl, lower alkyl-hydroxyphenyl, mono- or di-mercaptophenyl, mono- or di-lower alkoxyphenyl, lower alkoxy-hydroxyphenyl, lower hydroxyalkoxyphenyl, mono- or di-lower alkylthiophenyl, mono- or di-halogenophenyl, trifluoromethylphenyl, nitrophenyl mono- or diamino phenyl, di-lower alkylaminophenyl, lower alkanoylaminophenyl, carboxyphenyl or lower carbalkoxyphenyl, R₁ is phenyl, lower alkyl-phenyl, furyl, lower alkylfuryl, thienyl, lower alkylthienyl, tetrahydrofuryl, lower alkyltetrahydrofuryl, dihydropranyl or lower alkylidihydropranyl, and each of R₂ and R₃ is hydrogen, methyl or lower alkanoyl; or the lower alkyl esters, the amide or (di-lower alkyl-amino)-lower alkyl amides, wherein di-lower alkylamino is separated from amido-nitrogen by at least 2 carbon atoms, the alkali metal, alkaline earth metal or ammonium salts of said anthranilic acids or therapeutically useful acid addition salts of the amino or di-lower alkyl-amino compounds.

2. A compound as claimed in claim 1, in which formula R₂ is phenyl, 2-furyl, 2-thienyl, 2-tetrahydrofuryl, 2-methyl-2-tetrahydrofuryl or 2,3-dihydro-2-pyran, each of R₂ and R₃ is hydrogen or acetyl and R₁ is phenyl, mono- or dimethylphenyl, 2-hydroxyethylphenyl, mono- or dihydroxyphenyl, methyl-hydroxyphenyl, mercapto-phenyl, mono- or dimethoxyphenyl, methoxy-hydroxyphenyl, 2-hydroxyethoxyphenyl, fluorophenyl, chlorophenyl, trifluoromethylphenyl, nitrophenyl, mono- or diamino phenyl, dimethylaminophenyl, acetylaminophenyl, carboxyphenyl, carbomethoxyphenyl or carbethoxyphenyl; or the methyl or ethyl ester, 3-dimethylamino propylamide, the sodium, potassium or 2-hydroxyethylammonium salts of the carboxylic acids or the hydrochlorides of the mono- or diamino or dimethylamino compounds.

3. A compound as claimed in claim 2 and being the N-furfuryl-4-chloro-5-phenylsulfamoyl-anthranilic acid or the sodium salt thereof.

4. A compound as claimed in claim 2 and being the N-furfuryl - 4 - chloro-5-(hydroxyphenylsulfamoyl)-anthranilic acid, or the sodium salt thereof.

5. A compound as claimed in claim 2 and being the N-furfuryl - 4 - chloro-5-(aminophenylsulfamoyl)-anthranilic acid, the sodium salt or the hydrochloride thereof.

6. A compound as claimed in claim 5 and being the N-furfuryl-4-chloro-5-(2-aminophenylsulfamoyl)-anthranilic acid, the sodium salt or the hydrochloride thereof.

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C. M. S. JAISLE, Assistant Examiner

U.S. Cl. X.R.

260-239.65, 239.7, 239.75, 239.8, 239.9, 239.95, 397.7, 424-228, 229	
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United States Patent [19]
Helland

[11] 3,992,441
[45] Nov. 16, 1976

[54] SULFAMYL BENZOIC ACIDS

- [75] Inventor: Gerald F. Helland, Old Lyme, Conn.
[73] Assignee: Pfizer Inc., New York, N.Y.
[22] Filed: June 20, 1974

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Related U.S. Application Data

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- [52] U.S. Cl. 260/518 A
[51] Int. Cl.² C07C 101/42

[58] Field of Search 260/518 A

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Primary Examiner—Anton H. Sutto
Attorney, Agent, or Firm—Connolly and Hutz

[57] ABSTRACT
Certain mono- and disubstituted-5-sulfamylbenzoic acids, many of which are novel, and their use in lowering blood lipid levels in mammals.

16 Claims, No Drawings

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EXAMPLE 38

Starting with the requisite 2,4-disubstituted benzoic acid, chlorosulfonic acid and the appropriate amine, the procedure of Example 31 is repeated to provide the following congeners:

2,4-dichloro-5-dimethylaminosulfonylbenzoic acid; 2,4-dichloro-5-(4,4-dimethylpiperidinosulfonyl)benzoic acid; 2,4-difluoro-5-(3-p-bromophenylpropylaminosulfonyl)benzoic acid; 2,4-difluoro-5-morpholinosulfonylbenzoic acid; 2-fluoro-4-chloro-5-(3-chlorophenylaminosulfonyl)benzoic acid; 2-fluoro-4-chloro-5-hexamethyleneiminisulfonylbenzoic acid; 2-chloro-4-fluoro-5-(2,4-dimethylpiperidinosulfonyl)benzoic acid; 2-chloro-4-fluoro-5-(2-p-methylphenethylaminosulfonyl)benzoic acid; 2,4-dibromo-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid; 2,4-dibromo-5-diethylaminosulfonylbenzoic acid; 2,4-dibromo-5-phenylaminosulfonylbenzoic acid; 2-bromo-4-chloro-5-(4-methylpiperidinosulfonyl)benzoic acid; 2-bromo-4-chloro-5-hexamethyleneiminisulfonylbenzoic acid; 2-bromo-4-methyl-5-piperidinosulfonylbenzoic acid; 2-bromo-4-methyl-5-(2-p-chlorophenethylaminosulfonyl)benzoic acid; 2-methyl-4-bromo-5-diethylaminosulfonylbenzoic acid; 2-chloro-4-methyl-5-morpholinosulfonylbenzoic acid; 2-chloro-4-methoxy-5-(2-methylpiperidinosulfonyl)benzoic acid; 2-chloro-4-methoxy-5-(2-chloro-4-bromobenzylaminosulfonyl)benzoic acid; 2-bromo-4-methoxy-5-(2-[3,4-dimethylphenethyl]aminosulfonyl)benzoic acid; 2-chloro-4-methoxy-5-(3-[2-methyl-4-chlorophenylpropyl]aminosulfonyl)benzoic acid; 2-fluoro-4-methyl-5-piperidinosulfonylbenzoic acid; 2-fluoro-4-methyl-5-phenylaminosulfonylbenzoic acid; 2-fluoro-4-methoxy-5-hexamethyleneiminisulfonylbenzoic acid; 2,4-dimethyl-5-morpholinosulfonylbenzoic acid; 2,4-dimethyl-5-di-i-propylaminosulfonylbenzoic acid; 2-methyl-4-methoxy-5-di-n-propylaminosulfonylbenzoic acid; 2-methyl-4-methoxy-5-morpholinosulfonylbenzoic acid; 2-methyl-4-methoxy-5-phenylaminosulfonylbenzoic acid; and 2-methyl-4-methoxy-5-hexamethyleneiminisulfonylbenzoic acid.

EXAMPLE 39

2,6-Dichloro-5-piperidinosulfonylbenzoic Acid

To a stirred solution of chlorosulfonic acid (10.6 g.; 0.09 mole) is added 1.91 g. (0.01 mole) of commercially available 2,6-dichlorobenzoic acid and the resulting reaction solution heated to 155° C. for 75 min. The solution is cooled, poured into 100 ml. of ice-water and the resulting white precipitate filtered and dried, 1.8 g., m.p. 155–160° C. Recrystallization from chloroform gave 1.2 g. of 2,6-dichloro-5-chlorosulfonylbenzoic acid, m.p. 170–171° C.

Anal. Calc'd for $C_{12}H_7Cl_3O_4S$: C, 29.04; H, 1.04. Found: C, 29.30; H, 1.05.

b. 2,6-Dichloro-5-chlorosulfonylbenzoic acid (960 mg.; 3.3 m moles) is added portion-wise to 1.95 g. (0.0165 mole) of piperidine in 15 ml. of dry methylene chloride, and the mixture heated to reflux for 1.5 hrs. The solvent and excess amine are removed under reduced pressure and the residue dissolved in 15 ml. of 2N sodium hydroxide. The aqueous base solution is extracted (2 x 50 ml.) with ether and acidified with 6N hydrochloric acid. The precipitated gum is filtered, dried and allowed to crystallize in hexane, 1.1 g., m.p.

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145°–150° C. A small sample is recrystallized from acetonitrile, m.p. 142°–145° C.
Anal. Calc'd for $C_{12}H_{10}Cl_2O_4NSCl_2$: C, 42.62; H, 3.87; N, 4.14. Found: C, 42.56; H, 4.00; N, 4.02.

EXAMPLE 40

Starting with 2,6-dichloro-5-chlorosulfonylbenzoic acid prepared in Example 39a and the appropriate amine, the following analogs are prepared:

2,6-dichloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid, m.p. 157°–159° C.;
2,6-dichloro-5-di-n-propylaminosulfonylbenzoic acid, m.p. 137–138° C.;
2,6-dichloro-5-(2-p-chlorophenethylaminosulfonyl)benzoic acid, m.p. 90°–91° C.

EXAMPLE 41

Starting with 350 mg. of 2,6-dichloro-5-(2-p-chlorophenethylaminosulfonyl)benzoic acid and 1 ml. of ethyl iodide and following the procedure of Example 30b, 2,6-dichloro-5-(N-ethyl-N-[2-p-chlorophenethyl]aminosulfonyl)benzoic acid is prepared, m.p. 138°–139° C.

EXAMPLE 42

The procedure of Example 31 is repeated, starting with the appropriate amine, 2,6-disubstituted benzoic acid and chlorosulfonic acid, to provide the following compounds:

2,6-dichloro-5-morpholinosulfonylbenzoic acid; 2,6-dichloro-5-di-n-butylaminosulfonylbenzoic acid; 2,6-dichloro-5-(4-bromobenzylaminosulfonyl)benzoic acid; 2-fluoro-6-chloro-5-piperidinosulfonylbenzoic acid; 2-fluoro-6-chloro-5-hexamethyleneiminisulfonylbenzoic acid; 2-fluoro-6-chloro-5-dimethylaminosulfonylbenzoic acid; 2,6-difluoro-5-(3,4-dichlorophenylaminosulfonyl)benzoic acid; 2,6-difluoro-5-morpholinosulfonylbenzoic acid; 2,6-difluoro-5-(4,4-dimethylpiperidinosulfonyl)benzoic acid; 2,6-difluoro-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid; 2-methyl-6-chloro-5-diethylaminosulfonylbenzoic acid; 2-methyl-6-chloro-5-piperidinosulfonylbenzoic acid; 2-chloro-6-methyl-5-hexamethyleneiminisulfonylbenzoic acid; 2-chloro-6-methyl-5-(4-tolylaminosulfonyl)benzoic acid; 2-chloro-6-methyl-5-(3-[4-bromophenylpropyl]aminosulfonyl)benzoic acid; 2-methyl-6-bromo-5-piperidinosulfonylbenzoic acid; 2-methyl-6-bromo-5-(4-tolylaminosulfonyl)benzoic acid; 2-bromo-6-methyl-5-piperidinosulfonylbenzoic acid; 2-bromo-6-methyl-5-(4-tolylaminosulfonyl)benzoic acid; 2-chloro-6-bromo-5-di-n-propylaminosulfonylbenzoic acid; 2-chloro-6-bromo-5-morpholinosulfonylbenzoic acid; 2-bromo-6-chloro-5-piperidinosulfonylbenzoic acid; 2,6-dimethyl-5-hexamethyleneiminisulfonylbenzoic acid; 2,6-dimethyl-5-(4-biphenylaminosulfonyl)benzoic acid; 2,6-dimethyl-5-diethylaminosulfonylbenzoic acid; and 2,6-dimethyl-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid.

EXAMPLE 43

4-Chloro-5-di-n-butylsulfamylbenzoic Acid

To a solution of 3.9 g. (0.03 mole) of di-n-butylamine in 15 ml. of methylene chloride is added 2.5 g. (0.01 mole) of 4-chloro-5-chlorosulfonylbenzoic acid (*J. Pharm. Pharmacol.*, 683 (1962)), and the resulting reaction mixture allowed to stir at room temperature for 3

rated, dried over magnesium sulfate and concentrated to an oil which crystallizes on standing. The solid intermediate methyl 5-(cis-3,5-dimethylpiperidin-2-yl)-6-chlorobenzoate is triturated with hexane and filtered, 19.8 g., m.p. 92.5-93.5° C.

An aqueous solution of 4.2 g. (105 m moles) of sodium hydroxide in 130 ml. of water is added to 18 g. (52.5 m moles) of methyl 5-(cis-3,5-dimethylpiperidin-2-yl)-6-chlorobenzoate in 130 ml. of methanol, and resulting reaction mixture allowed to stir at 40° C. for 1 hr. The solution is poured into ice water (1.5 l.) and extracted several times with benzene. The aqueous phase is separated, acidified with 12N hydrochloric acid, and the precipitated product filtered and air dried, 17.3 g. Recrystallization from ethyl acetate-hexane gave the purified product, 16.4 g., m.p. 152.5°-153° C.

EXAMPLE 50

The procedure of Example 49 is repeated, starting with the requisite 2-substituted-3-nitrobenzoic acid methyl ester and appropriate amine, to provide the following congeners:

5-morpholin-2-yl-6-chlorobenzoic acid; 5-diethylamino-6-chlorobenzoic acid; 5-(2-p-chlorophenethylamino)-6-chlorobenzoic acid; 5-hexamethylenimine-6-fluorobenzoic acid; 5-piperidin-2-yl-6-fluorobenzoic acid; 5-di-n-propylamino-6-fluorobenzoic acid; 5-(2-p-bromophenethylamino)-6-fluorobenzoic acid; 5-phenylamino-6-bromobenzoic acid; 5-(cis-3,5-dimethylpiperidin-2-yl)-6-bromobenzoic acid; 5-dimethylamino-6-bromobenzoic acid; 5-hexamethylenimine-6-bromobenzoic acid; 5-piperidin-2-yl-6-bromobenzoic acid; 5-(2,4-dimethylpiperidin-2-yl)-6-methylbenzoic acid; 5-(4,4-dimethylpiperidin-2-yl)-6-methylbenzoic acid; 5-(2-p-chlorophenethylamino)-6-methylbenzoic acid; 5-(2,3-dichlorobenzylamino)-6-methylbenzoic acid; 5-di-n-butylamino-6-methylbenzoic acid; and 5-morpholin-2-yl-6-methylbenzoic acid.

EXAMPLE 51

Starting with the appropriate 5-sulfamylbenzoic acid and alkyl iodide and employing the alkylation procedure of Example 30b, the following analogs are synthesized:

2,3-difluoro-5-(N-methyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 2,3-difluoro-5-(N-ethyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 2-chloro-3-bromo-5-(N-n-propyl-N-[3,4-dichlorobenzylamino]sulfonyl)benzoic acid; 2-methyl-3-fluoro-5-(N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 2-chloro-3-methyl-5-(N-ethyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 2-methyl-3-chloro-5-(N-ethyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 2-fluoro-3-methyl-5-(N-methyl-N-phenylamino)sulfonyl)benzoic acid; 2,4-difluoro-5-(N-ethyl-N-[3-p-bromophenylpropylamino]sulfonyl)benzoic acid; 2-chloro-4-fluoro-5-(N-n-propyl-N-[2-p-tolylethylamino]sulfonyl)benzoic acid; 2,4-dibromo-5-(N-methyl-N-phenylamino)sulfonyl)benzoic acid; 2-bromo-4-methyl-5-(N-n-butyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 2-chloro-4-methoxy-5-(N-methyl-N-[3-(2-methyl-4-chlorophenylpropylamino]sulfonyl)benzoic acid; 2-fluoro-4-methyl-5-(N-n-propyl-N-phenylamino)sulfonyl)benzoic acid; 2,6-

dichloro-5-(N-n-butyl-N-[4-bromobenzylamino]sulfonyl)benzoic acid; 2,6-difluoro-5-(N-n-butyl-N-[3,4-dichlorophenylamino]sulfonyl)benzoic acid; 2-chloro-6-methyl-5-(N-ethyl-N-4-tolylamino)sulfonyl)benzoic acid; 2-chloro-6-methyl-5-(N-methyl-N-[3,4-bromophenylpropylamino]sulfonyl)benzoic acid; 2-methyl-6-bromo-5-(N-n-propyl-N-4-tolylamino)sulfonyl)benzoic acid; 2-bromo-6-methyl-5-(N-ethyl-N-4-tolylamino)sulfonyl)benzoic acid; 2,6-dimethyl-5-(N-methyl-N-4-biphenylamino)sulfonyl)benzoic acid; 4-bromo-5-(N-methyl-N-[4-bromobenzylamino]sulfonyl)benzoic acid; 4-methyl-5-(N-n-butyl-N-[3,5-dibromophenylamino]sulfonyl)benzoic acid; 4-methoxy-5-(N-ethyl-N-4-biphenylamino)sulfonyl)benzoic acid; 3-methyl-5-(N-ethyl-N-4-bromophenylamino)sulfonyl)benzoic acid; 3-methyl-5-(N-ethyl-N-[2-p-tolylethylamino]sulfonyl)benzoic acid; 3-chloro-5-(N-ethyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 3-trifluoro-5-(N-methyl-N-[3-p-bromophenylpropylamino]sulfonyl)benzoic acid; 5-(N-ethyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 5-(N-n-propyl-N-phenylamino)sulfonyl)benzoic acid; 5-(N-ethyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; and 2-fluoro-5-(N-methyl-N-phenylamino)sulfonyl)benzoic acid.

EXAMPLE 52

The procedure of Example 15 is repeated, starting with the requisite amine and 2-fluoro-5-sulfamylbenzoic acid, to give the following congeners:

2-diethylamino-3-fluoro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid; 2-piperidin-3-fluoro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid; 2-piperidin-3-fluoro-5-morpholin-2-yl)benzoic acid; 2-hexamethylenimine-3-fluoro-5-morpholin-2-yl)benzoic acid; 2-di-n-butylamino-3-chloro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid; 2-piperidin-3-chloro-5-diethylamino)benzoic acid; 2-piperidin-3-methyl-5-phenylamino)benzoic acid; 2-hexamethylenimine-3-chloro-5-piperidin-2-yl)benzoic acid; 2-(N-ethyl-N-n-propylamino)-3-trifluoromethyl-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid; 2-diethylamino-4-fluoro-5-(3-p-bromophenylpropylamino)benzoic acid; 2-piperidin-4-chloro-5-(3-chlorophenylamino)benzoic acid; 2-hexamethylenimine-4-chloro-5-hexamethylenimine)benzoic acid; 2-di-n-propylamino-4-methyl-5-piperidin-2-yl)benzoic acid; 2-di-n-butylamino-4-methoxy-5-hexamethylenimine)benzoic acid; 2-piperidin-6-fluoro-5-(3,4-dichlorophenylamino)benzoic acid; 2-diethylamino-6-fluoro-5-morpholin-2-yl)benzoic acid; 2-piperidin-6-fluoro-5-(4,4-dimethylpiperidin-2-yl)benzoic acid; 2-diethylamino-3-fluoro-5-(N-methyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 2-piperidin-3-fluoro-5-(N-ethyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 2-hexamethylenimine-3-methyl-5-(N-methyl-N-phenylamino)sulfonyl)benzoic acid; 2-di-n-propylamino-6-fluoro-5-(N-n-butyl-N-[3,4-dichlorophenylamino]sulfonyl)benzoic acid; and 2-piperidin-6-fluoro-5-(N-n-butyl-N-[3,4-dichlorophenylamino]sulfonyl)benzoic acid.

EXAMPLE 53

The procedure of Example 18 is repeated, starting with the appropriate 2-fluoro-5-sulfamylbenzoic acids

and methanol in place of isopropanol, to give the following compounds:

2-methoxy-3-fluoro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid; 2-methoxy-3-fluoro-5-morpholin-2-yl)benzoic acid; 2-methoxy-3-chloro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid; 2-methoxy-3-chloro-5-diethylamino)benzoic acid; 2-methoxy-3-chloro-5-piperidin-2-yl)benzoic acid; 2-methoxy-3-trifluoromethyl-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid; 2-methoxy-4-fluoro-5-(3-p-bromophenylpropylamino)benzoic acid; 2-methoxy-4-fluoro-5-morpholin-2-yl)benzoic acid; 2-methoxy-4-chloro-5-hexamethylenimine)benzoic acid; 2-methoxy-4-methyl-5-piperidin-2-yl)benzoic acid; 2-methoxy-4-methyl-5-phenylamino)benzoic acid; 2,4-dimethoxy-5-hexamethylenimine)benzoic acid; 2-methoxy-6-fluoro-5-(3,4-dichlorophenylamino)benzoic acid; 2-methoxy-3-fluoro-5-(N-ethyl-N-[2-p-chlorophenethylamino]sulfonyl)benzoic acid; 2-methoxy-3-methyl-5-(N-methyl-N-phenylamino)sulfonyl)benzoic acid; and 2-methoxy-4-methyl-5-(N-n-propyl-N-phenylamino)sulfonyl)benzoic acid.

EXAMPLE 54

A dry solid pharmaceutical composition is prepared by blending the following materials together in the specified weight proportions:

2-chloro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid	50
sodium citrate	25
alginate acid	10
polyvinylpyrrolidone	10
magnesium stearate	5

After the dried composition is thoroughly blended, tablets are punched from the mixture, each tablet being

of such size as to contain 100 mg. of the active ingredient. Tablets are also prepared containing, respectively, 5, 10, 25 and 50 mg. of the active ingredient, by employing the appropriate proportions of 2-chloro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid and excipient blend in each case.

EXAMPLE 55

A dry solid pharmaceutical composition is prepared by combining the following materials in the indicated weight proportions:

2-chloro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid	50
calcium carbonate	20
polyethylene glycol, average molecular weight 4000	30

The dry mixture is thoroughly agitated to obtain a completely uniform blend. Soft elastic and hard gelatin capsules containing this composition are then prepared, employing sufficient material to provide each capsule with 190 mg. of active ingredient.

EXAMPLE 56

Groups, each comprising 4 animals, of normal Sprague-Dawley (Charles River) male rats weighing from 160 to 220 grams are fed rat chow containing the test compounds for two overnight feeding periods. On the morning of the third day the animals are anesthetized and bled from the abdominal aorta. The total plasma cholesterol is then determined by the method of J. I. Carr and I. J. Drecker reported in *Clin. Chem.*, 2, 353 (1956). Most of the tests are conducted at a concentration in the feed of 0.15 to 0.25 weight percent of the compound under test, but lower levels are employed in some instances. The total quantity of test compound consumed is computed from feed consumption over the two-day period and is tabulated, in milligrams per kilogram body weight per day, along with the associated percent cholesterol fall measured:

Compound	% Cholesterol Fall	Daily Dosage mg./kg.
2-chloro-5-(trans-di-3,5-dimethylpiperidin-2-yl)benzoic acid	35	126
2-chloro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid	44	112
2-chloro-4-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid	inactive	182
2-bromo-5-(cis-3,5-dimethylpiperidin-2-yl)benzoic acid	40	120
2-bromo-5-(3-benzoyloxy-piperidin-2-yl)benzoic acid	25	114
2-chloro-5-(3-benzoyloxy-piperidin-2-yl)benzoic acid	26	129
2-chloro-5-(2,5-dimethylpiperidin-2-yl)benzoic acid	35	110
2-bromo-5-(3-trifluoromethyl-4-chlorophenylsulfamyl)benzoic acid	38	174
2-chloro-5-(3,5-dimethylmorpholin-2-yl)benzoic acid	29	156
2-isopropoxy-5-(3-methylpiperidin-2-yl)benzoic acid	22	149
2-hydroxy-5-(3-methylpiperidin-2-yl)benzoic acid	35	134
2-piperidin-5-(piperidin-2-yl)benzoic acid	35	129
2-bromo-5-(1-methyl-3-hydroxypropylsulfamyl)benzoic acid	16	279
2-bromo-5-(3-phenylpropylamino)benzoic acid	26	131
2-bromo-5-(4-m-tolyl-1-piperazylsulfamyl)benzoic acid	20	123
2-bromo-5-(2-carboxyphenylsulfamyl)benzoic acid	37	273
2-chloro-5-(2-oxopiperidin-2-yl)benzoic acid	30	136
2-pyrrolidin-5-(3,5-dimethylpiperidin-2-yl)benzoic acid	31	215
N-[2-chloro-5-(cis-3,5-dimethylpiperidin-2-yl)benzoate]glycine	35	180

EUROPEAN PATENT APPLICATION

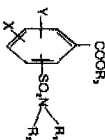
Application number: 82106408.8
Date of filing: 22.06.82
Int. Cl.: A 61 K 31/19, A 61 K 31/235,
A 61 K 31/33
// CO7C143/78, CO7C143/72,
CO7D295/22

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22.06.81 JP 98378/81

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Bulletin 83/1

Designated Contracting States: BE IT

Antiviral compositions and a method for treating virus diseases.
Antiviral compositions and use thereof which contain as active component aminosulfonylhalobenzoic acid derivatives of the formula:



wherein X and Y, independently of each other, denote hydrogen atom, fluorine atom, chlorine atom, bromine atom, amino group or nitro group, R1 denotes hydrogen atom or lower alkyl group, R2 denotes hydrogen atom, amino group, lower alkyl group, hydroxyalkyl group, lower alkoxy group, aryl group, guanidino group, quaternary group, ureido group, oxamoyl group or chlorosubstituted pyridinimino group, or R1 and R2 together with the nitrogen atom in the formula (I) may form a saturated heterocyclic group having 4 or 5 carbon atoms, in which the carbon atoms may be substituted by one or more oxygen atoms or nonsubstituted or lower alkyl group-substituted nitrogen atom, and R3 denotes hydrogen atom, cyclohexyl group, benzyl group, aryl group, or straight or branched alkyl group which consists of 1 to 12

carbon atoms, provided that 3-aminosulfonyl-4-halobenzoic acid is excluded from the compositions, or the salts thereof. They are effective for therapeutic treatment of various infectious diseases which are caused from viruses, for example, upper respiratory infection, pneumonia, Bronchitis and so on.

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Compound	Chemical Name	Melting Point (°C)	Property
21	2,4-dichloro-5-guanidino-sulfonylbenzoic acid	252 - 254	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
22	2,4-dichloro-5-guanidino-aminosulfonylbenzoic acid	198 - 199 (dec)	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
23	2,4-dichloro-5-semicarbazidesulfonylbenzoic acid	220 (dec)	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
24	2,4-dichloro-5-(2-oxamoylhydrazidino-sulfonyl)benzoic acid	217 - 219 (dec)	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
25	3-aminosulfonyl-5-chlorobenzoic acid	242 - 243	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
26	3-aminosulfonyl-5-bromobenzoic acid	241 - 244	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
27	2-aminosulfonyl-5-chlorobenzoic acid	182 - 183.5	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol

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Table 2 In Vitro Antiviral Activity

Compound	Virus	Minimum Inhibitory Concentration (µg/ml)									
		A	B	C	D	E	F	G	H	I	J
1		30	300	300	300	300	300	100	300	300	300
2		30	300	300	300	300	300	300	300	100	300
3		30	300	300	300	300	300	300	300	300	300
4		30	300	300	100	300	300	300	300	300	300
5		30	300	100	300	100	300	300	300	100	300
6		30	300	300	300	300	100	300	300	300	300
7		10	300	100	100	300	300	300	300	300	100
8		30	100	300	300	300	300	300	300	300	300
9		30	300	300	300	300	300	100	300	300	300
10		30	300	300	300	300	100	300	300	300	300
11		30	300	300	300	300	100	300	300	300	300
12		30	300	300	300	300	300	100	300	300	300
13		10	100	300	100	300	300	100	300	300	300
14		30	100	300	300	300	300	300	300	300	300
15		30	300	300	300	300	100	300	300	300	300
16		30	300	300	300	300	300	30	300	300	100
17		30	300	300	300	300	300	300	300	300	300
18		30	300	30	300	300	3	30	300	300	300
19		10	300	300	100	100	100	100	100	30	100
20		10	100	10	100	30	100	300	30	300	30
21		100	300	300	300	300	300	300	100	300	300
22		100	300	100	300	300	100	300	300	100	300
23		100	300	300	300	100	300	300	300	300	300
24		100	300	300	300	300	300	300	100	300	300
25		30	300	300	100	300	300	300	300	100	300
26		30	300	300	300	300	100	300	300	300	300
27		30	300	30	100	300	300	300	100	300	300

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Experimental Example 7: Acute Toxicity in Mice

Each compound of the invention was suspended in 5% Arabic gum solution and given orally (p.o.) or intraperitoneally (i.p.) to groups of ten ddY male mice weighed from 24 to 26 g at the dosage volume of 10 ml/kg. The mortality rate was observed for 7 days. LD₅₀ was determined according to the method of Wilcoxon and Litchfield. The results are shown in Table 10.

Table 10 LD₅₀ value (mg/kg)

Compound	Oral administration	Intra-peritoneal administration	Compound	Oral administration	Intra-peritoneal administration
1	>3,000	>1,000	15	>3,000	>1,000
2	>3,000	>1,000	16	>3,000	>1,000
3	>3,000	>1,000	17	>3,000	>1,000
4	>3,000	>1,000	18	>3,000	>1,000
5	>3,000	>1,000	19	>3,000	>1,000
6	>3,000	>1,000	20	>3,000	>1,000
7	>3,000	746	21	>3,000	987
8	>3,000	>1,000	22	>3,000	>1,000
9	>3,000	968	23	>3,000	>1,000
10	>3,000	>1,000	24	>3,000	>1,000
11	>3,000	>1,000	25	>3,000	>1,000
12	>3,000	>1,000	26	>3,000	>1,000
13	>3,000	>1,000	27	>3,000	>1,000
14	>3,000	>1,000			

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Table 10 - Continued

Compound	Oral administra- tion	Intra- peritoneal administra- tion	Compound	Oral administra- tion	Intra- peritoneal administra- tion
28	>3,000	>1,000	35	>3,000	>1,000
29	>3,000	>1,000	36	>3,000	>1,000
30	>3,000	>1,000	37	>3,000	>1,000
31	>3,000	>1,000	38	>3,000	>1,000
32	>3,000	>1,000	39	>3,000	>1,000
33	>3,000	>1,000	40	>3,000	>1,000
34	>3,000	>1,000	41	>3,000	>1,000
			42	>3,000	>1,000

As apparent from the above experimental examples, all of the compounds 1 - 42 have antiviral activity of wide spectrum and are of extremely high safety. Therefore, they have very high clinical utility for treating various infectious diseases which are caused from virus infection, for example, upper respiratory infection, pneumonia, Brouchitis and so on.

In case that the compounds of the present invention are administered to a human body, dosage for an adult is 30 - 5,000 mg per day for the compounds 1 - 6, 8 - 12, 14 - 18, 25 - 28, 31 - 33, 41, and 42; 10 - 5,000 mg per day for the compounds 7, 13, 19, 20, 30, 35, and 37; 50 - 5,000 mg per day for the compounds 21 - 24, 29, 34, 36, 38, 39, and 41. However, the dosage may be increased or decreased out of the above range according to symptoms, ages, and other conditions.

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6. Composition according to Claim 1, wherein the aminosulfonylhalogenobenzoic acid derivative of the general formula (I) is aminosulfonyl-2,4-dihalogenobenzoic acid (in the formula, X and Y denote fluorine atom, chlorine atom or bromine atom, and both of R_1 and R_2 denote hydrogen atom and R_3 denotes hydrogen atom, cyclohexyl group, benzyl group, aryl group, or straight or branched alkyl group which consists of 1 to 12 carbon atoms.

7. Composition according to Claim 1, wherein the aminosulfonylhalogenobenzoic acid derivative of the general formula (I) is 3-aminosulfonylhalogenobenzoic acid derivative.

8. Composition according to Claim 1, wherein the aminosulfonylhalogenobenzoic acid derivative of the general formula (I) is 3-aminosulfonyl-4,5-dichlorobenzoic acid derivative.

9. Composition according to Claim 1, wherein the aminosulfonylhalogenobenzoic acid derivative of the general formula (I) is 5-aminosulfonyl-2,4-dichlorobenzoic acid derivative (in the formula, X and Y denote chlorine atom, R_1 denotes hydrogen atom, R_2 denotes hydrogen atom, quanyl group, guanidino group, ureido group, oxamoylamino group, and R_3 denotes hydrogen atom, cyclohexyl group, benzyl group, aryl group, or straight or branched alkyl group which consists of 1 to 12 carbon atoms.

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[54] ELECTROSTATIC IMAGE DEVELOPING
TONER

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[21] Appl. No.: 245,542

[22] Filed: May 18, 1994

[30] Foreign Application Priority Data

May 24, 1993 [JP] Japan S-142553

[51] Int. Cl.⁴ G03G 9/097

[52] U.S. Cl. 430/110; 430/903

[58] Field of Search 430/110, 903

[56] References Cited

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5,346,794 9/1994 Anzai et al. 430/110

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2121204 12/1983 United Kingdom .
2121205 12/1983 United Kingdom .

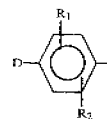
Primary Examiner—Roland Martin
Attorney, Agent, or Firm—Oblon, Spivak, McClelland,
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[57] ABSTRACT

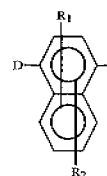
An electrostatic image developing toner containing a
compound of the following formula (1):



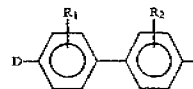
wherein X is



(wherein D is a hydrogen atom or an electron donating
group, and each of R₁ and R₂ which are independent of
each other, is a hydrogen atom, an alkyl group, a cyclo-
alkyl group, an alkoxy group, an aryl group, an aralkyl
group, a hydroxyl group, an amino group, a dialkyl-
amino group, a diarylamino group, a diaralkylamino
group, a halogen atom, a halogen-substituted alkyl
group, a halogen-substituted aryl group, a cyano group,
a formyl group, a carboxyl group, a carbamoyl group,
an N-substituted carbamoyl group, an alkoxycarbonyl
group, an acyloxy group, an acyl group, an arylcarbo-
nyl group, a nitro group, a sulfonic acid group, an alkyl-
sulfonyl group, a substituted sulfonyl group, a sulfa-
moyl group, an N-substituted sulfamoyl group or a
substituted sulfinyl group, provided that when D is a
hydrogen atom, R₁ and R₂ are not simultaneously hy-
drogen atoms and at least one substituent other than a
hydrogen atom is substituted at the 2-position, or R₁ and
R₂ together form a ring),

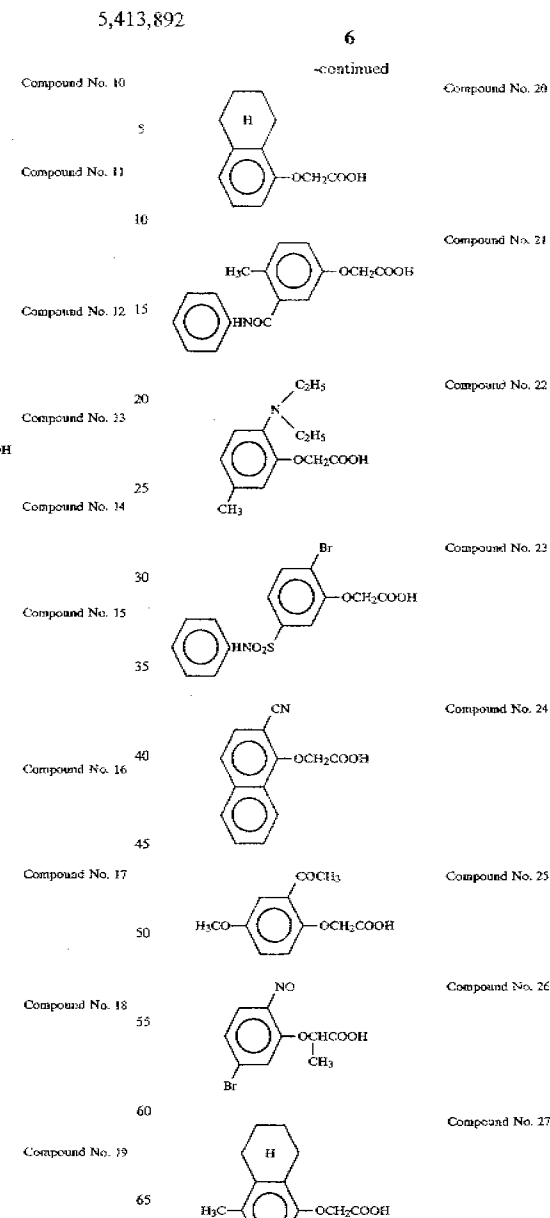
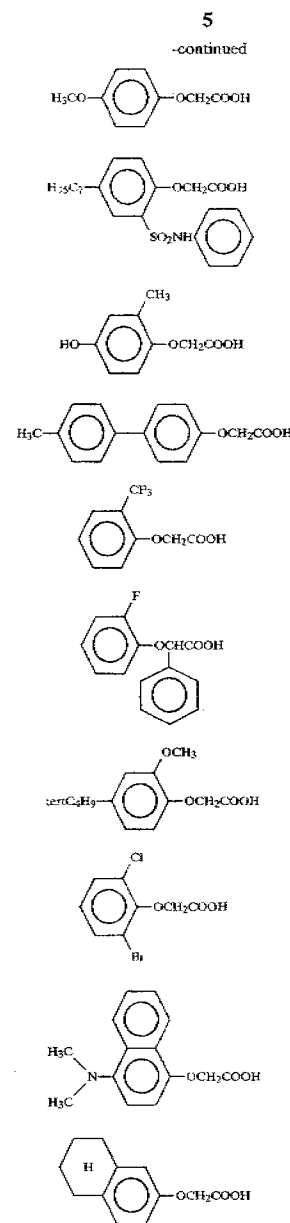


(wherein D, R₁ and R₂ are as defined above, or



(wherein D, R₁ and R₂ are as defined above.

4 Claims, No Drawings



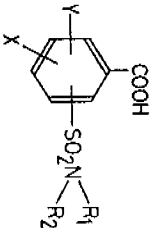
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(22) Date of filing 5 Nov 1981
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(33) 10 Nov 1980
(34) 22 Jun 1981
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211/36 237/10 295/00
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38Y 390 H
C2C 1580 215 220 227
22Y 250 252 25Y 311 313
314 316 31Y 320 321 32Y
332 337 338 342 34Y 360
361 364 368 367 36Y 368
494 510 51X 532 533
534 535 620 652 650 669
697 699 801 802 80Y AA
SF 5G
(56) Field of search
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(57) Antiviral compositions containing sulphonamide derivatives

(57) Antiviral compositions contain as active component aminosulfonylhalobenzoic acid derivatives of the formula:



wherein X and Y, independently of each other, denote hydrogen, fluorine, chlorine, bromine, amino or nitro, R₁ denotes hydrogen or lower alkyl, R₂ denotes hydrogen, amino, lower alkyl, hydroxyalkyl, lower alkoxy, aryl, guanlyl, guanidino, ureido, oxamoylamino or chloro-substituted pyridazinamino, or R₁ and R₂ together with the nitrogen atom in the formula (I) may form a saturated heterocyclic group having 4 or 5 carbon atoms, which may be substituted by oxygen, amino or alkylamino, and the salts thereof.

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TABLE 1 (Continued)

Compound		Melting Point (°C)	Property
8	4-chloro-3-methoxyamino-sulfonylbenzoic acid	205 - 206	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
9	4-chloro-3-hydroxyethyl-aminosulfonylbenzoic acid	177 - 178	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
10	4-chloro-3-N-methyl-hydroxyethylaminosulfonylbenzoic acid	155.5 - 156.5	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
11	4-chloro-3-hydrazino-sulfonylbenzoic acid	286.5 - 288 (dec)	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
12	4-chloro-3-isopropyl-aminosulfonylbenzoic acid	189 - 191	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
13	3-anilinosulfonyl-4-chlorobenzoic acid	208 - 210	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
14	4-chloro-3-[2-(6-chloro-pyridazine-3-yl)hydrazino-1-yl]sulfonylbenzoic acid	186 - 188	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol

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TABLE 1 (Continued)

Compound		Melting Point (°C)	Property
22	5-aminosulfonyl-2-bromo-4-chlorobenzoic acid	220 — 234	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
23	5-aminosulfonyl-2,4-dichlorobenzoic acid	232 — 233.5	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
24	3-aminosulfonyl-4,5-dichlorobenzoic acid	266 — 268	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
25	2,4-dichloro-5-guanidino-aminosulfonylbenzoic acid	252 — 254	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
26	2,4-dichloro-5-guanidino-aminosulfonylbenzoic acid	198 — 199 (dec)	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
27	2,4-dichloro-5-semi-carbazidesulfonylbenzoic acid	220 (dec)	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol
28	2,4-dichloro-5-oxaminic acid hydradinosulfonylbenzoic acid	217 — 219 (dec)	white crystalline powder; insoluble in benzene, hexane; soluble in hot water, methanol

TABLE 3
In Vitro Antiviral Activity

Compound	Virus	Minimum Inhibitory Concentration (µg/ml)									
		A	B	C	D	E	F	G	H	I	J
5		30	300	300	300	300	300	100	300	300	300
6		30	300	300	300	300	300	300	300	100	300
7		30	300	300	300	300	300	300	300	300	300
8		30	300	300	100	300	300	300	300	300	300
9		30	300	100	300	100	300	300	300	100	300
10		30	300	300	300	300	100	300	300	300	300
11		10	300	100	100	300	300	300	300	300	100
12		30	100	300	300	300	300	300	300	300	300
13		30	300	300	300	300	300	100	300	300	300
14		30	300	300	300	300	100	300	300	300	300
15		30	300	300	300	300	100	300	300	300	300
16		30	300	300	300	300	300	100	300	300	300
17		10	100	300	100	300	300	100	300	300	300
18		30	100	300	300	300	300	300	300	300	300
19		30	300	300	300	300	100	300	300	300	300
20		30	300	300	300	300	300	30	300	300	100
21		30	300	300	300	300	300	300	300	300	300
22		30	300	30	300	300	30	300	300	300	300
23		10	300	300	100	100	100	100	100	30	100
24		10	100	10	100	30	100	300	30	300	30
25		100	300	300	300	300	300	300	100	300	300
26		100	300	100	300	300	100	300	300	100	300
27		100	300	300	300	100	300	300	300	300	300
28		100	300	300	300	300	300	300	100	300	300
29		30	300	300	100	300	300	300	300	100	300
30		30	300	300	300	300	100	300	300	300	300
31		30	300	30	100	300	300	300	100	300	300

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EUROPEAN PATENT APPLICATION

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C 07 C 143/837, C 07 C 143/79,
C 07 D 295/22, C 07 D 237/20,
C 07 C 143/80
// A61K31/19, A61K31/235,
A61K31/535, A61K31/50,
A61K31/495

Priority: 22.06.81 JP 96377/81
06.05.82 JP 75781/82

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Date of publication of application: 05.01.83
Bulletin 63/1

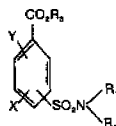
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Designated Contracting States: BE IT

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Aminosulfonylbenzoic acid derivatives.

Novel aminosulfonylbenzoic acid derivatives of the formula (I):



(I)

wherein X and Y, independently of each other, denote chlorine atom, bromine atom, hydrogen atom, amino group or nitro group, R₁ denotes hydrogen atom or a lower alkyl group, R₂ denotes hydrogen atom, amino group, a lower alkyl group, a hydroxyalkyl group, a lower alkoxy group, aryl group, guanidino group, ureid group, oxamoylamino group, or unsubstituted or halogen-substituted pyridazinamino group, or R₁ and R₂ together with a nitrogen atom in the formula (I) may form a saturated heterocyclic group of 4 or 5 carbon atoms in which the carbon atoms may be replaced by an oxygen atom or unsubstituted or lower alkyl-substituted nitrogen atom, and R₃ denotes hydrogen atom, alkyl group, alkenyl group, cycloalkyl group, or benzyl group.

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Example 3:

After 2.55 g of 3-chlorosulfonyl-4-chlorobenzoic acid and 1.94 g of sodium carbonate were dissolved into a solvent consisting of the two phases of 10 ml of water and 10 ml of chloroform, 0.93 g of aniline was dropped therein under stirring and cooling with ice. After 5 hour reaction at room temperature, the reaction mixture was separated into two phases. After addition of 10 g of ice to the aqueous layer, it was adjusted with 6 N hydrochloric acid to the pH of lower than 2 and the precipitated crystals were filtered off and washed with water. The crystals thus obtained were recrystallized from the mixed solvent of water and methanol, yielding 2.65 g of 3-anilinosulfonyl-4-chlorobenzoic acid as white crystals. The product showed the melting point of 208 - 210°C when measured in accordance with the prescription of the Japanese Pharmacopeia. The result of elementary analysis of this product is as follows:

	C	H	Cl	N	S
Calculated	50.09	3.23	11.37	4.49	10.28
Found	50.32	3.40	11.20	4.41	10.09

Example 4:

1.08 g of guanidine sulfate and 2.90 g of 5-chlorosulfonyl-2,4-dichlorobenzoic acid were successively added into 1.22 g of sodium hydroxide dissolved in 10 ml of water under stirring and cooling with ice. After the reaction was effected at room temperature for 2 hours and then 10 g of ice was added to the reaction mixture, it was adjusted with 6 N hydrochloric acid to the pH of lower than 2 thereby precipitating crystals. The crystals were filtered off and washed with water.

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In the following, other examples of the compounds according to the present invention are shown.

Examples 7 - 20

	Compound Name	Preparation Method *	Appearance	Melting Point (°C)
7	3-ethylaminosulfonyl-4-chlorobenzoic acid	1	white crystal	190.5 - 192.5
8	3-dimethylaminosulfonyl-4-chlorobenzoic acid	1	ditto	248.5 - 249.5
9	3-aminosulfonyl-5-bromobenzoic acid	1	ditto	241 - 244
10	3-hydroxyethylaminosulfonyl-4-chlorobenzoic acid	2	ditto	177 - 178
11	3-N-methylhydroxyethylaminosulfonyl-4-chlorobenzoic acid	2	ditto	155.5 - 156.5
12	3-(pyrrolidine-1-yl)sulfonyl-4-chlorobenzoic acid	2	ditto	237 - 239
13	3-isopropylaminosulfonyl-4-chlorobenzoic acid	3	ditto	189 - 191
14	3-methoxyaminosulfonyl-4-chlorobenzoic acid	4	ditto	205 - 206
15	5-guanidinoaminosulfonyl-2,4-dichlorobenzoic acid	4	ditto	198 - 199 (decomposed)
16	5-semicarbazidosulfonyl-2,4-dichlorobenzoic acid	4	ditto	220 (decomposed)
17	5-(2-oxanonylhydrazinosulfonyl)-2,4-dichlorobenzoic acid	4	ditto	217 - 219 (decomposed)
18	2-amino-5-aminosulfonyl-4-chlorobenzoic acid	1	ditto	> 300
19	4-chloro-3-[(2-(6-chloropyridazine-3-yl)-hydrazino-1-yl)-sulfonyl]benzoic acid	2	ditto	186 - 188
20	3-(4-methylpiperazine-1-yl)sulfonyl-4-chlorobenzoic acid	2	ditto	120 - 121

Note: Numerals 1 - 4 in the column of "Preparation Method" correspond to the above-mentioned Examples 1 - 4.

385
382

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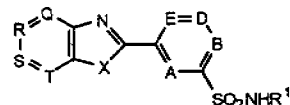
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(54) Title: HETEROBIARYLSULPHONAMIDES AND THEIR USE AS PDE 7 INHIBITORS



(1)

(57) Abstract: Compounds of formula (1) are described,
wherein R¹ represents an aryl or heteroaryl group; A, B, D
and E, which may be the same or different, each represents
a nitrogen atom or a C(R²) group [in which R² is a hydrogen
or halogen atom or an alkyl, haloalkyl, alkoxy, haloalkoxy,
hydroxy, -NO₂ or -CN group] provided that two or more of
A, B, D and E are C(R²) groups; X represents an oxygen or
sulphur atom or a N(R³) group in which R³ is a hydrogenatom or an alkyl group; Q, R, S and T, which may be the same or different each represents a nitrogen atom or a group C(R⁴) [in
which R⁴ is an atom or group -L¹(Alk¹)₂L²(R⁵)₃], provided that two or more of Q, R, S and T are C(R⁴) groups. The compounds are
potent and selective inhibitors of the enzyme phosphodiesterase 7 and are of use in the treatment of autoimmune and other diseases
in which inhibition of the enzyme can have a beneficial effect.X in compounds of formulae (1) and (1a) is in particular an oxygen atom or
a -NH group.

Particularly useful compounds according to the invention include:

- 5 N-(4-Chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonamide;
N-(4-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonamide;
N-(3-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonamide;
N-(3,5-Dichlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-
sulfonamide;
- 10 N-(4-Bromo-2-chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-
sulfonamide;
N-Ethyl-4-[3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]-
benzamide;
4-[3-(7-Nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid
- 15 ethyl ester;
N-(4-Chloro-2-methylphenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-
sulfonamide;
2-[3-(2-Chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic
acid methyl ester;
- 20 2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]-3H-benzimidazole-4-
carboxylic acid;
2-[3-(5-Chloro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid;
2-[3-(2-Chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic
acid;
- 25 2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-7-carboxylic
acid;
2-[3-(5-Chlorobenzoxazol-2-yl)benzenesulfonylamino]benzoic acid;
2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]benzoxazole-4-carboxylic
acid;
- 30 N-(4-Chloro-2-methylphenyl)-3-(4-nitrobenzoxazol-2-yl)benzene-
sulfonamide;
N-(4-Bromophenyl)-3-(4-methylbenzoxazol-2-yl)benzenesulfonamide;
3-(4-Nitrobenzoxazol-2-yl)-N-(4-trifluoromethylphenyl)benzene-
sulfonamide;
- 35 N-(4-Cyanophenyl)-3-(4-nitrobenzoxazol-2-yl)benzenesulfonamide;

D10

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INTERMEDIATE 20**3-Amino-2-hydroxybenzoic acid methyl ester**

Prepared from 3-aminosalicylic acid (0.5g) to give the title compound (0.04g) as a tan solid.

5 TLC R_f 0.8 (ethyl acetate).

EXAMPLE 1**N-(4-Chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide**

10 A mixture of 3-(4-chlorophenylsulfamoyl)benzoic acid (120mg), 3-nitro-1,2-phenylenediamine (59mg) and trimethylsilyl polyphosphate (1ml) in 1,2-dichlorobenzene (10ml) was heated to reflux for 2h under a nitrogen atmosphere and then left to stand at room temperature for 36h. The mixture was diluted with water (30ml), neutralized with 2N sodium hydroxide and extracted with dichloromethane (4 x 30ml). The combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica eluting with 50% ethyl acetate in hexane to give the title compound (19mg) as a yellow solid.

20 TLC R_f 0.43 (50% ethyl acetate in hexane).
¹H NMR (200MHz, DMSO-d₆) 7.10 (2H, d), 7.30 (2H, d), 7.50 (1H, t), 7.70-7.80 (1H, m), 7.85-7.95 (1H, m), 8.10-8.20 (2H, m), 8.55-8.65 (1H, m), 8.80 (1H, s).

25 The following compounds were prepared by a similar procedure:

EXAMPLE 2**N-(4-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide**

30 Prepared from 3-nitro-1,2-phenylenediamine (51mg) and 3-(4-cyanophenylsulfamoyl)benzoic acid (100mg) to provide the title compound (17mg) as an orange solid.

TLC R_f 0.33 (5% methanol in dichloromethane).

35 ¹H NMR (200MHz, DMSO-d₆) 7.30 (2H, d), 7.49 (1H, t), 7.69 (2H, d), 7.55-7.82 (1H, m), 7.97 (1H, d), 8.15-8.26 (2H, m), 8.67 (1H, d), 8.90 (1H, s).

EXAMPLE 3**N-(2-Chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide**

Prepared from 3-nitro-1,2-phenylenediamine (62mg) and 3-(2-chlorophenylsulfamoyl)benzoic acid (127mg) to provide the title compound (15mg) as a yellow solid.

TLC R_f 0.55 (50% ethyl acetate in hexane).

¹H NMR (200MHz, DMSO-d₆) 7.15-7.30 (3H, m), 7.39-7.50 (2H, m), 7.72-7.39 (2H, m), 8.14-8.25 (2H, m), 8.69 (1H, d), 8.79 (1H, s).

EXAMPLE 4**N-(3-Cyanophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide**

Prepared from 3-nitro-1,2-phenylenediamine (101mg) and 3-(3-cyanophenylsulfamoyl)benzoic acid (200mg) to provide the title compound (64mg) as an orange solid.

TLC R_f 0.48 (5% methanol in dichloromethane).

¹H NMR (200MHz, DMSO-d₆) 7.42-7.54 (5H, m), 7.78 (1H, t), 7.94 (1H, d), 8.15-8.28 (2H, m), 8.67 (1H, d), 8.87 (1H, s), 10.98 (1H, s), 13.56 (1H, s).

EXAMPLE 5**N-(3,5-Dichlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzene-sulfonamide**

25 Prepared from 3-nitro-1,2-phenylenediamine (88mg) and 3-(3,5-dichlorophenylsulfamoyl)benzoic acid (200mg) to provide the title compound (82mg) as a pale orange solid.

TLC R_f 0.4 (50% ethyl acetate in hexane).

¹H NMR (200MHz, CDCl₃) 7.07 (1H, s), 7.09 (1H, s), 7.10 (1H, s), 7.38 (1H, t), 7.68 (1H, t), 7.96 (1H, d), 8.05-8.20 (4H, m), 8.45 (1H, d), 8.81 (1H, s).

EXAMPLE 6**N-(4-Bromo-2-chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonamide**

35

Prepared from 3-nitro-1,2-phenylenediamine (98mg) and 3-(4-bromo-2-chlorophenylsulfamoyl)benzoic acid (250mg) to provide the title compound (43mg) as a brown solid.

TLC R_f 0.45 (50% ethyl acetate in hexane).

5 ¹H NMR (200MHz, CDCl₃) 7.11 (1H, s), 7.42-7.51 (3H, m), 7.65 (1H, d), 7.73 (1H, d), 7.90 (1H, d), 8.21 (1H, d), 8.26 (1H, d), 8.41 (1H, d), 8.59 (1H, s).

EXAMPLE 7

10 N-Ethyl-4-[3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzamide

Prepared from 3-nitro-1,2-phenylenediamine (88mg) and 3-(4-ethyl-carbamoylphenylsulfamoyl)benzoic acid (200mg) to provide the title compound (14mg) as a yellow solid.

15 TLC R_f 0.5 (ethyl acetate).

¹H NMR (400MHz, CDCl₃) 1.11 (3H, t), 3.29 (2H, q), 7.26-7.33 (2H, m), 7.41 (1H, t), 7.65-7.70 (2H, m), 7.90-7.95 (2H, m), 8.05-8.13 (3H, m), 8.23 (2H, d), 8.35 (1H, s), 8.75 (1H, t), 10.86 (1H, s), 13.07 (1H, s).

EXAMPLE 8

20 4-[3-(7-Nitro-1H-benzimidazol-2-yl)benzenesulfonylamino]benzoic acid ethyl ester

3-Nitro-1,2-phenylenediamine (319mg) and pyridine (0.34ml) were added to a suspension of 4-(3-chlorocarbonylbenzenesulfonylamino)benzoic acid

25 ethyl ester (765mg) in dichloromethane (40ml) under a nitrogen atmosphere. The reaction was stirred at room temperature for 5h and then left to stand for 2 days. The mixture was diluted with dichloromethane (30ml) and washed with saturated aqueous sodium bicarbonate solution (80ml). The organic phase was dried (magnesium sulfate) and the solvent removed *in vacuo* to give the amide as a mixture of isomers. The crude amide was combined with phosphorus oxychloride (10ml) under a nitrogen atmosphere, heated to reflux for 100 minutes, then allowed to cool. The mixture was poured into ice-water (100ml) and neutralized with 2N sodium hydroxide solution. Saturated aqueous sodium bicarbonate solution (60ml) was added and the aqueous phase was extracted with ethyl acetate (3 x 70ml). Water (150ml) was added to

the combined organic phases and the pH was adjusted to 3 with 2N aqueous hydrochloric acid. The organic layer was washed with brine (100ml), dried (magnesium sulfate) and the solvent removed *in vacuo* to give a brown solid. Purification by column chromatography on silica eluting with 33% hexane in ethyl acetate gave the title compound (80mg) as a brown solid.

TLC R_f 0.64 (33% hexane in ethyl acetate).

5 ¹H NMR (400MHz, 130°, DMSO-d₆) 1.25 (3H, t), 4.25 (2H, q), 7.30 (2H, d), 7.40-7.45 (1H, t), 7.70-7.75 (1H, t), 7.80 (2H, d), 7.95-8.00 (1H, m), 8.15 (2H, bs), 8.45-8.55 (1H, m), 8.80 (1H, s).

EXAMPLE 9

2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]-3H-benzimidazole-5-carboxylic acid methyl ester

15 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (441mg) and methyl 3,4-diaminobenzoate (255mg) were added to a suspension of 3-(4-chloro-2-methyl-phenylsulfamoyl)benzoic acid (500mg) in dichloromethane (40ml) under a nitrogen atmosphere. The reaction was stirred at room temperature for 18h. The mixture was diluted with dichloromethane (20ml) then washed with water (100ml) and saturated aqueous sodium bicarbonate solution (100ml). The organic phase was dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the amide as a mixture of isomers. The crude amide was combined with phosphorus oxychloride (10ml) under a nitrogen atmosphere, heated to reflux for 1h and then allowed to cool. The mixture was poured into ice-water (100ml) and neutralized with 2N aqueous sodium hydroxide solution. Saturated aqueous sodium bicarbonate solution (60ml) was added and the aqueous phase was extracted with ethyl acetate (3 x 70ml). The combined organic phases were dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the title compound (700mg) as a pale brown solid.

30 TLC R_f 0.6 (33% hexane in ethyl acetate).

¹H NMR (200MHz, DMSO-d₆) 2.00 (3H, s), 3.90 (3H, s), 6.95 (1H, d), 7.10-7.25 (2H, m), 7.60-7.90 (4H, m), 8.15-8.35 (1H, m), 8.40-8.50 (1H, m), 8.60 (1H, s), 9.85-9.95 (1H, bs), 13.60 (1H, s).

35

The following compounds were prepared by a similar procedure:

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EXAMPLE 10**N-(4-Chloro-2-methylphenyl)-3-(7-nitro-1H-benzimidazol-2-yl)-benzenesulfonamide**

- 5 Prepared from 3-(4-chloro-2-methylphenylsulfamoyl)benzoic acid (300mg) and 3-nitro-1,2-phenylenediamine (141mg) to give the title compound (187mg) as a pale brown solid.

TLC R_f 0.4 (5% methanol in dichloromethane).

- 10 ¹H NMR (200MHz, DMSO-d₆) 2.05 (3H, s), 6.95 (1H, d), 7.15-7.25 (1H, m), 7.30 (1H, s), 7.45-7.55 (1H, m), 7.75-7.85 (2H, m), 8.10-8.25 (2H, m), 8.60-8.80 (2H, b).

EXAMPLE 11**2-[3-(2-Chlorophenylsulfamoyl)phenyl]-3H-benzimidazole-4-carboxylic acid methyl ester**

- 15 Prepared from 2,3-diaminobenzoic acid methyl ester (67mg) and 3-(2-chlorophenylsulfamoyl)benzoic acid (126mg) to afford the title compound (54mg) as an off-white solid.

TLC R_f 0.4 (50% ethyl acetate in hexane).

- 20 ¹H NMR (200MHz, CDCl₃) 4.07 (3H, s), 7.06-7.14 (2H, m), 7.26-7.42 (3H, m), 7.65 (1H, t), 7.76 (1H, d), 7.88 (1H, d), 7.79 (1H, d), 8.07 (1H, d), 8.39 (1H, d), 8.46 (1H, s).

EXAMPLE 12**2-[3-(4-Chloro-2-methylphenylsulfamoyl)phenyl]-1H-benzimidazole-4-carboxylic acid methyl ester**

Prepared from 3-(4-chloro-2-methylphenylsulfamoyl)benzoic acid (425mg) and 2,3-diaminobenzoic acid methyl ester (217mg) to give the title compound (540mg) as a brown solid.

- 30 TLC R_f 0.52 (5% methanol in dichloromethane).

¹H NMR (200MHz, DMSO-d₆) 2.00 (3H, s), 4.00 (3H, s), 6.95 (1H, d), 7.10-7.20 (1H, m), 7.25 (1H, s), 7.30-7.45 (1H, m), 7.75 (2H, d), 7.85 (1H, d), 8.05 (1H, d), 8.55-8.65 (1H, m), 8.70 (1H, s), 9.90 (1H, s), 12.75 (1H, s).

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U1S S2410

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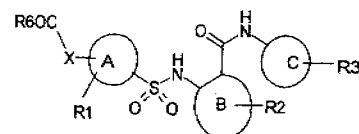
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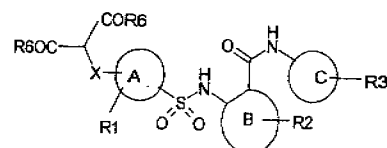
(54) Abstract Title

Aromatic sulfonamides and their use in treating bacterial diseases

(57) Compounds of formula 1 or 2 wherein ring A is a phenyl ring or aromatic heterocycle and rings B and C are each independently a phenyl ring or heterocycle. Rings A, B and C are optionally substituted by one or more groups R1, R2 and R3 respectively. X is a spacer group and R6 is hydroxyl, C1-4 alkoxy or NR4R5 wherein R4 and R5 are each independently H, C1-6 alkyl, C2-6 alkenyl, C1-4 aralkyl or C1-4alkyleneCO2C1-4alkyl. In particular, each of rings A, B and C is a phenyl ring and the spacer group X is a direct bond, an alkylene group, an alkenylene group or an alkylene group which further contains an ether, thioether or amino group. When present, substituents R1, R2 and R3 are preferably chloro, carboxamide, cyano, methoxy or nitro groups. The compounds may be useful as antibacterial agents in the treatment of bacterial diseases and infections.



Formula 1



Formula 2

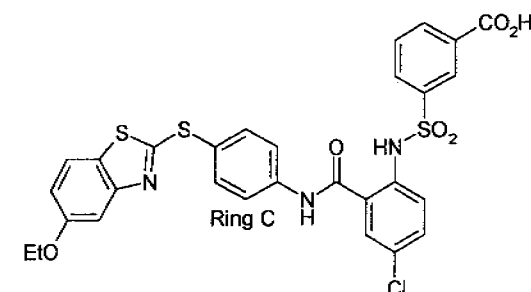
GB 2 378 179 A

COMPOUNDS AND THEIR THERAPEUTIC USE

Background of the Invention

Several chemical classes of compound are known that possess considerable antibacterial activity, and these have proven of immense value in the treatment of bacterial diseases and infection. They include among others, the penicillins, the cephalosporins, the aminoglycoside antibiotics, vancomycin analogues and the sulfonamide drugs.

Compounds of similar structure to those of the invention have been described before as Cathepsin D inhibitors. However, there are no reports of antibacterial activity. For example, Biorg. Med. Chem. Lett. (1999), 9(17) 2531-2536 describes the synthesis and structure-activity relationships of compound A



15 Compound A

This paper claims only compounds containing a heterocyclic thio-ether function on ring C, which is essential for Cathepsin D inhibition.

Summary of the Invention

20 The invention relates to a group of carboxyphenylsulfonamide compounds, defined by Formulae 1 and 2, which exhibit antibacterial activity.

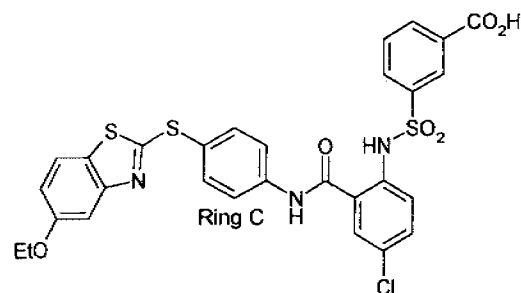
D11

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COMPOUNDS AND THEIR THERAPEUTIC USE**Background of the Invention**

Several chemical classes of compound are known that possess considerable antibacterial activity, and these have proven of immense value in the treatment of bacterial diseases and infection. They include among others, the penicillins, the cephalosporins, the aminoglycoside antibiotics, vancomycin analogues and the sulfonamide drugs.

Compounds of similar structure to those of the invention have been described before as Cathepsin D inhibitors. However, there are no reports of antibacterial activity. For example, *Biorg. Med. Chem. Lett.* (1999), 9(17) 2531-2536 describes the synthesis and structure-activity relationships of compound A

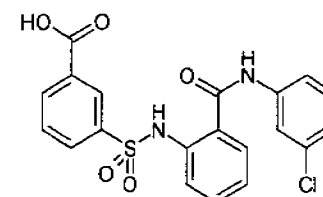


15 Compound A

This paper claims only compounds containing a heterocyclic thio-ether function on ring C, which is essential for Cathepsin D inhibition.

Summary of the Invention

The invention relates to a group of carboxyphenylsulfonamide compounds, defined by Formulae 1 and 2, which exhibit antibacterial activity.

Formula 1**5. 2-(3-Carboxybenzenesulfonylamino)-N-(3-chlorophenyl)benzamide**

5

To Wang resin (0.034 mmol) in an IRORI™ minikan, pre-swelled in DMF, was added 3-carboxy-N-[2-(trimethylsilylethoxycarbonyl)phenyl]-benzenesulfonamide (**3**, 43mg, 0.102 mmol), HATU (39 mg, 0.102 mmol), di-isopropylethylamine (15 μ l, 0.95 mmol) and DMAP (1 mg, 0.01 mmol). The reaction mixture was agitated overnight and washed with DMF (3 mL), methanol (3 mL), and DCM (3 mL x2).

The minikan was treated with TBAF (3 mL, 1M in THF) for 1 hour and washed with THF (3 mL) and DCM (3 mL x3). The minikan was treated with sodium iodide (3 mL, 1M in acetone) and washed with acetone (3 mL x3) and DMF (3 mL).

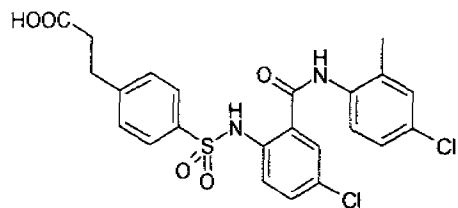
To the minikan was added DMF (3 mL), and 3-chloroaniline (43 mg, 0.34 mmol), HATU (39 mg, 0.102 mmol) and di-isopropylethylamine (15 μ l, 0.95 mmol) were added. The minikan was agitated overnight and washed with DMF (3 mL), MeOH (3ml) and DCM (3 mL x3). The resin was cleaved using TFA/DCM (1:1, 0.5 hr. x2). The solvent was evaporated to yield 2-(3-carboxybenzenesulfonylamino)-N-(3-chlorophenyl)benzamide. m/z 429 (M-H), 431 (M+H).

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6. 2-(4-Carboxyethylbenzenesulfonylamino)-5-chloro-N-(4-chloro-2-methylphenyl)benzamide

(from 4 and 4-chloro-2-methylaniline)

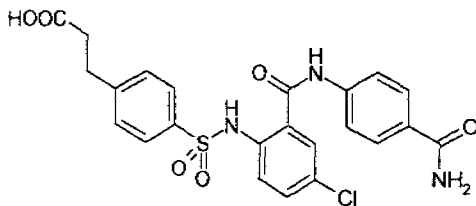


5

m/z 505 (M-H), 507 (M+H).

7. N-(4-Carbamoylphenyl)-2-(4-carboxyethylbenzenesulfonylamino)-5-chlorobenzamide

(from 4 and 4-aminobenzamide)



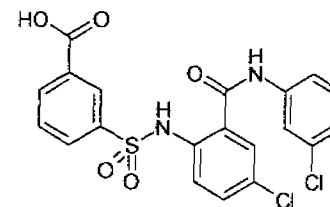
10

m/z 500 (M-H), 502 (M+H).

14

8. 2-(3-Carboxybenzenesulfonylamino)-5-chloro-N-(3-chlorophenyl)benzamide

(from 1 and 3-chloroaniline)

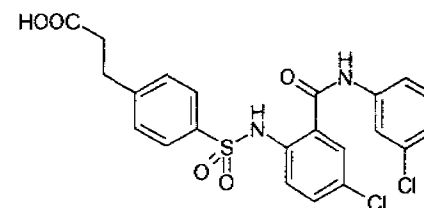


5

m/z 463 (M-H), 465 (M+H).

9. 2-(4-Carboxyethylbenzenesulfonylamino)-5-chloro-N-(3-chlorophenyl)benzamide

10 (from 4 and 3-chloroaniline)



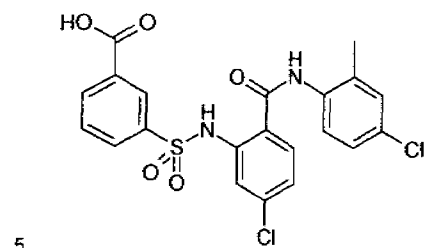
m/z 491 (M-H), 493 (M+H).

15

15

10. 2-(3-Carboxybenzenesulfonylamino)-4-chloro-N-(4-chloro-2-methylphenyl)benzamide

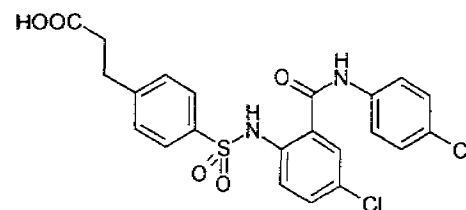
(from 2 and 4-chloro-2-methylaniline)



m/z 477 (M-H), 479 (M+H).

11. 2-(4-Carboxyethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide

10 (from 4 and 4-chloroaniline)

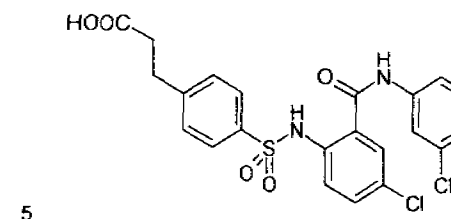


m/z 491 (M-H), 493 (M+H)

16

12. 2-(4-Carboxyethylbenzenesulfonylamino)-5-chloro-N-(3-cyanophenyl)benzamide

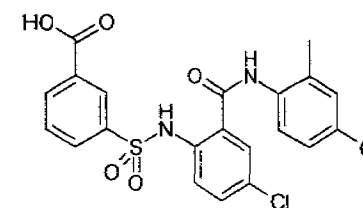
(from 4 and 3-cyanoaniline)



m/z 482 (M-H), 484 (M+H).

13. 2-(3-Carboxybenzenesulfonylamino)-5-chloro-N-(4-chloro-2-methylphenyl)benzamide

10 (from 1 and 4-chloro-2-methylaniline)



m/z 477 (M-H), 479 (M+H).

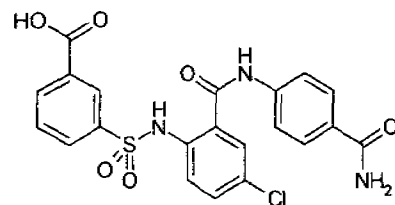
15

17

14. N-(4-Carbamoylphenyl)-2-(3-carboxybenzenesulfonylamino)-5-chlorobenzamide

(from 1 and 4-aminobenzamide)

5

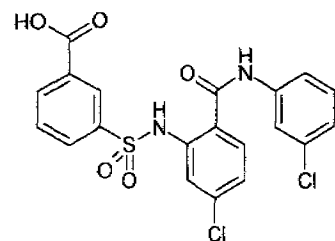


m/z 472 (M-H), 474 (M+H).

15. 2-(3-Carboxybenzenesulfonylamino)-4-chloro-N-(3-chlorophenyl)benzamide

(from 2 and 3-chloroaniline)

10



m/z 463 (M-H), 465 (M+H).

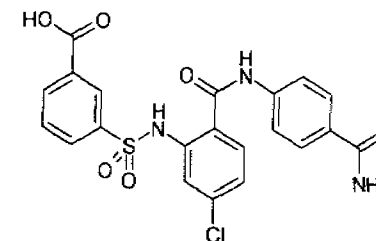
15

18

16. 2-(3-Carboxybenzenesulfonylamino)-4-chloro-N-(4-carbamoylphenyl)benzamide

(from 2 and 4-aminobenzamide)

5

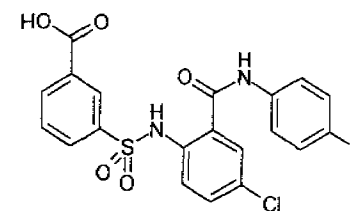


m/z 472 (M-H), 474 (M+H).

17. 2-(3-Carboxybenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide

(from 2 and 4-chloroaniline)

10



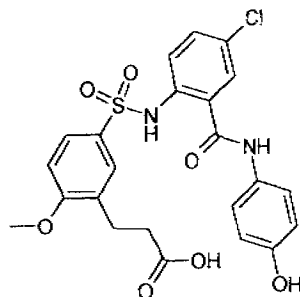
15 m/z 463 (M-H)

20

85. 2-(3-Carboxyethyl-4-methoxybenzenesulfonylamino)-5-chloro-N-(4-hydroxyphenyl)benzamide
(from 84 and 4-hydroxyaniline)

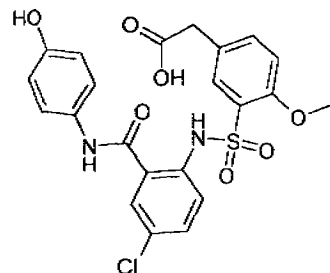
5

10



m/z 503 (M-H), 505 (M+H).

15 90. 2-(5-Carboxymethyl-2-methoxybenzenesulfonylamino)-5-chloro-N-(4-hydroxyphenyl)benzamide
(from 89 and 4-hydroxyaniline)



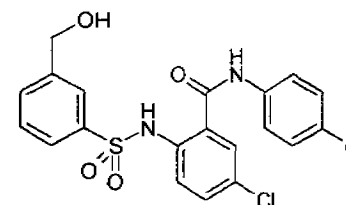
m/z 489 (M-H), 491 (M+H).

20

21

18. 2-(3-Hydroxymethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide

5

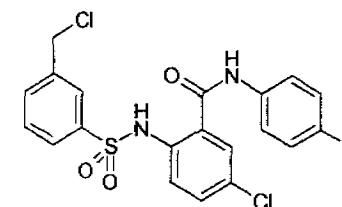


To 2-(3-methoxycarbonylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (17, 480 mg, 1 mmol) in THF (10 mL) under nitrogen, was added lithium borohydride (1 mL, 1 mmol, 1M in THF) drop-wise. The reaction mixture was stirred for 6 hours and partitioned between ethyl acetate (25 mL), water (25 mL) and 2M HCl (3 mL). The organic layer was washed with water (10 mL), brine (10 mL), and the solvent evaporated. Trituration with dichloromethane gave 2-(3-hydroxymethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide as a solid (135 mg, 0.3 mmol, 30%).

¹H NMR (400 MHz) d6 DMSO, δ 10.49 (1H, s), 7.82 (1H, s), 7.74 (1H, m), 7.68 (1H, dd), 7.58 (1H, m), 7.51 (1H, m), 7.45-7.35 (4H, m), 4.44 (2H, s).
m/z 449 (M-H).

19. 2-(3-Chloromethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide

20

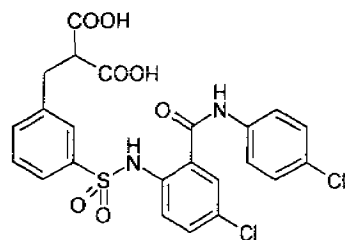


22

2-(3-hydroxymethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (**18**, 1.9 g, 4.2 mmol) was heated to reflux in thionyl chloride (20 mL) for one hour. The thionyl chloride was removed by distillation and the reaction mixture partitioned between water (20 mL) and DCM (20 mL). The organic layer was evaporated to yield 2-(3-chloromethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide m/z 467 (M-H).

20. m-[4-Chloro-2-(4-chlorophenylcarbamoyl)phenylaminosulfonyl]-benzylmalonic acid

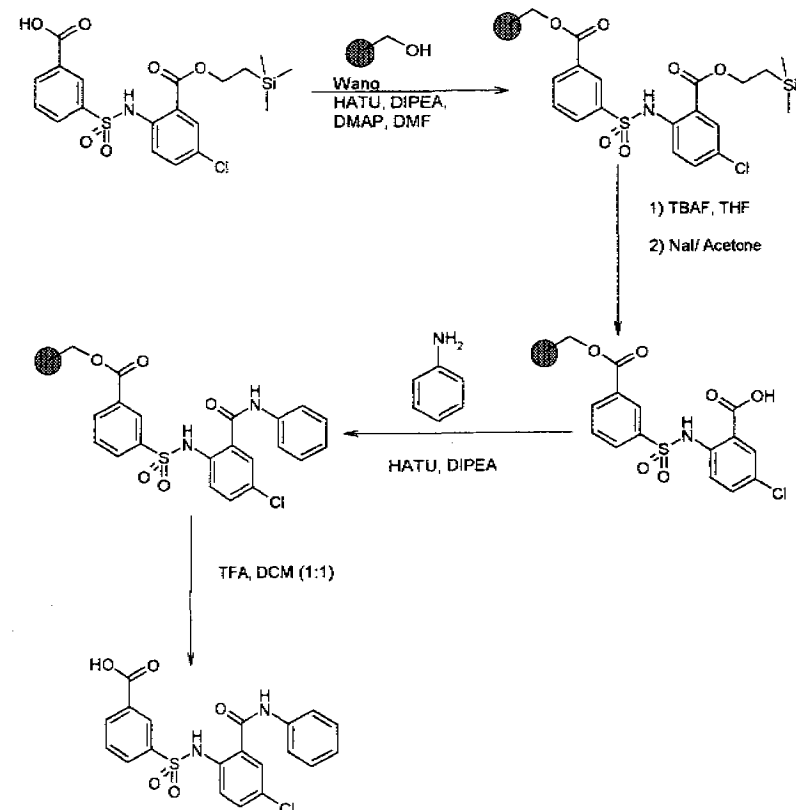
10



To 2-(3-chloromethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (**19**, 1.9 g, 4 mmol) in THF (20 mL) was added diethyl malonate (0.6 mL, 4 mmol), lithium hexamethyldisilazide (8 mL, 8 mmol, 1M in THF) and sodium iodide (1 mg) and the reaction mixture heated to reflux for 1 hour. 1M NaOH (10 mL) was added and the reaction mixture stirred overnight at room temperature. The organic layer was removed and the aqueous layer acidified with 1M HCl (15 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with sat. NaHCO_3 (10 mL), 1M HCl (20 mL), water (20 mL) and brine (20 mL). The solvent was evaporated to yield m-[4-Chloro-2-(4-chlorophenylcarbamoyl)phenylaminosulfonyl]benzylmalonic acid (0.58 g, 23%). ^1H NMR (400 MHz) CDCl_3 δ 7.79 (1H, d), 7.69 (3H, m), 7.59-7.53 (2H, m), 7.46-7.39 (3H, m), 7.31 (2H, m), 3.99 (2H, d), 3.57 (1H, t). m/z 535 (M-H).

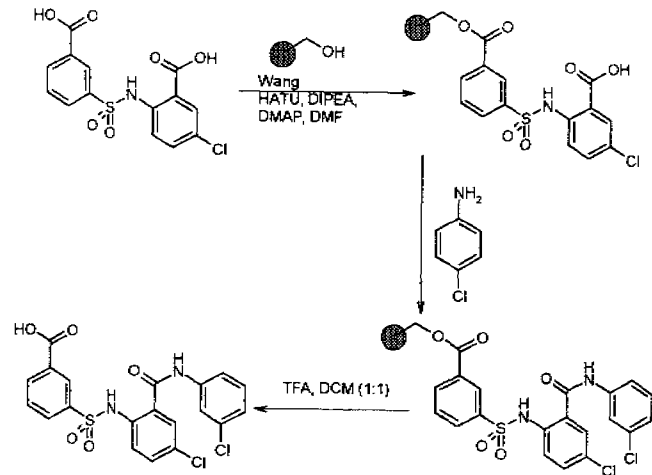
28

Library Synthesis



29

Alternative Library Synthesis

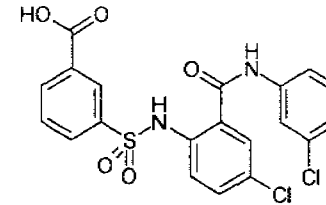


5

Sample Synthesis

30

29. 2-(3-carboxybenzenesulfonylamino)-5-chloro-N-(3-chlorophenyl)benzamide



5

To Wang resin (0.034 mmol) in a minikan, pre-swelled in DMF, was added 2-(3-carboxybenzenesulfonylamino)-5-chlorobenzoic acid (42mg, 0.126 mmol), HATU (90 mg, 0.238 mmol), di-isopropylethylamine (38 μ l, 0.204 mmol) and DMAP (1 mg, 0.01 mmol). The reaction mixture was agitated overnight and

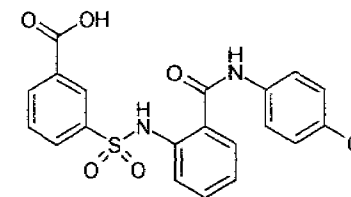
10

washed with DMF (3 mL). To the minikan was added DMF (3 mL), and 3-chloroaniline (43 mg, 0.34 mmol). The minikan was agitated overnight and washed with DMF (3 mL), MeOH (3ml) and DCM (3 mL x3). The resin was cleaved using TFA/DCM (1:1, 0.5 hr. x2). The solvent was evaporated to yield 2-(3-carboxybenzenesulfonylamino)-N-(3-chlorophenyl)benzamide.

15

m/z 463 (M-H), 465 (M+H).

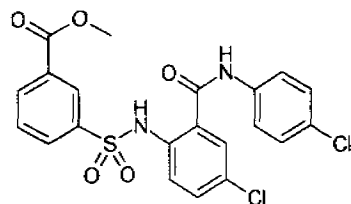
Validation of regiochemistry



and the resulting solid was washed with water and dried in a desiccator to give methyl 3-(chlorosulfonyl)benzoate (1.9 g, 8.1 mmol, 84%).

¹H NMR (400 MHz) DMSO-*d*₆ 12.82 (1H, bs), 8.20 (1H, t), 7.90 (1H, dt), 7.85 (1H, dt), 7.49 (1H, dt), 3.86 (3H, s).

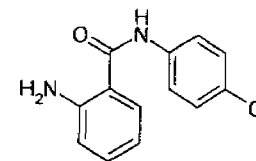
5 **33. 2-(3-Methoxycarbonylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide**



To methyl 3-(chlorosulfonyl)benzoate (5 g, 21 mmol) and 2-amino-5-chloro-N-(4-chlorophenyl)benzamide (4.1 g, 15 mmol) in dry THF (20 mL) at
10 -78°C under nitrogen, was added lithium hexamethyldisilazide (55 mL, 55 mmol, 1M in THF) drop-wise, and the solution allowed to warm to room temperature over 1 hour. The solution was stirred for 4 hours and partitioned between hydrochloric acid (50 mL, 1M aqueous) and ethyl acetate (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL) and evaporated. The
15 resulting solid was triturated with methanol and dried to give 2-(3-carboxymethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (3.6 g, 7.5 mmol, 50%).

¹H NMR (400 MHz) DMSO-*d*₆ 10.36 (2H, s), 8.22 (1H, s), 8.08 (1H, d), 7.89 (1H, d), 7.73 (1H, d), 7.65-7.60 (4H, m), 7.41 (2H, d), 7.36 (1H, d), 3.80 (3H, s). *m/z*
20 477 (M-H), 479 (M+H).

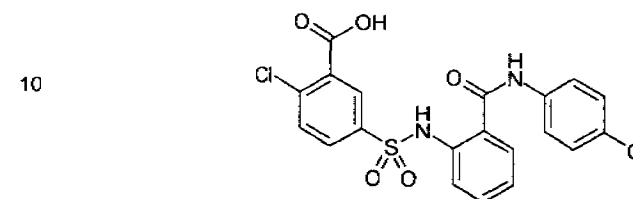
34. 2-amino-N-(4-chlorophenyl)benzamide



Synthesised from isatoic anhydride and 4-chloroaniline according to the method for compound 30.

5 *M/z* 245 (M-H), 269 (M+Na).

35. 2-(3-Carboxy-4-chlorobenzenesulfonylamino)-N-(4-chlorophenyl)benzamide

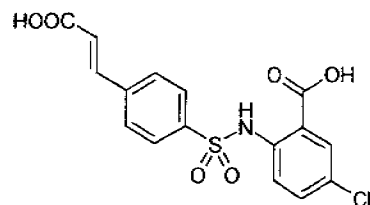


To 2-chloro-5-(fluorosulfonyl)benzoic acid (0.67 g, 2.8 mmol) and 2-amino-N-(4-chlorophenyl)benzamide (0.7 g, 2.8 mmol) in dry THF (20 mL) at
15 -78°C under nitrogen, was added lithium hexamethyldisilazide (11.2 mL, 11.2 mmol, 1M in THF) dropwise, and the solution allowed to warm to room temperature over 1 hour. The solution was stirred for 4 hours. Water (25 mL)
20 was added and the organic layer removed. The aqueous layer was acidified with 1M HCl (25 mL) and extracted with ethyl acetate (25 mL). The organic layer was washed with water (20 mL) and brine (20 mL) and the solvent evaporated. The resulting solid was triturated with ethyl acetate and dried to yield 2-(3-carboxy-4-chlorobenzenesulfonylamino)-N-(4-chlorophenyl)benzamide (0.52 g, 1.12 mmol,
25 40%).

To a solution of methyl 5-chloro-2-(4-iodobenzenesulfonylamino)benzoate (3.53 g, 7.8 mmol) and palladium acetate (17.5 mg, 0.078 mmol) in DMF, was added DIPEA (1.35 mL, 7.8 mmol) and ethyl acrylate (10 mL, 9.2 mmol) and the solution heated to 100°C for 5 hours. The DMF was evaporated and the residue partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with brine, the solvent evaporated and the resulting solid evaporated to give methyl 5-chloro-2-(4-carboxyvinylbenzenesulfonylamino)benzoate (2.1 g, 0.50 mmol, 64%).

¹H NMR (400 MHz) DMSO δ 10.34 (1H, s), 7.91 (2H, d), 7.78 (3H, m), 7.7-7.6 (2H, m), 7.46 (1H, dd), 6.76 (1H, d), 4.20 (2H, q), 3.78 (3H, s), 1.25 (3H, t). m/z 422 (M-H), 424 (M+H).

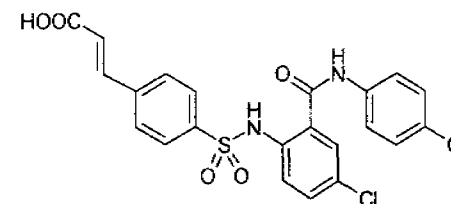
38. 5-Chloro-2-(4-carboxyvinylbenzenesulfonylamino)benzoic acid



To methyl 5-chloro-2-(4-carboxyvinylbenzenesulfonylamino)benzoate (1.0 g, 2.4 mmol) in methanol (10 mL) was added sodium hydroxide (10 mL, 1M aqueous) and heated to reflux for 1 hour. The solution was acidified with HCl (10 mL, 2M aqueous) and the resulting solid washed with water and dried to give 5-Chloro-2-(4-carboxyvinylbenzenesulfonylamino)benzoic acid (0.6 g, 1.56 mmol, 65%).

¹H NMR (400 MHz) DMSO δ 12.6 (1H, bs), 11.12 (1H, bs), 7.9-7.8 (5H, m), 7.7-7.5 (3H, m), 6.65 (1H, d). m/z 380 (M-H).

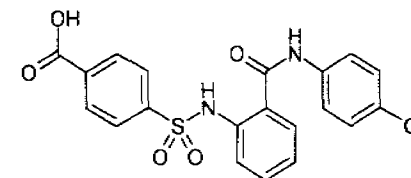
39. 2-(4-Carboxyvinylbenzenesulfonylamino)-N-(4-chlorophenyl)benzamide.



To Wang resin (60 mg, 0.1 mmol), pre-swelled in DMF (3 mL), was added HATU (0.27 g, 0.7 mmol), DIPEA (80 mL, 0.7 mmol), DMAP (10 mg), and 5-chloro-2-(4-carboxyvinylbenzenesulfonylamino)benzoic acid (115 mg, 0.3 mmol) and agitated overnight. The resin was washed with DMF (3 mL) and a solution of 4-chloroaniline (130 mg, 1 mmol) in DMF (3 mL) added. The resin was agitated overnight and washed with DMF (3 mL), methanol (3 mL) and dichloromethane (3 mL x2). The product was cleaved using TFA/dichloromethane (1:1) to give 2-(4-carboxyvinylbenzenesulfonylamino)-N-(4-chlorophenyl)benzamide.

M/z 489 (M-H).

40. 2-(4-Carboxybenzenesulfonylamino)-N-(4-chlorophenyl)benzamide

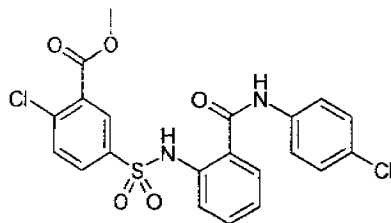


15

Synthesised from 4-(chlorosulfonyl)benzoic acid and 2-amino-N-(4-chlorophenyl)benzamide according to the method for compound 35.

M/z 429 (M-H), 431 (M+H), 453 (M+Na).

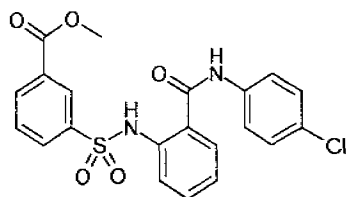
41. 2-(3-Methoxycarbonyl-4-chlorobenzenesulfonylamino)-N-(4-chlorophenyl)benzamide



To a solution of 2-(3-carboxy-4-chlorobenzenesulfonylamino)-N-(4-chlorophenyl)benzamide (232 mg, 0.5 mmol) in dry THF (3 mL) at 0°C was added triethylamine (70 μ L, 0.5 mmol), followed by ethyl chloroformate (50 μ L, 0.5 mmol) dropwise. The mixture was stirred for 1 hr, then methanol (5 mL) added. The mixture was evaporated, then the residue partitioned between ethyl acetate (25 mL) and 1M NaOH (10 mL). The organic layer was washed with water (20 mL) and brine (20 mL) and the solvent evaporated. The resulting solid

was purified with dichloromethane and dried to yield 2-(3-methoxycarbonyl-4-chlorobenzenesulfonylamino)-N-(4-chlorophenyl)benzamide (0.08 g, 0.167 mmol, 33%).

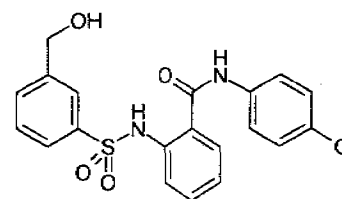
42. 2-(3-Methoxycarbonylbenzenesulfonylamino)-N-(4-chlorophenyl)benzamide



Synthesised from methyl 3-(chlorosulfonyl)benzoate and 2-amino-N-(4-chlorophenyl)benzamide according to the method for compound 33.

M/z 443 (M-H), 445 (M+H), 467 (M+Na).

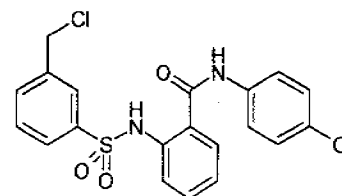
43. 2-(3-Hydroxymethylbenzenesulfonylamino)-N-(4-chlorophenyl)benzamide



Synthesised from 2-(3-methoxycarbonylbenzenesulfonylamino)-N-(4-chlorophenyl)benzamide according to the method for compound 18.

M/z 415 (M-H), 439 (M+Na).

44. 2-(3-Chloromethylbenzenesulfonylamino)-N-(4-chlorophenyl)benzamide

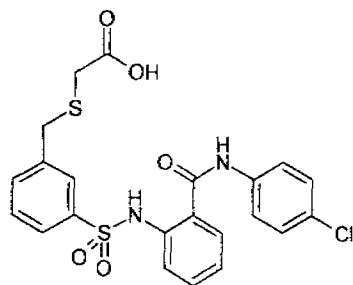


Synthesised from 2-(3-hydroxymethylbenzenesulfonylamino)-N-(4-chlorophenyl)benzamide according to the method for compound 19.

m/z 433 (M-H).

357

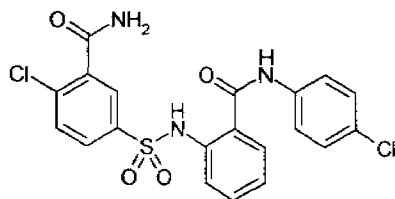
45. m-[2-(4-chlorophenylcarbamoyl)phenylaminosulfonyl]-benzylmercaptoacetic acid



5 Synthesised from 2-(3-chloromethylbenzenesulfonylamino)-N-(4-chlorophenyl)benzamide and ethyl mercaptoacetate according to the method for compound 20.

m/z 489 (M-H), 513 (M+Na).

46. 2-(3-Carbamoyl-4-chlorobenzenesulfonylamino)-N-(4-chlorophenyl)benzamide

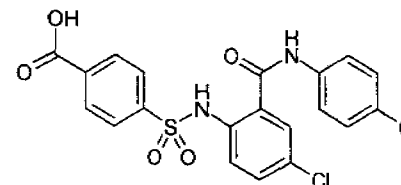


To a solution of 2-(3-carboxy-4-chlorobenzenesulfonylamino)-N-(4-chlorophenyl)benzamide (232 mg, 0.5 mmol) in dry THF (3 mL) at 0°C was

added triethylamine (70 μ L, 0.5 mmol), followed by ethyl chloroformate (50 μ L, 0.5 mmol) dropwise. The mixture was stirred for 1 hr, then 0.88 s.g. ammonia (5 mL) added. The mixture was partitioned between ethyl acetate (25 mL) and water (50 mL). The organic layer was washed with water (20 mL) and brine (20 mL) and the solvent evaporated. The resulting solid was triturated with dichloromethane and dried to yield 2-(3-carbamoyl-4-chlorobenzenesulfonylamino)-N-(4-chlorophenyl)benzamide (0.09 g, 0.19 mmol, 39%).

^1H NMR (400 MHz) DMSO δ 10.64 (1H, bs), 10.49 (1H, bs), 8.01 (1H, s), 7.8-7.75 (3H, m), 7.70 (2H, d), 7.61 (1H, d), 7.49 (1H, t), 7.44 (2H, d), 7.33 (1H, d), 7.27 (1H, t). m/z 462 (M-H), 464 (M+H), 486 (M+Na).

47. 2-(4-Carboxybenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide

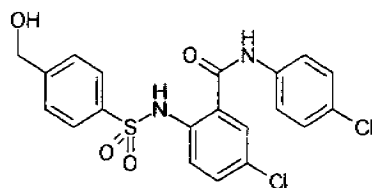


15 Synthesised from 4-(chlorosulfonyl)benzoic acid and 2-amino-5-chloro-N-(4-chlorophenyl)benzamide according to the method for compound 35.

^1H NMR (400 MHz) DMSO δ 13.71 (1H, bs), 11.01 (1H, bs), 8.41 (2H, dd), 8.25 (2H, dd), 8.07 (2H, dd), 7.83 (2H, dd), 8.22 (1H, d), 7.91 (1H, bs), 7.78 (1H, d). m/z 463 (M-H), 465 (M+H), 487 (M+Na).

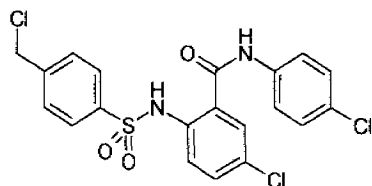
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48. 2-(4-Hydroxymethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide



To a solution of 2-(4-carboxybenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (2.26 g, 4.9 mmol) in dry THF (15 mL) under nitrogen was added 1M borane in THF (19.6 mL, 19.6 mmol) and the solution stirred overnight. The reaction was quenched with methanol, then evaporated. The residue was partitioned between ethyl acetate (35 mL) and 2M HCl (35 mL). The organic layer was washed with water (20 mL) and brine (20 mL) and the solvent evaporated to yield 2-(4-hydroxymethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (1.76 g, 3.9 mmol, 80%). m/z 449 (M-H).

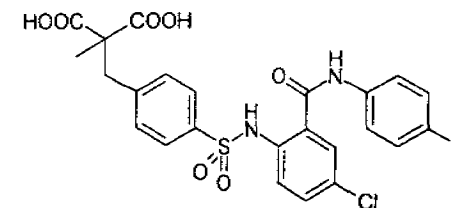
49. 2-(4-Chloromethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide



15

Synthesised from 2-(4-hydroxymethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide according to the method for compound 19.
 m/z 467, 469, 471 (M-H), 469, 471, 473 (M+H), 491, 493, 495 (M+Na).

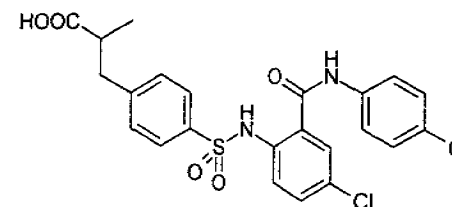
50. p-[4-Chloro-2-(4-chlorophenylcarbonyl)phenylaminosulfonyl]benzyl methylmalonic acid



5 Synthesised from 2-(4-chloromethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide and diethyl methylmalonate according to the method for compound 20.

m/z 549 (M-H), 551 (M+H), 573 (M+Na).

51. 3-[p-[4-Chloro-2-(4-chlorophenylcarbonyl)phenylaminosulfonyl]phenyl]-2-methylpropionic acid



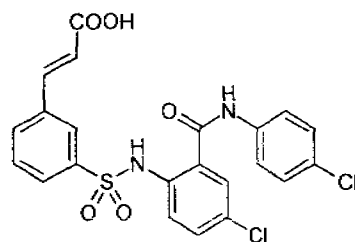
To a solution of p-[4-chloro-2-(4-chlorophenylcarbonyl)phenylaminosulfonyl]benzyl methylmalonic acid (21 mg, 38 μ mol) in DMF (5 mL) was added lithium iodide (1 mg) and the solution heated to reflux for 2 hr. The solvent was evaporated, then the residue partitioned between ethyl acetate (10 mL) and brine (10 mL) and the solvent evaporated. The residue was triturated

559

with dichloromethane and dried to yield 3-[p-[4-chloro-2-(4-chlorophenylcarbamoyl)phenylaminosulfonyl]phenyl]-2-methylpropionic acid (9 mg, 18 μ mol, 47%). m/z 505 (M-H), 507 (M+H), 529 (M+Na).

53. 2-(3-Carboxyvinylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)-

benzamide



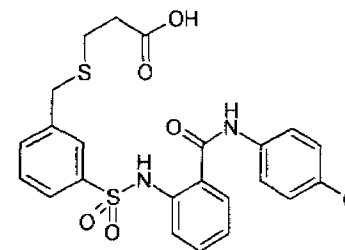
A solution of DMSO (0.22 mL) in dichloromethane (5 mL) was added to a stirred solution of 2M oxalyl chloride in dichloromethane (0.64 mL, 1.28 mmol) at -78°C, under nitrogen. After 5 minutes a solution of 2-(3-hydroxymethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (230 mg, 0.51 mmol) in THF (5 mL) was added. After a further 15 minutes, triethylamine (0.78 mL, 5.6 mmol) was added and the mixture allowed to warm to room temperature over 1 hour. The reaction mixture was then cooled to 0°C and a solution of (ethoxycarbonylmethylene)triphenylphosphorane (267 mg, 0.767 mmol) in THF (5 mL). The mixture was stirred at room temperature overnight. The reaction mixture was washed with 2M HCl (40 mL), water (50 mL) and brine (25 mL) and the solvent evaporated. The residue was dissolved in methanol (10 mL), 1M NaOH added (5 mL) and the mixture stirred overnight. The reaction mixture was partitioned between water and ethyl acetate, the aqueous layer separated, acidified and extracted into ethyl acetate. The organic layer was re-extracted with saturated NaHCO₃ and this aqueous layer re-acidified, the

solid collected and dried to yield 2-(3-carboxyvinylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (15 mg, 0.03 mmol, 6%).

m/z 489 (M-H), 491 (M+H), 513 (M+Na).

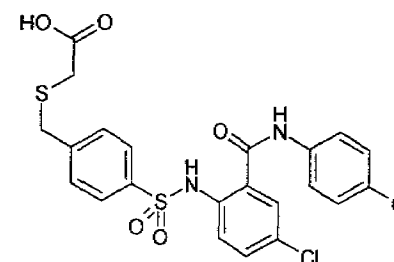
53. 3-{m-[2-(4-Chlorophenylcarbamoyl)phenylaminosulfonyl]-

benzylmercapto}propionic acid



Synthesised from 2-(3-chloromethylbenzenesulfonylamino)-N-(4-chlorophenyl)benzamide and 3-mercaptopropionic acid according to the method for compound 20. m/z 503 (M-H), 505 (M+H), 527 (M+Na).

54. p-[4-Chloro-2-(4-chlorophenylcarbamoyl)phenylaminosulfonyl]-benzylmercaptoacetic acid

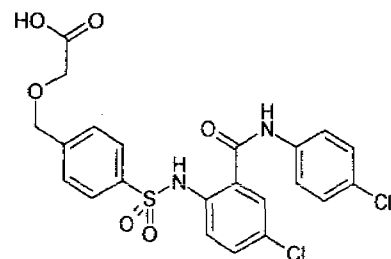


45

Synthesised from 2-(4-chloromethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide and ethyl mercaptoacetate according to the method for compound 20.

m/z 523 (M-H).

- 5 **55. p-[4-Chloro-2-(4-chlorophenylcarbamoyl)phenylaminosulfonyl]-benzyloxyacetic acid**

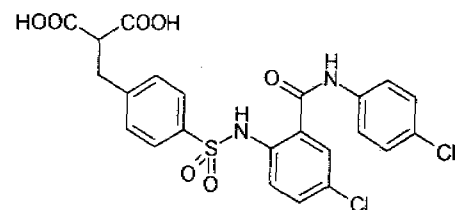


- 10 Synthesised from 2-(4-chloromethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide and ethyl hydroxyacetate according to the method for compound 20.

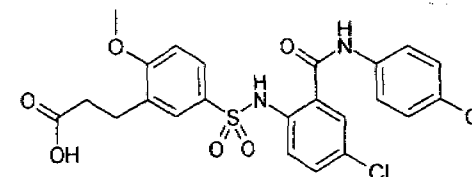
m/z 507 (M-H).

- 56. p-[4-Chloro-2-(4-chlorophenylcarbamoyl)phenylaminosulfonyl]benzyl malonic acid**

15



- 61. 2-(3-Carboxyethyl-4-methoxybenzenesulfonylamino)-4-chloro-N-(4-chlorophenyl)benzamide**



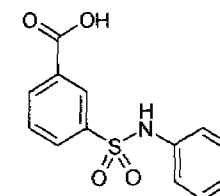
5

Synthesised from 5-(chlorosulfonyl)-2-methoxyphenylpropionic acid and 2-amino-5-chloro-N-(4-chlorophenyl)benzamide according to the method for compound 33.

- ¹H NMR (400 MHz) DMSO δ 10.58 (1H, bs), 10.32 (1H, bs), 8.08 (1H, d), 7.75 (3H, m), 7.58 (1H, d), 7.41 (4H, m), 6.87 (1H, d), 3.77 (3H, s), 2.81 (2H, t), 2.57 (2H, t).

m/z 521 (M-H), 545 (M+Na).

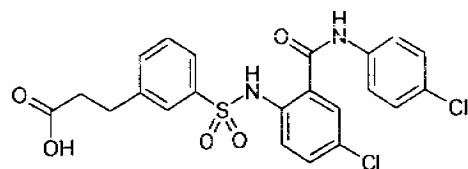
- 62. 3-(Phenylsulfamoyl)benzoic acid**



15

To a solution of 3-(chlorosulfonyl)benzoic acid (10.0 g, 46 mmol) in THF (15 mL), at 0°C, was added aniline (8.3 mL, 8.46 g, 91 mmol) dropwise, then the mixture stirred, at room temperature, for 1 hour. The mixture was filtered and the

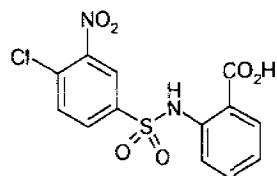
67. 2-(3-Carboxyethylbenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide



Synthesised from 3-(carboxyethyl)benzenesulfonyl chloride and 2-amino-5-chloro-N-(4-chlorophenyl)benzamide according to the method for compound 33.

m/z 491 (M-H), 493 (M+H), 515 (M+Na).

68. 2-(4-Chloro-3-nitrophenylsulfonylamino)benzoic acid



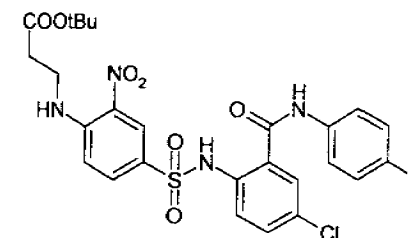
10

To anthranilic acid (343 mg, 2.5 mmol) in 1 M aqueous sodium carbonate (5 mL) was added 4-chloro-3-nitrobenzenesulfonyl chloride (507 mg, 2.5 mmol) and the mixture heated at 60 °C until the sulfonyl chloride dissolved and then stirred for a further 15 h at room temperature. The reaction mixture was poured into water and acidified with 2 N HCl(aq). The precipitate was filtered off and dried under vacuum in a desiccator to give 2-(4-chloro-3-nitrophenylsulfonylamino)benzoic acid as a white solid (461 mg, 52%).

^1H NMR (400MHz) DMSO δ 11.3 (1H, bs.), 8.52 (1H, d), 8.10 (1H, dd), 7.99 (1H, d), 7.91 (1H, dd), 7.57 (1H, dd), 7.47 (1H, d), 7.21 (2H, dd). m/z 355 (M-H), 357 (M+H).

residue was taken up in $(\text{CH}_2\text{Cl})_2$ (5 mL) and treated with a solution of 4-chloroaniline (328 mg, 2.6 mmol) and triethylamine (0.39 mL, 2.6 mmol) in 1,2-dichloroethane (5 mL). The solution was heated under reflux for 2 h then stirred for 16 h at room temperature. The solvent was evaporated and the residue was chromatographed on silica using CH_2Cl_2 to give the N-(4-chlorophenyl)-2-(4-chloro-3-nitrophenylsulfonylamino)-5-chlorobenzamide as a solid (600 mg, 46%). ^1H NMR (400MHz) CDCl_3 δ 10.15 (1H, bs.), 8.10 (1H, d), 7.85 (1H, dd), 7.65 (1H, dd), 7.59 (1H, bs), 7.46-7.44 (4H, m), 7.37 - 7.29 (4H, m). m/z 500 and 502 (both M-H).

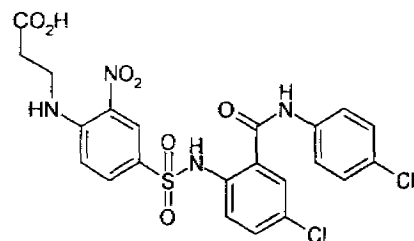
71. 2-(4-tert-Butyloxycarbonylaminophenylsulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide



To N-(4-chlorophenyl)-2-(4-chloro-3-nitrophenylsulfonylamino)-5-chlorobenzamide (170 mg, 0.34 mmol) in toluene (10 mL) was added potassium carbonate (280 mg, 2 mmol), with stirring, followed by palladium acetate (2 mg), then triphenylphosphine (2 mg), then a solution of β -alanine tert-butyl ester (185 mg, 1 mmol) in water (10 mL). The mixture was heated to reflux overnight, cooled, then partitioned between water and ethyl acetate. The organic layer was separated, then the solvent evaporated to give 2-(4-tert-butyloxycarbonylaminophenylsulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (98 mg, 16 mmol, 47%). m/z 607 (M-H), 609 (M+H).

for

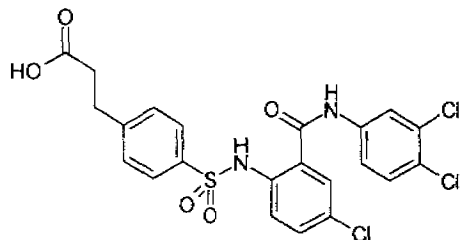
72. 2-(4-Carboxyethylamino-3-nitrobenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide



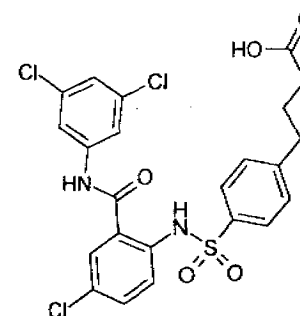
A solution of 2-(4-tert-butyloxycarbonyl-ethylamino-3-nitrobenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (90 mg, 0.18 mmol) in 1:1 dichloromethane:trifluoroacetic acid (10 mL) was stirred for 4 hours. Dichloromethane (30 mL) was added and the organics washed with water (50 mL). The organic layer was separated and, on standing, a precipitate formed and was collected to give 2-(4-carboxyethylamino-3-nitrobenzenesulfonylamino)-5-chloro-N-(4-chlorophenyl)benzamide (54 mg, 0.98 mmol, 56%).

¹H NMR (400MHz) CDCl₃ δ 12.5 (1H, bs), 10.4 (1H, bs), 10.0 (1H, bs), 8.5 (1H, m), 8.2 (1H, m), 7.7 (1H, d), 7.6 (4H, dd), 7.4 (1H, dd), 7.35 (2H, dd), 7.0 (1H, d), 3.5 (2H, t), 2.6 (2H, t). m/z 551 (M-H).

73. 2-(4-Carboxyethylbenzenesulfonylamino)-5-chloro-N-(3,4-dichlorophenyl)benzamide
(from 4 and 3,4-dichloroaniline)

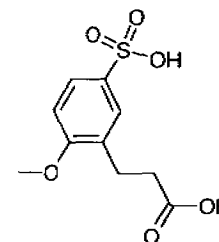


m/z 527 (M-H), 529 (M+H).



m/z 539 (M-H), 541 (M+H).

80. 3-Carboxyethyl-4-methoxybenzenesulfonic acid

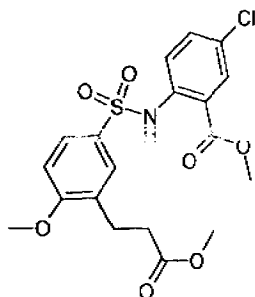


To 3-(2-methoxyphenyl)propionic acid (10.0g, 55 mmol) in dichloromethane (50 mL) was added CH₂SO₄ (3.1 mL, 55 mmol) and the mixture stirred for 1 hour. The solvent was evaporated to give 3-carboxyethyl-4-methoxybenzenesulfonic acid (14.3g, 55 mmol, 100%). m/z (of the carboxylate methyl ester) 273 (M-H).

A solution of 3-carboxyethyl-4-methoxybenzenesulfonic acid (21.0g, 77 mmol) in thionyl chloride (80 mL) was heated to reflux for 2 hours. The solvent was evaporated, the residue partitioned between dichloromethane (100 mL) and water (100 mL), then the organic layer separated and evaporated to give 4-methoxy-3-(methoxycarbonylethyl)benzenesulfonyl chloride (20.1g, 72 mmol, 94%).

^1H NMR (400 MHz) DMSO δ 7.44 (1H, d), 7.39 (1H, s), 6.91 (1H, d), 3.79 (3H, s), 3.57 (3H, s), 2.81 (2H, t), 2.53 (2H, t). m/z (of the sulfonic acid hydrolysis product) 273 (M-H).

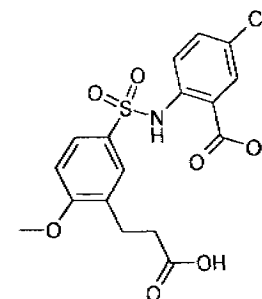
10 **83. Methyl 3-[5-(4-chloro-2-methoxycarbonylphenylaminosulfonyl)-2-methoxyphenyl]propionate**



Synthesised from 4-methoxy-3-(methoxycarbonylethyl)benzenesulfonyl chloride and methyl 2-amino-5-chlorobenzoate according to the method for compound 77.

15 m/z 440 (M-H), 442 (M+H), 464 (M+Na).

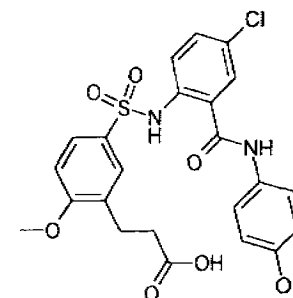
84. 3-[5-(4-Chloro-2-carboxyphenylaminosulfonyl)-2-methoxyphenyl]propionic acid



5 Synthesised from methyl 3-[5-(4-chloro-2-methoxycarbonylphenylaminosulfonyl)-2-methoxyphenyl]propionate according to the method for compound 78.

m/z 412 (M-H), 414 (M+H), 436 (M+Na).

10 **85. 2-(3-Carboxyethyl-4-methoxybenzenesulfonylamino)-5-chloro-N-(4-hydroxyphenyl)benzamide**
(from 84 and 4-hydroxyaniline)



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US 2003/0187001A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2003/0187001 A1
(43) Pub. Date: Oct. 2, 2003(54) 4-AMINOPYRROLOPYRIMIDINES AS
KINASE INHIBITORS(76) Inventors: DAVID CALDERWOOD,
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secution application (CPA) filed under 37
CFR 1.53(d).

(21) Appl. No.: 09/399,083

(22) Filed: Sep. 17, 1999

Related U.S. Application Data

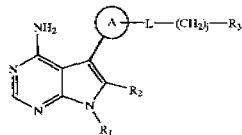
(63) Continuation-in-part of application No. 09/042,702,
filed on Mar. 17, 1998, now Pat. No. 6,001,839.(60) Provisional application No. 60/100,954, filed on Sep.
18, 1998.

Publication Classification

(51) Int. Cl.⁷ A61K 31/519; C07D 487/02
(52) U.S. Cl. 514/265.1; 544/280

(57) ABSTRACT

Chemical compounds having structural formula 1

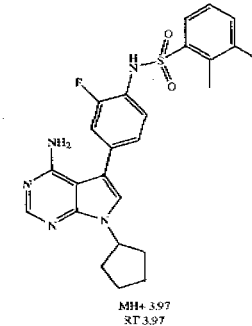
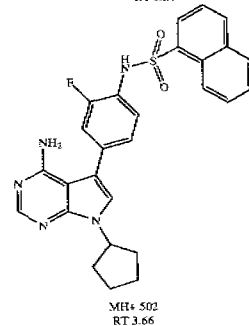
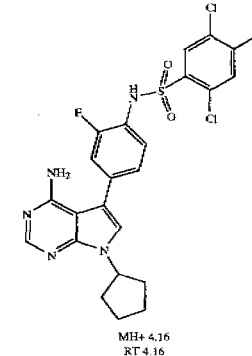
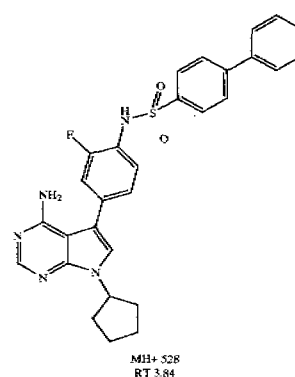
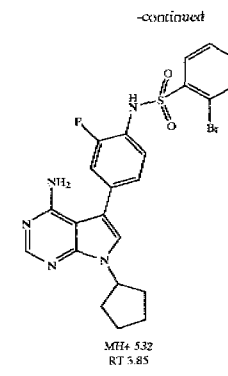
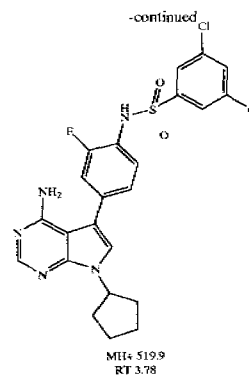


and physiologically acceptable salts thereof, are inhibitors of serine/threonine and tyrosine kinase activity. Several of the kinases whose activity is inhibited by these compounds are involved in immunologic, hyperproliferative or angiogenic processes. Thus, these compounds can ameliorate disease states where angiogenesis or endothelial cell hyperproliferation is a factor. These compounds can be used to treat cancer, hyperproliferative disorders, rheumatoid arthritis, disorders of the immune system, transplant rejection, and inflammatory disorders.

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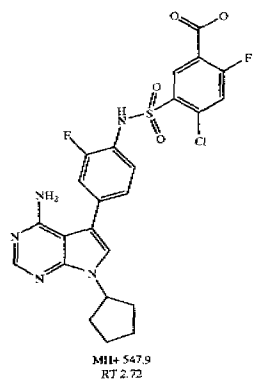
Oct. 2, 2003



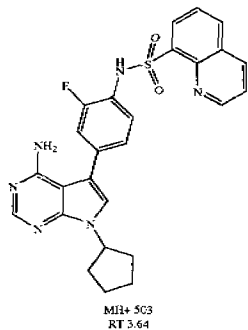
D12

165

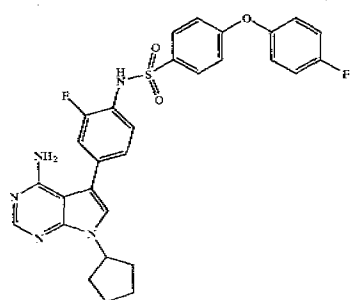
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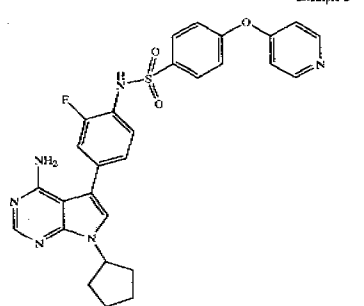
Example 245



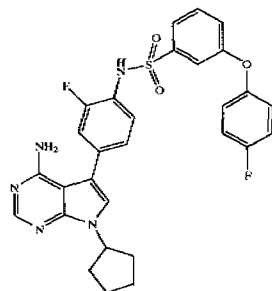
Example 246



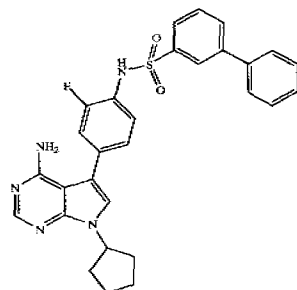
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Example 248



Example 249



[0633] General Synthesis for Examples 250-269

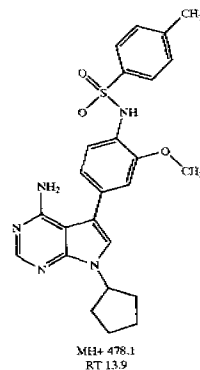
[0634] To a 0.225 M solution of 5-(4-amino-3-methoxyphenyl)-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (or 5-(4-amino-3-fluorophenyl)-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine or 5-(4-amino-3-chlorophenyl)-7-cyclopentyl-7H-pyrrolo[2,3-d]pyrimidin-

4-amine) in pyridine was added one equivalent of substituted arylsulfonyl chloride. This mixture was heated with mixing at 45° C. for 24 h. The product was purified from the reaction mixture by preparative C18 RP-HPLC. Analytical RP-HPLC RT listed in the table were obtained on a Hypersil HyPurity Elite C18 column (5 μ m, 200Å) 250x4.6 mm) using a linear gradient of 25-100% acetonitrile/0.1 M ammonium acetate over 25 min at 1 ml/min.

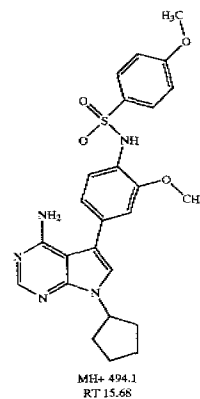
[0635] Note that appropriate protecting group manipulation may be required when introducing reactive substituents.

[0636] Compounds 250-269 were prepared by the general method described above. The molecular weight as determined by mass spectrometry (MH⁺) and the HPLC retention times (RT) in minutes are listed with each example.

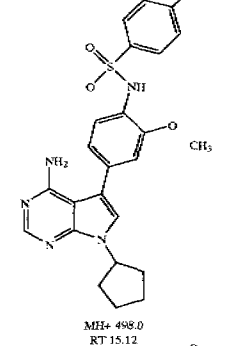
Example 250



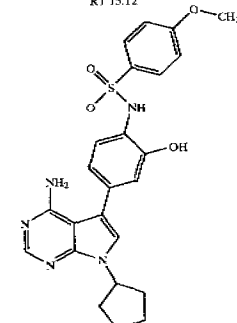
Example 251



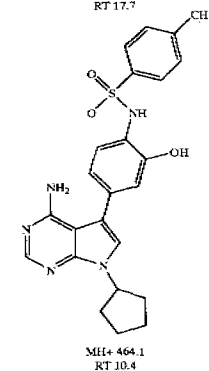
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Example 253



Example 254



REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 18918

Por la cual se niega una patente de invención

Rad. PCT/06-89826

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 3, numeral 30 del decreto 3523 de 2009, y

CONSIDERANDO:

PRIMERO: Que la solicitud de patente de invención titulada "COMPUESTOS DE HETEROARIL- Y FENILSULFAMOILO SUSTITUIDOS", que corresponde a la solicitud internacional PCT/IB 2005/000526 de fecha 28 de febrero del 2005, fue radicada en esta Superintendencia el 07 de septiembre del 2006 bajo el número 06-089826-00000-0000, para que se iniciara la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales.(...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente"*.

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 352 a 406 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del solicitante, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 13918

Por la cual se niega una patente de invención

Rad. PCT/06-89826

RESUELVE:

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPUESTOS DE HETEROARIL- Y FENILSULFAMOILO SUSTITUIDOS", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Carlos Reinaldo Olarte García, en su calidad de apoderado de Pfizer Products Inc., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los

13 ABR. 2010

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


GUSTAVO VALBUENA QUIÑONES

Doctor
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Diagonal 34 N° 5 – 28.
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