

286
103

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicación : 00077374 00000001
Fecha (AMD): 2000-12-19 16:16:00 Folios: 99
Trámite : 002 PATENTES D 1 REGISTRO/ 444 RESPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re: P1.-F. HOFFMANN-LA ROCHE A.G.-Solicitud de Patente de Invención para "DERIVADOS DE BENZODIAZEPINA".-Clase A.61.-Expediente número 00-077.374.

1. Me refiero a mi solicitud de 11 de Diciembre de 2000 y al auto dictado por ese Despacho notificado por Estado el 30 de Noviembre del mismo año.
2. Anexas me permito presentar a usted:
 - (1) En original y dos copias, una de ellas de 6cm x 6cm, Arte Final de la fórmula química característica del invento, para la publicación en la Gaceta de la Propiedad Industrial; y
 - (2) Copia auténtica debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber la solicitud europea número 99120519.6 de 15 de Octubre de 1999, junto con su traducción oficial número 5,765 correspondiente a las legalizaciones y reivindicaciones.
3. Anexo también me permito acompañar copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá de los documentos que acreditan la calidad de traductor oficial de la señora María Luisa Brigard de Restrepo, quien elaboró la traducción de la solicitud europea número 99120519.6 de 15 de Octubre de 1999, respecto de la cual se reivindica prioridad en el presente caso.
4. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,


JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS



Royal
Technologies S.A.
Procesamiento de Documentos

204

Expediente No		00-077-374	No de Folio
Item		No de unidades	✓
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA	1	
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones: Sobre Sin documento

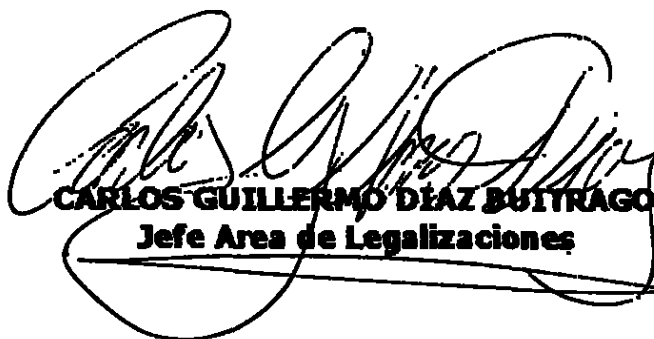
**EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DEL MINISTERIO DE
RELACIONES EXTERIORES**

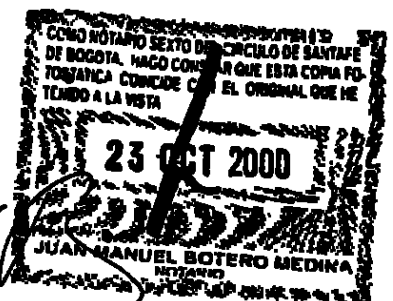
CERTIFICA

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma de la señora **MARIA LUISA DE BRIGARD DE RESTREPO**, como traductora e intérprete oficial para los idiomas **INGLES - ESPAÑOL, ESPAÑOL-INGLES**, según resolución 0793 del 21 de marzo de 1958

La anterior certificación se expide a solicitud de la interesada quien se identificó con cédula de ciudadanía No. 20.024.691 expedida en Santa Fe de Bogotá.

Dada en Santa Fe de Bogotá, D.C. a los veinticinco (25) días de marzo de 1999


CARLOS GUILLERMO DIAZ BUTRAGO
Jefe Area de Legalizaciones



F. Hoffmann
20399
~~209~~
206

TRADUCCION OFICIAL No. 5.765

de un documento escrito en INGLES, el cual para su identificación se sella con el sello
del Traductor al mismo tiempo que la presente. -

Oficina Europea de Patentes

Certificado

TRADUCCION OFICIAL No. 5.765
F. Hoffmann
20399
~~209~~
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Los documentos anexos son copias exactas de la solicitud de patentes europea descrita en
las páginas siguientes, tal como fue presentada originalmente.

Solicitud de Patente No. 99120519.6

Por el Presidente de la Oficina Europea de Patentes

(Firma)

I.L.C. HATTEN-HECKMAN

LA HAYA, 12/10/00

PAGINA 2 DEL CERTIFICADO

Solicitud No. 99120519.6

Fecha de Presentación: 15/10/99

Solicitantes:

210
207

F. HOFFMANN-LA ROCHE AG

4070 Basilea

SUIZA

Título de la Invención:

Derivados de Benzodiazepina

Prioridades reivindicadas:

Estado

Fecha

No. de Registro:

TRANSMICION OFICIAL No. 5.765
sin
Maria Luisa Brizuela de Rodero
Intérprete Oficial
no. 2702 del Mta. de Justicia

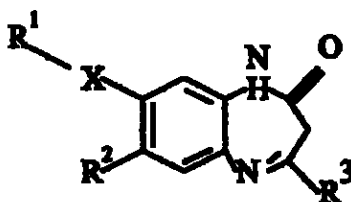
Clasificación Internacional de Patentes:

Estados contratantes designados en la fecha de presentación: AT/BE/CH/CY/DE/
DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE

Anotaciones:

REIVINDICACIONES

1. Compuestos de la fórmula general



1

en donde

X es un enlace simple o un grupo etinodiilo, en el que

en el caso de que X sea un enlace simple,

PROCESO. OFICIAL NO. 5765
[Signature]
 María Luisa Brizuela de Rodríguez
 Intérprete Oficial
 C. No. 8788 del Min. de Justicia

R¹ es hidrógeno, halógeno; nitro; alquilo inferior; halo-alquilo inferior; cicloalqueno inferior opcionalmente sustituido con oxígeno; benzilo opcionalmente sustituido con alquilo inferior, halo-alquilo inferior o halógeno; fenilo opcionalmente sustituido con halógeno, alquilo inferior, halo-alquilo inferior, ciclo-alquilo inferior, alcoxi inferior o halo-alcoxi inferior; un anillo heterocíclico de 5 o 6 miembros, opcionalmente sustituido con oxo, benciloxi, benzilo, metanosulfonilo, bencenosulfonilo o acetilo; naftilo;

en el caso de que X sea un grupo etinodiilo,

R¹ es hidrógeno; alquilo inferior; haloalquilo inferior; cicloalquilo inferior opcionalmente sustituido con alquilo inferior, halo-alquilo inferior, alcoxi inferior, haloalcoxi inferior o halógeno; cicloalqueno inferior opcionalmente sustituido con alquilo inferior, haloalquilo inferior, alcoxi inferior, haloalcoxi inferior o halógeno; alqueno inferior; fenilo opcionalmente sustituido con halógeno, alquilo inferior, halo-alquilo inferior, cicloalquilo

inferior, alcoxi inferior o halo-alcoxi inferior; un anillo heterocíclico de 5 o 6 miembros, opcionalmente sustituido con alquilo inferior, halógeno, oxo, benciloxi, benzofilo, metanosulfonilo, bencenosulfonilo o acetilo;

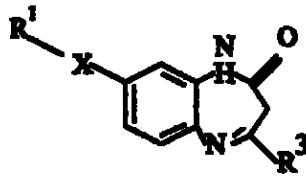
R² es hidrógeno; alquilo inferior; halógeno; ciano; benzofilo opcionalmente sustituido con alquilo inferior, haloalquilo inferior o halógeno; fenilo opcionalmente sustituido con halógeno, alquilo inferior, haloalquilo inferior, cicloalquilo inferior, alcoxi inferior, haloalcoxi inferior; fenoxi opcionalmente sustituido con halógeno, alquilo inferior, haloalquilo inferior, cicloalquilo inferior, alcoxi inferior, haloalcoxi inferior, heterocíclico de 5 o 6 miembros opcionalmente sustituido con alquilo inferior, halógeno o hidroxil;

R³ es fenilo sustituido en la posición meta con halógeno, ciano, alquilo inferior, alcoxi inferior, halo-alquilo inferior, etinilo, nitro, morfolino-4-carbonilo o 4-alquilo inferior-piperazina-1-carbonilo; aminocarbonilo; mono-alquilaminocarbonilo inferior; dialquilaminocarbonilo inferior; trimetilsililo-etinilo; imidazolilo opcionalmente sustituido con alquilo inferior o halógeno; tiofenilo opcionalmente sustituido con halógeno, hidroxil, alcoxi inferior o ciano; piridinilo opcionalmente sustituido con alquilo inferior o halógeno;

con la condición de que, si X es un enlace simple, R³ es piridinilo y R² es hidrógeno y R¹ no es hidrógeno o metilo,

y sus sales de adición farmacéuticamente aceptables.

2. Compuestos acordes con la reivindicación 1 que son

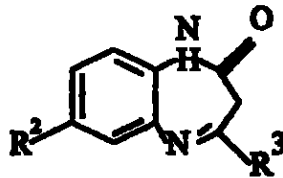


Ia

en donde X, R² y R³ tienen el mismo significado que en la reivindicación 1

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 LUIS BRIGAND DE RODRIGO
 del 10 de Agosto del 2012

3. Compuestos acordes con la reivindicación 1 que son



Ib

en donde X, R² y R³ tienen el mismo significado que en la reivindicación 1.

4. Compuestos acordes con la reivindicación 1 en los que R³ es fenilo sustituido en la posición meta con ciano, halógeno, azido, haloalquilo inferior, alcoxi inferior, cicloalquilo inferior o haloalcoxi inferior; imidazolilo; morfolino-4-carbonilo; 4-metil-piperazina-1-carbonilo; 3-carboxiamino-fenil.

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5. Compuestos acordes con la reivindicación 1 que son

3-(7-yodo-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-(4-oxo-7-feniletinil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

INTERPRETE OFICIAL No. 5.765
Marta Luisa Briceño de Restrepo
Interprete Oficial
antes del MIA de Justicia

3-(4-oxo-7-p-toliletinil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-[7-(2-cloro-feniletinil)-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il) -
benzonitrilo;

4-(3-cloro-fenil)-8-feniletinil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

4-(3-imidazol-1-il-fenil)-8-feniletinil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

3-[7-(4-metoxi-fenil) 4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]-
benzonitrilo;

3-(4-oxo-7-tiofen-3-il-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-(7-furan-2-il-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-[7-(4-etil-fenil)-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]-benzonitrilo;

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3-(4-oxo-7-fenil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

4-(3-yodo-fenil)-8-feniletinil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

4-(3-azido-fenil)-8-fenil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

PROSECUTOR GENERAL OFICIAL NO. 5.765
On R
Maria Luisa Brizard de Rodriguez
Interprete Oficial
NOTA del Ministerio de Justicia

3-[7-(2-metoxi-fenil)-4-oxo-4,5-dihidro-benzo[b][1,4]diazepin-2-il]benzonitrilo;

3-(7-furan-3-il-4-oxo-4,5-dihidro-benzo[b][1,4]diazepin-2-il]benzonitrilo;

3-[7-(4-cloro-fenil)-4-oxo-4,5-dihidro-benzo[b][1,4]diazepin-2-il]benzonitrilo;

3-[7-(4-cloro-feniletinil)-4-oxo-4,5-dihidro-benzo[b][1,4]diazepin-2-il]benzonitrilo;

8-feniletinil-4-(3-trifluorometil-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

4-(3-cloro-fenil)-8-fenil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

3-(7-naftalen-1-il-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]benzonitrilo;

3-(4-oxo-7-tiazol-2-iletinil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]benzonitrilo;

3-(4-oxo-7-p-tolil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-(4-oxo-7-tiofen-2-il-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-(4-oxo-7-piridin-2-iletinil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

5.765
Marta Ludes Brigard de Restrepo
Intendente General
del MIA de la Nación

4-(3-metoxifenil)-8-feniletinil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

3-(4-oxo-7-piridin-2-il-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-(4-oxo-7-m-tolil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-[7-(3,4-dicloro-fenil)-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]-benzonitrilo;

8-fenil-4-(3-trifluorometil-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

3-[7-(2-cloro-fenil)-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]-benzonitrilo;

8-benzoil-4-(3-cloro-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

3-(7-benzoil-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

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3-[7-(3-metoxi-fenil)-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il] -
benzonitrilo;

3-(4-oxo-7-piridin-3-il-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

8-(6-benciloxi-piridin-3-il)-4-(3-trifluorometil-fenil)-1,3-dihidro-
benzo[b][1,4]diazepin-2-ona;

OFICIAL No. 5.765
Marta Lúcia Brigand de Andrade
Intendente Oficial
Ass. Ma. STGE do Min. da Justiça

3-[4-oxo-7-(4-trifluorometoxi-fenil)-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il]-
benzonitrilo;

3-(4-oxo-7-piridin-4-il-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-[4-oxo-7-(1,2,3,6-tetrahidro-piridin-4-il)-4,5-dihidro-3H-benzo[b][1,4]diazepin-
2-il)-benzonitrilo;

3-[7-(1-metanosulfonil-1,2,3,6-tetrahidro-piridin-4-il)-4,5-dihidro-3H -
benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-[7-(1-acetil-1,2,3,6-tetrahidro-piridin-4-il)-4,5-dihidro-3H -
benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-[7-(metoxi-feniletinil)-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il) -
benzonitrilo;

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3-(4-oxo-7-tiofen-2-iletinil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il) -
benzonitrilo;

4-[3-(morfolina-4-carbonil)-fenil]-8-feniletinil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona; 3.765

4-[3-(4-metil-piperazina-1-carbonil)-fenil]-8-feniletinil-1,3-dihidro-3H-benzo[b][1,4]diazepin-2-ona;

TRANSMICION OFICIAL NO. 3.765
Luis Briceño de Rostro
Jefe de Oficina
de Asesoría

3-(4-oxo-7-feniletinil-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzamida;

3-(7-cloro-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo;

3-(4-oxo-4-oxo-8-tiofen-2-il-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il) -
benzonitrilo;

3-(8-cloro-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-benzonitrilo; y

7-cloro-4-(3-trifluorometil-fenil)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona.

6. Compuestos acordes con la reivindicación 1 en los que R¹ es tiofen-2-ilo opcionalmente sustituido con ciano, tiofen-3-ilo o piridin-4-ilo.
7. Compuestos acordes con la reivindicación 6 que son

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8-fenil-4-tiofen-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

4-(3-cloro-tiofen-2-il)8-piridin-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

8-yodo-4--tiofen-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

8-fenil-4--tiofen-3-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

TRADUCCION OFICIAL NO. 5.765
Luis Enrique de Restrepo
Interprete Oficial
del MIA de Justicia

4-(3-cloro-tiofen-2-il)-8-o-tolil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

8-benzoil-tiofen-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

4-(3-cloro-tiofen-2-il)-8-fenil-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

8-(6-oxo-1,6-dihidro-piridin-3-il)-4-tiofen-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

9 8-(6-benciloxi-piridin-3-il)4-(3-cloro-tiofen-2-il)-1,3-dihidro - benzo[b][1,4]diazepin-2-ona;

8-(cloro-4-tiofen-2-il)-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

2-(7-cloro-4-oxo-4,5-dihidro-3H-benzo[b][1,4]diazepin-2-il)-tiofeno-3 - carbonitrilo;

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2-oxo-4-tiofen-2-il-2,3-dihidro-3H-benzo[b][1,4]diazepin-7-carbonitrilo;

7-metil-4-tiofen-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

7-fenil-4-tiofen-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

7-yodo-4-tiofen-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

REGISTRO OFICIAL N.º 5.765
[Firma]
Marta Luisa Brizuela de Estrada
Interprete Oficial
Cm. N.º. 0722 del Min. de Justicia

7-cloro-4-(3-cloro-tiofen-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

8-metil-4-tiofen-2-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona; y

8-feniletinil-4-piridin-4-il-1,3-dihidro-benzo[b][1,4]diazepin-2-ona;

8. Un medicamento que contiene uno o varios compuestos de una cualquiera de las reivindicaciones 1 a 7 y/o uno o varias de sus sales de adición de ácido farmacéuticamente aceptables.
9. Un medicamento acorde con la reivindicación 5 para el tratamiento o prevención de desórdenes neurológicos agudos y/o crónicos, tales como psicosis, esquizofrenia, enfermedad de Alzheimer, desórdenes cognositivos y déficit de memoria, funcionamiento cerebral causado por operaciones de "bypass" o trasplantes, suministro deficiente de sangre al cerebro, lesiones de la médula

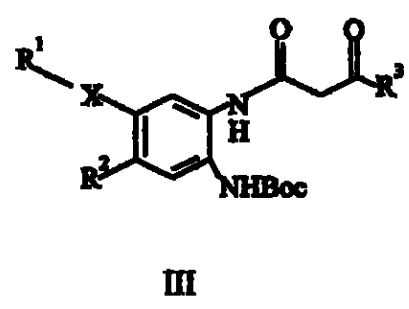
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espinal, lesiones de la cabeza, hipoxia causada por preñez, paro cardíaco e hipoglicemia, dolor agudo y crónico, corea de Huntington, esclerosis amiotrófica lateral (ALS), demencia causada por medicamentos, lesiones de los ojos, retinopatía, parquinsonismo idiopático o parquinsonismo causado por medicamentos lo mismo que condiciones que conducen a funciones deficientes de glutamato, tales como, por ejemplo, espasmos musculares, convulsiones, migraña, incontinencia urinaria, adición a la nicotina, psicosis, adición a opiáceos, ansiedad, vómito, disquinesia y depresión.

5.765-
Marta Luisa Briceño
Interventora Oficial
Cm. No. 0792 del Min. de Justicia

10. Un procedimiento para preparar compuestos de la fórmula 1 definida en la reivindicación 1, que consiste en

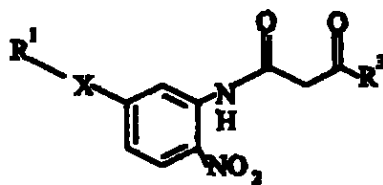
a) descomponer el grupo protector de BOC en compuestos de la fórmula general III



y luego someter a ciclo el compuesto desprotegido, o

b) reducir el grupo nitro de los compuestos de la fórmula general IV al grupo

amino

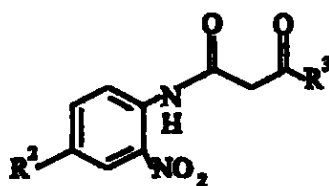


IV

REGISTRO OFICIAL NO. 5765
CTB
 María Luisa Brizuela de Restrepo
 Interpuesta Oficial
 San. No. 0782 del Min. de Justicia

y luego calentar la mezcla para lograr la producción de ciclo.

11. Un procedimiento para preparar compuestos de la fórmula Ib definida en la reivindicación 3, que consiste en reducir el grupo nitro de los compuestos de la fórmula general IV al grupo amino



XVI

y luego calentar la mezcla para lograr la producción de ciclo.

12. El uso de uno o varios compuestos acordes con las reivindicaciones 1 a 4 y/o una o varias de sus sales de adición de ácido farmacéuticamente aceptables, para la fabricación de medicamentos para el tratamiento o prevención de enfermedades.

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13. El uso acorde con la reivindicación 12 para el tratamiento o prevención de desórdenes neurológicos agudos y/o crónicos, tales como psicosis, esquizofrenia, enfermedad de Alzheimer, desórdenes cognositivos y déficit de memoria, funcionamiento cerebral causado por operaciones de "bypass" o transplantes, suministro deficiente de sangre al cerebro, lesiones de la médula espinal, lesiones de la cabeza, hipoxia causada por preñez, paro cardíaco e hipoglicemia, dolor agudo y crónico, corea de Huntington, esclerosis amiotrópica lateral (ALS), demencia causada por medicamentos lo mismo que condiciones que conducen a funciones deficientes de glutamato, tales como, por ejemplo, espasmos musculares, convulsiones, migraña, incontinencia urinaria, adicción a la nicotina, psicosis, adicción a opiáceos, ansiedad, vómito, disquinesia y depresión.

14. La invención descrita aquí antes.

ES TRADUCCION FIEL Y COMPLETA, de la cual queda copia en los archivos de esta oficina de traducciones, para su confrontación y a la que me remito.

Derechos de Traducción: \$135.000,00

BOGOTA, 31 DE OCTUBRE DEL 2000.

5-765
María Luisa Brigard de Rodas
María Luisa Brigard de Rodas
Intérprete Oficial
Cm. No. 6792 del Mta. de Justicia



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F. Hoffmann

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Bescheinigung

Certificate

Attestation

Die angehefteten Unterla-
gen stimmen mit der
ursprünglich eingereichten
Fassung der auf dem näch-
sten Blatt bezeichneten
europäischen Patentanmel-
dung überein.

The attached documents
are exact copies of the
European patent application
described on the following
page, as originally filed.

Les documents fixés à
cette attestation sont
conformes à la version
initialement déposée de
la demande de brevet
européen spécifiée à la
page suivante.

OFFICIAL No. 5.764
Maria Luisa Brizard Rodriguez
Intérprete Oficial
Ley de 1789 del Ministerio de Justicia

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99120519.6

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE,
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**Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation**

Anmeldung Nr.:
Application no.:
Demande n°: 99120519.6

Anmeldetag:
Date of filing:
Date de dépôt: 15/10/99

PROSECUTOR. OFFICIAL no. 5.764
Maria Luisa Brigard de Rodero
Intéressé
Sec. de l'OSI de l'OSI de l'OSI

Anmelder:
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Benzodiazepin derivatives

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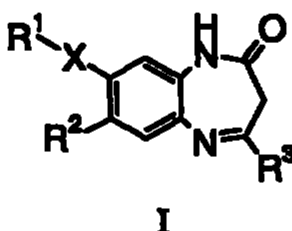
EPO-Munich
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15. Okt. 1999

Case 20399

Benzodiazepin derivatives

The present invention relates to compounds of general formula I



wherein

5 X is a single bond or an ethynediyl group, wherein,

in case X is a single bond,

R¹ is hydrogen; halogen; nitro; lower alkyl; lower halo-alkyl; lower cycloalkyl, optionally substituted with oxygen; benzoyl optionally substituted with lower alkyl, lower halo-alkyl, halogen; phenyl, optionally substituted with halogen, lower alkyl, lower halo-alkyl, lower
10 cycloalkyl, lower alkoxy, lower halo-alkoxy; 5 or 6 membered heterocyclic ring, optionally substituted with oxo, benzyloxy, benzoyl, methanesulfonyl, benzenesulfonyl, acetyl; naphthyl;

in case X is an ethynediyl group,

R¹ is hydrogen; lower alkyl; lower halo-alkyl; lower cycloalkyl, optionally substituted with
15 lower alkyl, lower halo-alkyl, lower alkoxy; lower halo-alkoxy, halogen; lower cycloalkenyl, optionally substituted with lower alkyl, lower halo-alkyl, lower alkoxy, lower halo-alkoxy, halogen; lower alkenyl; phenyl optionally substituted with halogen, lower alkyl, lower halo-

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alkyl, lower cycloalkyl, lower alkoxy, lower halo-alkoxy; 5 or 6 membered heterocyclic ring, optionally substituted with lower alkyl, halogen, oxo, benzyloxy, benzoyl, methanesulfonyl, benzenesulfonyl, acetyl;

- 5** R^2 is hydrogen, lower alkyl; halogen; cyano; benzoyl optionally substituted with lower alkyl, lower halo-alkyl, halogen; phenyl optionally substituted with halogen, lower alkyl, lower halo-alkyl, lower cycloalkyl, lower alkoxy, lower halo-alkoxy; phenoxy optionally substituted with halogen, lower alkyl, lower halo-alkyl, lower cycloalkyl, lower alkoxy, lower halo-alkoxy; 5 or 6 membered heterocyclic ring, optionally substituted with lower alkyl, halogen, hydroxy
- 10** R^3 is phenyl substituted in meta position with halogen, cyano, lower alkyl, lower alkoxy, lower halo-alkyl, azido, ethynyl, nitro, morpholine-4-carbonyl, 4-lower alkyl-piperazine-1-carbonyl; aminocarbonyl; mono-lower alkylaminocarbonyl; di-lower alkylaminocarbonyl; trimethylsilyl-ethynyl; imidazolyl optionally substituted with lower alkyl, halogen; thiophenyl, optionally substituted with halogen, hydroxy, lower alkoxy, lower alkyl, cyano;
- 15** pyridinyl, optionally substituted with lower alkyl, halogen;

with the proviso that, if X is a single bond, R^3 is pyridinyl and R^2 is hydrogen, R^1 is not hydrogen, methyl;

and their pharmaceutically acceptable acid addition salts.

- 20** It has surprisingly been found that the compounds of general formula I are metabotropic glutamate receptor antagonists. Compounds of formula I are distinguished by valuable therapeutic properties.

In the central nervous system (CNS) the transmission of stimuli takes place by the interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

- 25** L-glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays a critical role in a large number of physiological processes. The glutamate-dependent stimulus receptors are divided into two main groups. The first main group forms ligand-controlled ion channels. The metabotropic glutamate receptors (mGluR) form the second main group and, furthermore, belong to the family of G-protein-coupled receptors.

- 30** At present, eight different members of these mGluR are known and of these some even have sub-types. On the basis of structural parameters, the different influences on the synthesis of secondary metabolites and the different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups:

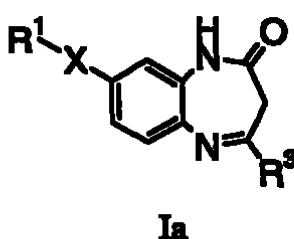
mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the group II can be used for the treatment or prevention of acute and/or chronic neurological disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are chronic and acute pain, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depressions.

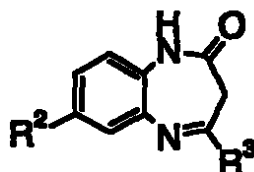
Objects of the present invention are compounds of formula I and their pharmaceutically acceptable salts per se and as pharmaceutically active substances, their manufacture, medicaments based on one or more compounds in accordance with the invention and their production, as well as the use of the compounds in accordance with the invention in the control or prevention of illnesses of the aforementioned kind, and, respectively, for the production of corresponding medicaments.

One aspect of the present invention refers to compounds of general formula I being



wherein X, R¹ and R³ have the same meaning as above.

A further aspect of the present invention refers to compounds of general formula I being



Ib

wherein R^2 and R^3 have the same meaning as above.

Preferred compounds of formula I in the scope of the present invention are those in which R^3 is phenyl substituted in meta position by cyano, halogen, azido, lower halo-alkyl, lower alkyl, lower alkoxy, lower cycloalkyl, lower halo-alkoxy; 1-imidazolyl, morpholine-4-carbonyl; 4-methyl-piperazine-1-carbonyl; 3-carboxyamino-phenyl.

The following are examples of such compounds:

- 3-(7-Iodo-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(4-Oxo-7-phenylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 10 3-(4-Oxo-7-p-tolyethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-[7-(2-Chloro-phenylethynyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 4-(3-Chloro-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 3-[7-(4-Methoxy-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-
- 15 benzonitrile;
- 3-(4-Oxo-7-thiophen-3-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(7-Furan-2-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-[7-(4-Ethyl-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-(4-Oxo-7-phenyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 20 4-(3-Iodo-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 4-(3-Azido-phenyl)-8-phenyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 3-[7-(2-Methoxy-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-(7-Furan-3-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 25 3-[7-(4-Chloro-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-[7-(4-Chloro-phenylethynyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 8-Phenylethynyl-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 4-(3-Chloro-phenyl)-8-phenyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 30 4-(3-Imidazol-1-yl-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 3-(7-Naphthalen-1-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;

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- 3-(4-Oxo-7-thiazol-2-ylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(4-Oxo-7-p-tolyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(4-Oxo-7-thiophen-2-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 5 3-(4-Oxo-7-pyridin-2-ylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 4-(3-Methoxy-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 3-(4-Oxo-7-pyridin-2-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(4-Oxo-7-m-tolyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 10 3-[7-(3,4-Dichloro-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 8-Phenyl-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 3-[7-(2-Chloro-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 8-Benzoyl-4-(3-chloro-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 15 3-(7-Benzoyl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-[7-(3-Methoxy-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-(4-Oxo-7-pyridin-3-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 8-(6-Benzoyloxy-pyridin-3-yl)-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-
- 20 benzo[b][1,4]diazepin-2-one;
- 3-[4-Oxo-7-(4-trifluoromethoxy-phenyl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-(4-Oxo-7-pyridin-4-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-[4-Oxo-7-(1,2,3,6-tetrahydro-pyridin-4-yl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-
- 25 yl]-benzonitrile;
- 3-[7-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-[7-(1-Acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 80 3-[7-(4-Methoxy-phenylethynyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-(4-Oxo-7-thiophen-2-ylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 4-[3-(Morpholine-4-carbonyl)-phenyl]-8-phenylethynyl-1,3-dihydro-
- 85 benzo[b][1,4]diazepin-2-one;
- 4-[3-(4-Methyl-piperazine-1-carbonyl)-phenyl]-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;

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- 3-(4-Oxo-7-phenylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzamide;
 3-(7-Chloro-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
 3-(4-Oxo-8-thiophen-2-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
 3-(8-Chloro-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile; and
 5 7-Chloro-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

Compounds of formula I, in which R³ is thiophen-2-yl, optionally substituted with halogen, ciano; thiophen-3-yl; pyridin-4-yl are also preferred.

The following are examples of such compounds:

- 8-Phenyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 10 4-(3-Chloro-thiophen-2-yl)-8-pyridin-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 8-Iodo-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 8-Phenyl-4-thiophen-3-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 4-(3-Chloro-thiophen-2-yl)-8-o-tolyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 8-Benzoyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 15 4-(3-Chloro-thiophen-2-yl)-8-phenyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 8-(6-Oxo-1,6-dihydro-pyridin-3-yl)-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 8-(6-Benzoyloxy-pyridin-3-yl)-4-(3-chloro-thiophen-2-yl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 20 8-Chloro-4-(3-chloro-thiophen-2-yl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 2-(7-Chloro-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-thiophene-3-carbonitrile;
 2-Oxo-4-thiophen-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine-7-carbonitrile;
 7-Methyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 25 7-Phenyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 7-Iodo-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
 7-Chloro-4-(3-chloro-thiophen-2-yl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one
 8-Methyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one; and
 8-Phenylethynyl-4-pyridin-4-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

- 30 All tautomeric forms of the compounds of invention are also embraced herewith.

The term "lower alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1-7 carbon atoms, preferably with 1-4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and the like.

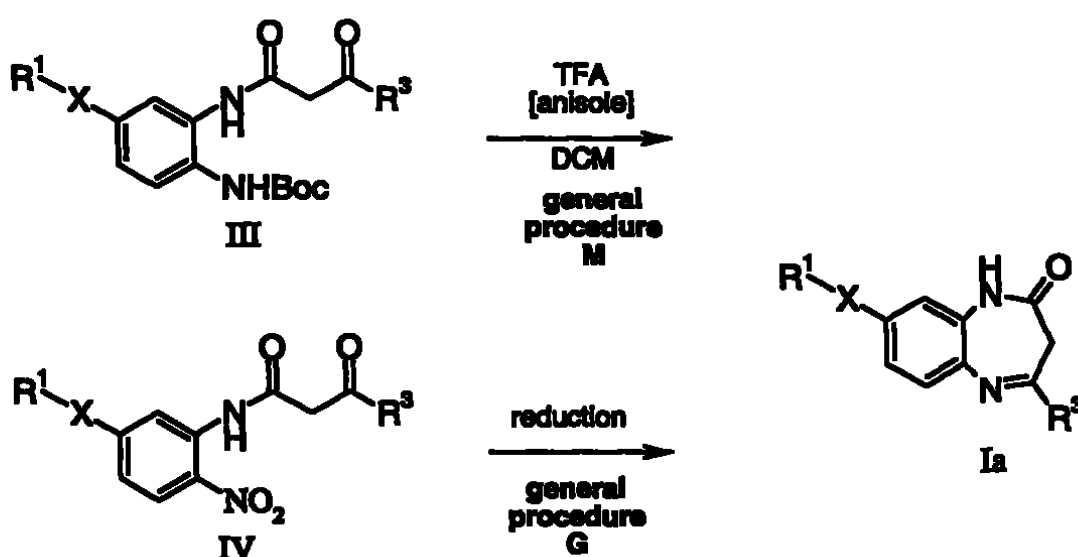
The term "lower alkoxy" denotes a lower alkyl residue in the sense of the foregoing definition bonded via an oxygen atom.

The term "halogen" embraces fluorine, chlorine, bromine and iodine.

The expression "5 or 6 membered heterocyclic ring" embraces thiophene, furan, thiazol,
5 pyridine, partially hydrated pyridine.

The compounds of general formula Ia and their pharmaceutically acceptable salts can be manufactured according to the following methods:

Scheme A



- 10 Compounds of general formula Ia, in which R^1 , R^3 and X are as described above can be prepared according to scheme A, by, for example, cleaving the BOC protecting group in compounds of general formula III, and concomitant cyclization of the deprotected compound. The deprotection-cyclization step can be carried out by treating the compounds of general formula III with a bronsted acid like for example trifluoroacetic acid in an inert solvent like for example dichloromethane (DCM). The reaction is preferably carried out at temperatures between 0°C and 50°C. It may be advantageous to use also anisole as a carbocation scavenger in the reaction mixture.
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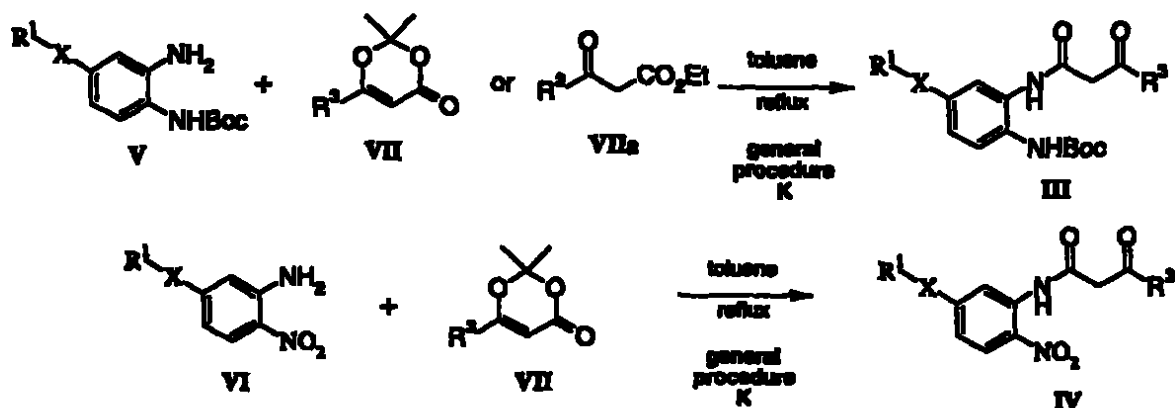
In addition, compounds of general formula Ia, in which R^1 , R^3 and X are as described above can be prepared according to scheme A, by for example reducing the nitro group in
20 compounds of general formula IV to the amino group and subsequent heating of the reaction mixture to achieve the cyclization. The reduction can for example be carried out using hydrogen gas in presence of a suitable catalyst like for example Raney-Nickel. Another possible reduction method is using stannous(II)chloride in ethanol at

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- 8 -

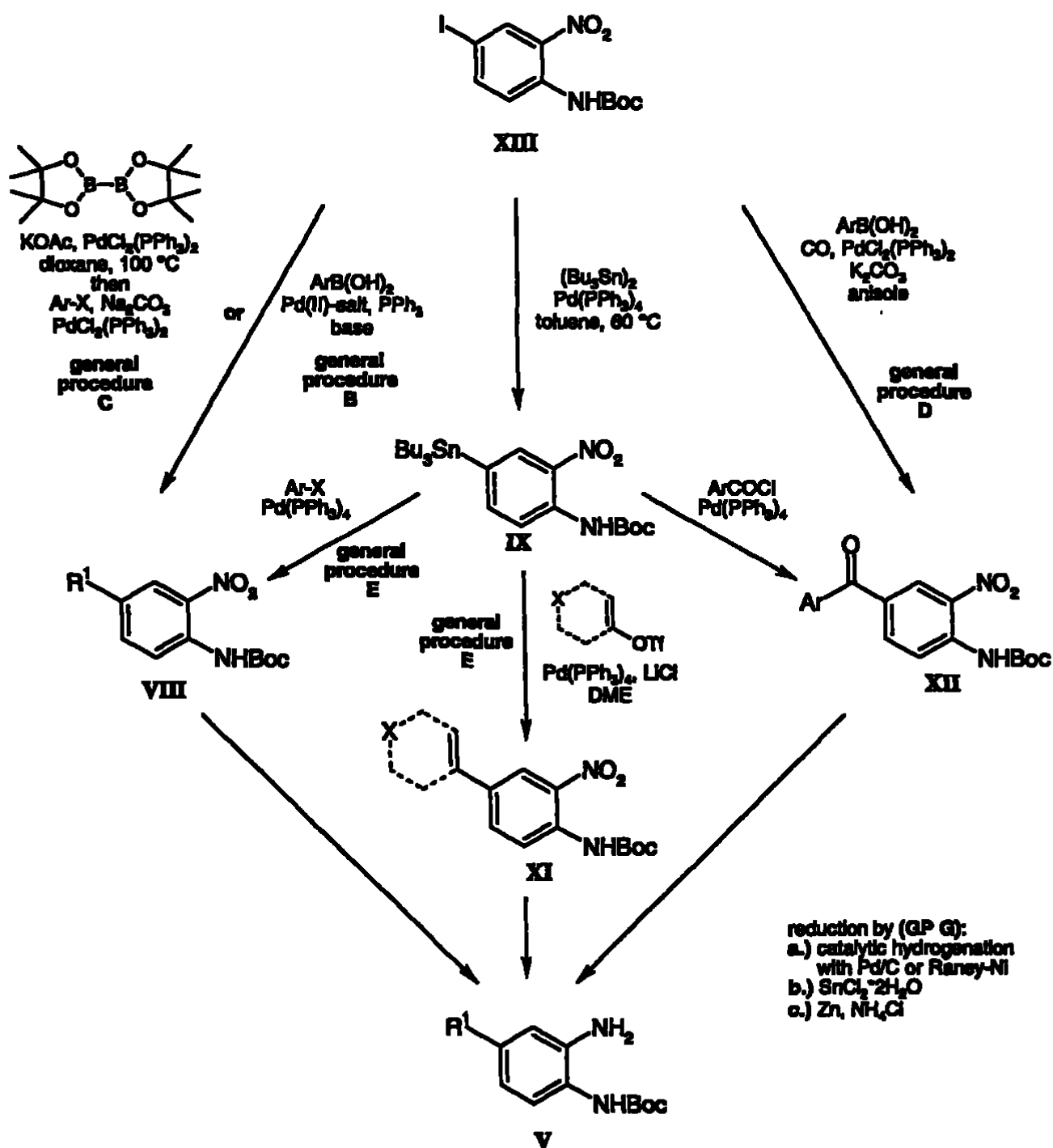
temperatures between 70°C and 80°C or zinc-powder in the presence of ammonium chloride at temperatures between 20°C and 80°C.

Scheme B



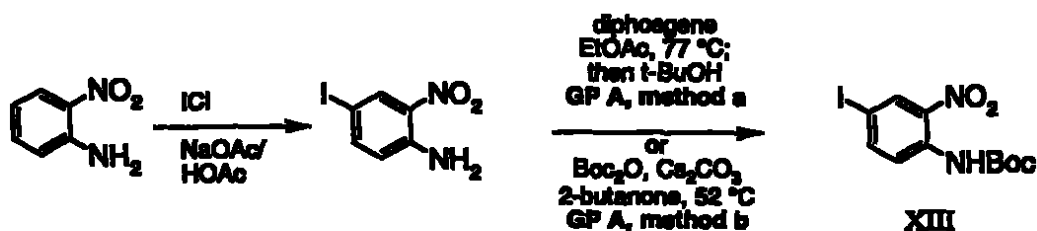
- 5 Compounds of general formula III and IV, in which R^1 , R^3 and X are as described above can be prepared according to scheme B by for example reacting a compound of general formula V or VI, respectively, with a dioxinone (general formula VII) in an inert solvent like for example toluene or xylene at elevated temperatures, preferably between 80°C and 160°C.
- 10 Alternatively, compounds of general formula III can also be prepared by for example reaction of a compound of general formula V with a β -ketoester (general formula VIIa), in which R^3 is as described above using the same conditions as described for the reaction with the dioxinones.

Scheme C



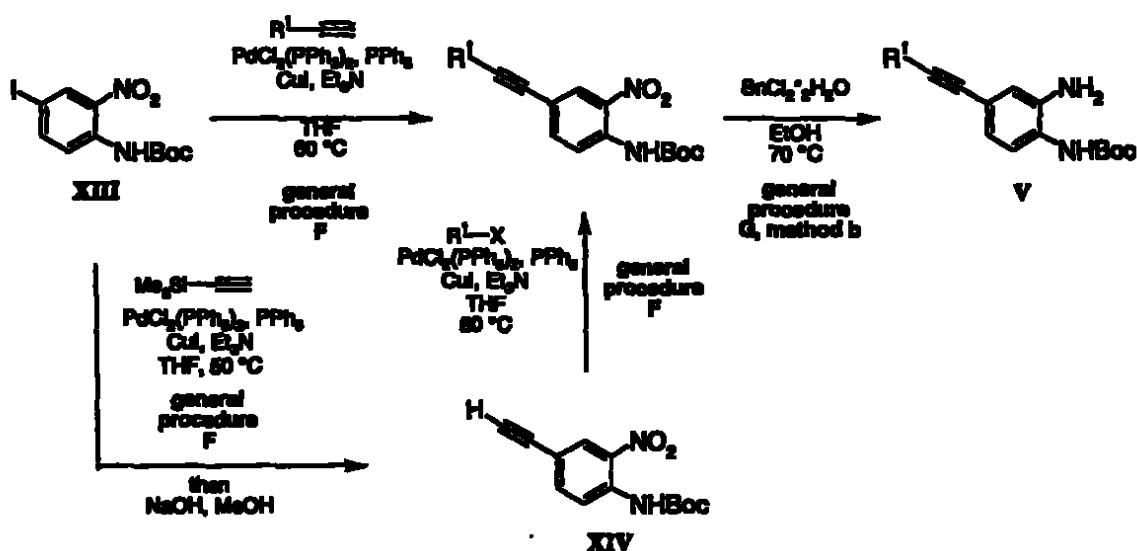
According to scheme C, compounds of general formula V in which R^1 is as described
 5 above for compounds where X is a single bond can be prepared by different routes from
 the iodo-compound XIII, depending on the nature of R^1 . As shown in scheme C, the key
 steps are coupling reactions of Suzuki- and Stille-type in presence or absence of
 carbonmonoxide. The exact conditions for the respective compounds can be found in the
 experimental part.

Scheme D



According to scheme D, the key intermediate iodide XIII can be prepared from commercially available 2-nitroanilin by a standard iodination-protection sequence.

Scheme E



According to scheme E, compounds of general formula V in which R¹ is as described above for compounds where X is an ethynediyl group can be prepared by different routes from the iodo-compound XIII, depending on the nature of R¹. As shown in Scheme E, the transformation can for example be carried out

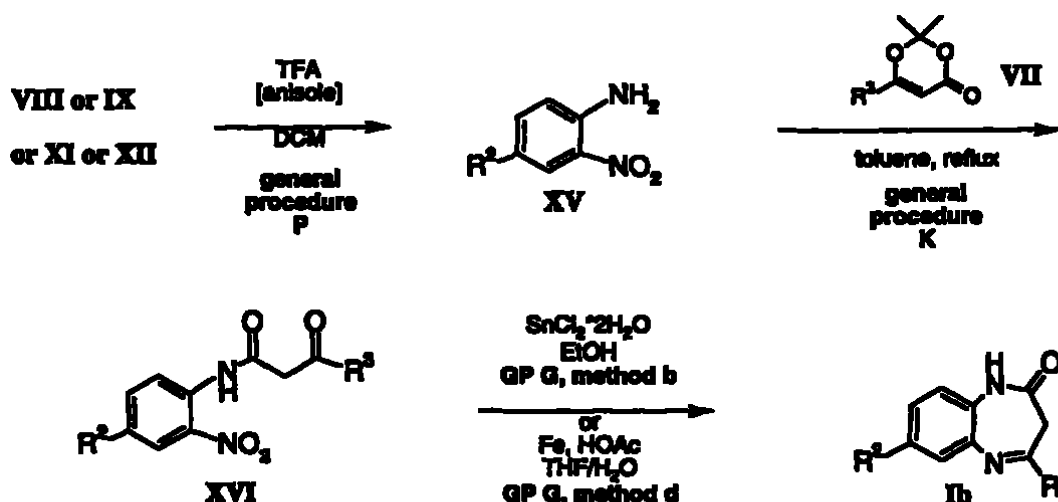
a) by directly attaching the R¹-alkynediyl-substituent via a Sonogashira-type coupling followed by the reduction of the nitro group or

b) by two stepwise Sonogashira -type couplings, in which first trimethylsilyl-acetylene is coupled to Iodine XIII to yield, after deprotection with sodium hydroxide in methanol, the intermediate XIV which then can be transformed via a second Sonogashira-type coupling with the appropriate reactant R¹-I, R¹-Br or R¹-OSO₂CF₃ and reduction of the nitro group to the desired compounds.

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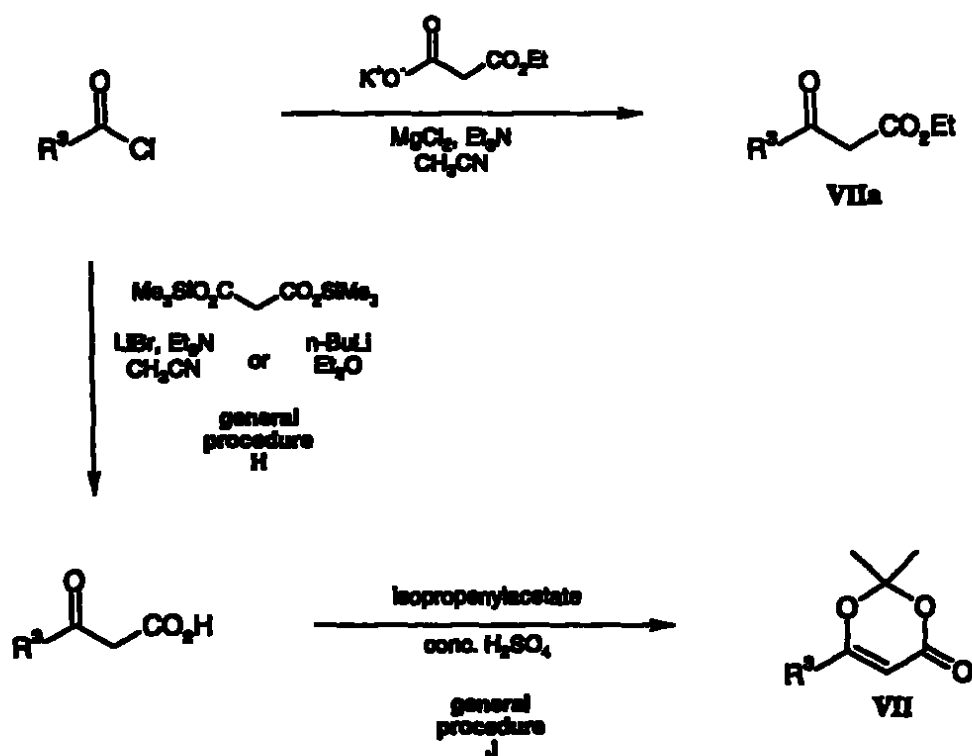
The exact conditions for the respective compounds can be found in the experimental part.

Scheme F



According to scheme F, compounds of general formula Ib, in which R^2 and R^3 represent the substituents as described above, can be prepared from a subset of the intermediates of general formula VIII, IX, XI and XII (scheme C) in which $\text{R}^1\text{-X-}$ is identical to R^2 . The reaction sequence can be carried out as for example shown in scheme F by deprotection of the said subset of compounds using the conditions described above to yield compounds of general formula XV in which R^2 represents the substituents as already described. Reacting the compounds of general formula XV with dioxinones VII as described in scheme B gives rise to intermediates of general formula XVI which, after reduction of the nitro group using the methods described for scheme C and cyclization, furnish the target compounds of general formula Ib. The exact conditions for the respective compounds can be found in the experimental part.

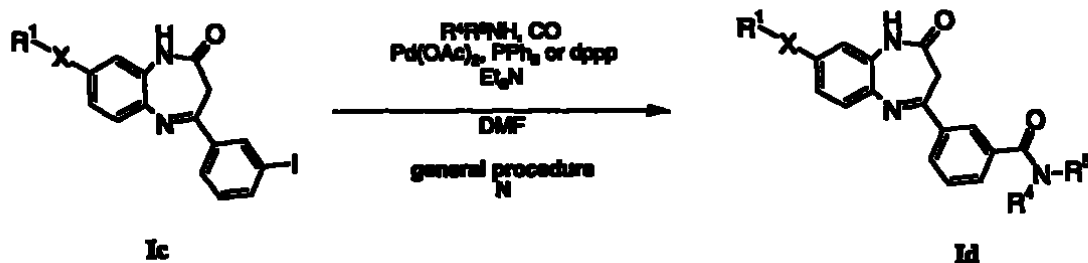
Scheme G



According to Scheme G, the dioxinones and β -keto esters building blocks with the general formula VII and VIIa can be prepared by methods known to someone skilled in the art from the corresponding carboxylic acid chlorides R^2-COCl . The exact conditions for some representative compounds can be found in the experimental part.

Another synthetic route to prepare compounds of general formula Id, in which R^1 and X have the meaning as described above and R^3 is a phenyl-carboxamide of general formula $\text{C}(\text{O})\text{NR}^4\text{R}^5$, in which R^4 and R^5 are hydrogen, lower alkyl or R^4 and R^5 together form a morpholino-residue or a N-methyl-piperazine is outlined in scheme H:

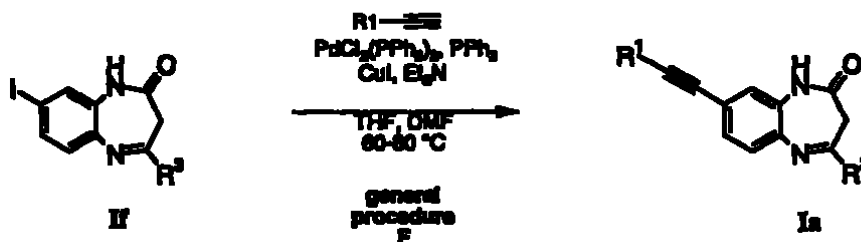
Scheme H



The exact conditions for the respective compounds can be found in the experimental part.

- 5 Still another way to prepare compounds of general formula Ia is the reaction of 4-aryl-8-iodo-1,3-dihydro-benzo[b][1,4]diazepin-2-ones (General formula If, Synthetic Scheme I) with alkynes of general formula $R^1-CC\equiv$, in which R^1 has the meaning as described above, in a Sonogashira-coupling.

Scheme I



The exact conditions for the respective compounds can be found in the experimental part.

The pharmaceutically acceptable salts can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid,

- 15 hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid,

p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I.

The compounds of formula I and their pharmaceutically acceptable salts are metabotropic glutamate receptor antagonists and can be used for the treatment or prevention of acute and/or chronic neurological disorders, such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are acute and chronic pain, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatin capsules. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatin capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

- 5 As mentioned earlier, medicaments containing one or more compounds of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable
- 10 substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being

15 preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The present invention relates also to the use of compounds of formula I and of pharmaceutically acceptable salts thereof for the production of medicaments, especially for

20 the control or prevention of acute and/or chronic neurological disorders of the aforementioned kind.

The compounds of the present invention are group II mGlu receptor antagonists as determined using the assay described by Cartmell et al. (*Br. J. Pharmacol.*, 1998, 123(3), 497-504).

- 25 The compounds show activities, as measured in the assay described below, of 50 μ M or less, typically 3 μ M or less, and ideally of 0.5 μ M or less.

[³H]-LY354740 binding on mGlu2 transfected CHO cell membranes

Transfection and cell culture

- cDNA encoding the rat mGlu2 receptor protein in pBluescript II was obtained from Prof.
- 80 S. Nakanishi (Kyoto, Japan), and subcloned into the eukaryotic expression vector pcDNA I-amp from Invitrogen (NV Leek, The Netherlands). This vector construct (pcD1mGR2) was co-transfected with a psvNeo plasmid encoding the gene for neomycin resistance, into

CHO cells by a modified calcium phosphate method described by Chen & Okayama (1988). The cells were maintained in Dulbecco's Modified Eagle medium with reduced L-glutamine (2mM final concentration) and 10% dialyzed foetal calf serum from Gibco BRL (Basel, Switzerland). Selection was made in the presence of G-418 (1000 ug/ml final).

- 5 Clones were identified by reverse transcription of 5µg total RNA, followed by PCR using mGlu2 receptor specific primers 5'-atcactgttgggtttctggcactg-3' and 5'-agcatcactgtgggtggcataggagc-3' in 60mM Tris HCl (pH 10), 15mM (NH₄)₂SO₄, 2 mM MgCl₂, 25 units/ml Taq Polymerase with 30 cycles annealing at 60°C for 1 min., extension at 72°C for 30s, and 1 min. 95°C denaturation.

10 *Membrane preparation*

Cells, cultured as above, were harvested and washed three times with cold PBS and frozen at -80°C. The pellet was resuspended in cold 20 mM HEPES-NaOH buffer containing 10 mM EDTA (pH 7.4), and homogenised with a polytron (Kinematica, AG, Littau, Switzerland) for 10s at 10 000rpm. After centrifugation for 30 min. at 4°C, the pellet was

- 15 washed once with the same buffer, and once with cold 20 mM HEPES-NaOH buffer containing 0.1 mM EDTA, (pH 7.4). Protein content was measured using the Pierce method (Socochim, Lausanne, Switzerland) using bovine serum albumin as standard.

[³H]-LY354740 binding

After thawing, the membranes were resuspended in cold 50mM Tris-HCl buffer

- 20 containing 2 mM MgCl₂ and 2 mM CaCl₂, (pH 7) (binding buffer). The final concentration of the membranes in the assays was 25 µg protein/ml. Inhibition experiments were performed with membranes incubated with 10 nM [³H]-LY354740 at room temperature, for 1 hour, in presence of various concentrations of the compound to be tested. Following the incubations, membranes were filtered onto Whatmann GF/C glass
25 fiber filters and washed 5 times with cold binding buffer. Non specific binding was measured in the presence of 10 µM DCG IV (TOCRIS No. 0975). After transfer of the filters into plastic vials containing 10 ml of Ultima-gold scintillation fluid (Packard, Zürich, Switzerland), the radioactivity was measured by liquid scintillation in a Tri-Carb 2500 TR counter (Packard, Zürich, Switzerland).

30 *Data analysis.*

The inhibition curves were fitted with a four parameter logistic equation giving IC50 values, and Hill coefficients.

EXAMPLES

General procedure A (Synthetic Scheme D):

Preparation of (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl esters from 4-iodo-2-nitroanilines.

5 Method a

To a solution of diphosgene (4.1 mL, 34.1 mmol) in EtOAc (40 mL) at 0 °C was added a solution of the 4-iodo-2-nitroaniline (45.5 mmol) in EtOAc (200-500 mL), and the mixture was heated to reflux for 18 h. The solvent was removed in vacuum to leave a brown solid, which was triturated with hot hexane (200 mL). The solid material was
10 filtered off and the filtrate was concentrated under reduced pressure to leave the pure 4-iodo-2-nitrophenylisocyanate as a yellow solid. This material was refluxed in a mixture of excess tert.-BuOH in CH₂Cl₂ for 2.5 h. Removal of the solvent left an orange solid which was purified by silica gel column chromatography with hexane/EtOAc to give the (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester as a yellow solid.

15 Method b

To a mixture of the 4-iodo-2-nitroaniline (142 mmol) and cesium carbonate (55.5 g, 170 mmol) in 2-butanone (740 mL) was dropwise added a solution of Boc₂O (37.8 g, 173 mmol) in 2-butanone (170 mL) and the resulting mixture was stirred at 52 °C for 26 h. The solvent was removed in vacuum, the residue was treated with a mixture of H₂O (240 mL) and MeOH (240 mL) and extracted with hexane (3 x 500 mL). The combined hexane
20 layer was washed with brine (200 mL) and all aqueous layers were reextracted with hexane (300 mL). All combined hexane layers were dried over MgSO₄, filtered and the solvent was removed in vacuum to give an orange solid, which was purified by silica gel column chromatography with hexane/EtOAc to give the (4-iodo-2-nitro-phenyl)-carbamic acid
25 tert.-butyl ester as a yellow solid.

Example A1

(4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester.

Prepared the isocyanate from 4-iodo-2-nitroaniline (12.0 g, 45.5 mmol; prepared from 2-nitroaniline according to Wilson, J. Gerald; Hunt, Frederick C. Aust. *J. Chem.* 1983, 36,
30 2317-25; CAS-No. [20691-72-9]) with diphosgene (4.1 mL, 34.1 mmol) in EtOAc (250

mL), followed by treatment with tert.-BuOH (12 mL) in CH₂Cl₂ (60 mL) according to the general procedure A (method a). Obtained as a yellow solid (8.23 g, 82 %).

MS (EI) 390 (M⁺); mp 92-94 °C.

5 General procedure B (Synthetic Scheme C)

Preparation of (4-aryl-2-nitro-phenyl)-carbamic acid tert.-butyl esters by direct Suzuki-coupling of (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl esters with arylboronic acids.

10 A mixture of the (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (3.0 mmol), the arylboronic acid (4.5 mmol) and PdCl₂(PPh₃)₂ (2 mol%) was refluxed in 1,4-dioxane (25 mL) and 2M Na₂CO₃-sol. (7.5 mL) [or alternatively with 1M NaHCO₃-sol. (7.5 mL), LiCl (6.0 mmol) and (Ph₃P)₄Pd (3 mol%) in DME (30 mL); also possible with Et₃N (9.0 mmol), Pd(OAc)₂ (3 mol%), PPh₃ (6 mol%) in DMF (10 mL) at 100 °C] until tlc indicated
15 complete conversion of the iodide. The mixture was transferred into a separating funnel, H₂O (25 mL) was added and the product was extracted with ether or EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL) and dried over Na₂SO₄. Removal of the solvent left a brown residue, which was purified by silica gel column chromatography with cyclohexane/ether or cyclohexane/EtOAc to give the title compound.

20 Example B1

(4'-Methoxy-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) and 4-methoxyphenylboronic acid according to the general procedure B. Obtained as a yellow solid (637 mg).

25 MS (ESI) 343 [(M-H)⁻]; mp 107-109 °C.

Example B2

(2-Nitro-4-thiophen-3-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) and 3-thiopheneboronic acid according to the general procedure B. Obtained as a yellow solid (326 mg).

MS (ISN) 319 [(M-H)].

5 Example B3

(4-Furan-2-yl-2-nitro-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) and furan-2-boronic acid according to the general procedure B. Obtained as an orange solid (282 mg).

10 MS (EI) 304 (M⁺); mp 169-172 °C.

Example B4

(4'-Ethyl-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) and 4-ethylbenzene boronic acid according to the general procedure B. Obtained as an orange solid (689 mg).

MS (EI) 343 [(M+H)⁺]; mp 94-99 °C.

Example B5

(3-Nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (994 mg, 2.73 mmol) and phenyl boronic acid (576 mg, 3.00 mmol) according to the general procedure B. Obtained as a bright yellow solid (800 mg).

MS (EI) 314 (M⁺); mp 119-121 °C.

Example B6

(4-Furan-3-yl-2-nitro-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) and furan-3-boronic acid according to the general procedure B. Obtained as an orange solid (855 mg).

MS (ISP) 322 [(M+NH₄)⁺] and 327 [(M+Na)⁺]; mp 105-110 °C.

5 Example B7

(4-Naphthalen-1-yl-2-nitro-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) and 1-naphthylboronic acid according to the general procedure B. Obtained as a yellow foam (1.0 g).

10 MS (ISP) 363 [(M-H)⁻]; mp 60-66 °C.

Example B8

(3'-Methoxy-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) and 3-methoxyphenylboronic acid according to the general procedure B. Obtained as an

15 orange solid (818 mg).

MS (ISP) 345 [(M-H)⁻], 362 [(M+NH₄)⁺] and 367 [(M+Na)⁺]; mp 104-107 °C.

Example B9

(3-Nitro-4'-trifluoromethoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

20 Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) and 4-(trifluoromethoxy)benzene boronic acid according to the general procedure B. Obtained as an orange solid (569 mg).

MS (ISP) 397 [(M-H)⁻]; mp 145-147 °C.

General procedure C (Synthetic Scheme C)

25 Preparation of (4-aryl-2-nitro-phenyl)-carbamic acid tert.-butyl esters by Suzuki-coupling of (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl esters with bis(pinacolato)diboron and subsequent reaction with aryl halides.

A mixture of the (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (2.0 mmol), bis(pinacolato)diboron (2.2 mmol), KOAc (6.0 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (3 mol%) in 1,4-dioxane (25 mL) was stirred at 100 °C until tlc indicated complete conversion of the iodide [cf. *Tetr. Lett.* 1997, 38, 3841-3844]. After addition of the aryl halide (4.0 mmol),

5 $\text{PdCl}_2(\text{PPh}_3)_2$ (3 mol%) and 2M Na_2CO_3 -sol. (7.5 mL) the mixture was stirred at 100 °C until tlc indicated complete conversion of the intermediate boronic ester. The mixture was transferred into a separating funnel, H_2O (30 mL) was added and the product was extracted with ether or EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4 . Removal of the solvent left a brown residue, which

10 was purified by silica gel column chromatography with cyclohexane/ether or cyclohexane/EtOAc to give the title compound.

Example C1

(2'-Methoxy-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1),

15 bis(pinacolato)diboron and 2-iodoanisole according to the general procedure C. Obtained as a yellow solid (735 mg).

MS (EI) 344 (M^+)

Example C2

(4'-Chloro-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

20 Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1), bis(pinacolato)diboron and 1-chloro-4-iodobenzene according to the general procedure C. Obtained as a yellow solid (779 mg).

MS (ISN) 347 [$(M-H)^+$]; mp 150-155 °C (dec.).

Example C3

25 (2-Nitro-4-thiophen-2-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1), bis(pinacolato)diboron and 2-iodothiophene according to the general procedure C. Obtained as a yellow solid (91 mg).

MS (ISN) 319 [$(M-H)^+$].

Example C4

(4'-Methyl-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1), bis(pinacolato)diboron and 4-iodotoluene according to the general procedure C. Obtained
5 as an orange solid (542 mg).

MS (ISP) 346 $[(M+NH_4)^+]$ and 367 $[(M+Na)^+]$; mp 105-108 °C.

Example C5

(2-Nitro-4-pyridin-2-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1),
10 bis(pinacolato)diboron and 2-bromopyridine according to the general procedure C.
Obtained as a yellow solid (407 mg).

MS (ISP) 316 $[(M+H)^+]$.

Example C6

(3'-Methyl-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

15 Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1),
bis(pinacolato)diboron and 3-iodotoluene according to the general procedure C.
Obtained as a yellow solid (524 mg).

MS (ISP) 346 (M^+) and 674 $[(2M+NH_4)^+]$; mp 83-85 °C.

Example C7

20 **(3',4'-Dichloro-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.**

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1),
bis(pinacolato)diboron and 3,4-dichloro-iodobenzene according to the general procedure
C. Obtained as a yellow solid (540 mg).

MS (EI) 382 (M^+) .

234

Example C8

(2'-Chloro-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1), bis(pinacolato)diboron and 1-chloro-2-iodobenzene according to the general procedure

5 C. Obtained as a yellow oil (886 mg).

MS (ISN) 347 [(M-H)⁻].

Example C9

(2'-Methyl-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1),

10 bis(pinacolato)diboron and 2-iodotoluene according to the general procedure C. Obtained as a yellow oil (755 mg).

MS (ISN) 327 [(M-H)⁻].

Example C10

(2-Nitro-4-pyridin-3-yl-phenyl)-carbamic acid tert.-butyl ester.

15 Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1), bis(pinacolato)diboron and 3-bromopyridine according to the general procedure C. Obtained as a yellow solid (587 mg).

MS (ISP) 316 [(M+H)⁺]; mp 107-109 °C.

Example C11

20 (2-Nitro-4-pyridin-4-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1), bis(pinacolato)diboron and 4-bromopyridine according to the general procedure C. Obtained as a yellow solid (379 mg).

MS (ISP) 316 [(M+H)⁺].

General procedure D (Synthetic Scheme C)

Preparation of (4-aryl-2-nitro-phenyl)-carbamic acid tert.-butyl esters by carbonylative Suzuki-coupling of (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl esters with aryl boronic acids

- 5 A mixture of the (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (1.0 mmol), aryl boronic acid (1.1 mmol), K_2CO_3 (3.0 mmol) and $PdCl_2(PPh_3)_2$ (3 mol%) in anisole (6 mL) was stirred at 80 °C under a CO-atmosphere until tlc indicated complete conversion of the iodide [cf. *Tetr. Lett.* 1993, 34, 7595-7598]. The mixture was transferred into a separating funnel, H_2O (30 mL) was added and the product was extracted with EtOAc (2 x 100 mL).
- 10 The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4 . Removal of the solvent left a yellow residue, which was purified by silica gel column chromatography with or hexane/EtOAc to give the title compound.

Example D1

(4-Benzoyl-2-nitro-phenyl)-carbamic acid tert.-butyl ester

- 15 Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (364 mg, 1.0 mmol) and phenylboronic acid (134 mg, 1.1 mmol) according to the general procedure D. Obtained as a yellow solid (242 mg).

MS (EI) 342 (M^+).

Example D2

- 20 (2-Nitro-4-tributylstannanyl-phenyl)-carbamic acid tert.-butyl ester

A solution of (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (3.64 g, 10 mmol), hexabutylstannane (7.5 mL, 15 mmol) and $(Ph_3P)_4Pd$ (116 mg, 0.1 mmol) in toluene (20 mL) was heated to 60° C for 5 days [cf. *Bull. Chem. Soc. Jpn.* 1983, 56, 3855-3856]. The reaction mixture was diluted with toluene (150 mL), washed with aqueous KF-sol. (2 x 50 mL), brine and dried over $MgSO_4$. Removal of the solvent in vacuum left a brown oil, which was purified by silica gel column chromatography with hexane/ether 49:1 to give the (2-nitro-4-tributylstannanyl-phenyl)-carbamic acid tert.-butyl ester as a yellow liquid (3.8 g, 72 %).

MS (EI) 467, 469, 471 [all (M -butyl) $^+$].

- 30 **General procedure E (Synthetic Scheme C)**

235

Preparation of (4-aryl-2-nitro-phenyl)-carbamic acid tert.-butyl esters or (4-{alkenyl-, cycloalkenyl- or heterocycloalkenyl}-2-nitro-phenyl)-carbamic acid tert.-butyl esters by Stille-coupling of (2-nitro-4-tributylstannanyl-phenyl)-carbamic acid tert.-butyl ester with aryl halides or vinyl triflates or Stille-coupling of (4-iodo-2-nitrophenyl)-carbamic acid tert.-butyl ester with trialkylarylstannanes.

A mixture of (2-nitro-4-tributylstannanyl-phenyl)-carbamic acid tert.-butyl ester (Example D2) (525 mg, 1.0 mmol), aryl halide or vinyl triflate (0.95-6.0 mmol), anhydrous LiCl (126 mg, 3.0mmol) and Pd(PPh₃)₄ (5 mol%) in DME (3 mL) was stirred at 100 °C under argon atmosphere until tlc indicated complete consumption of the stannane. The reaction was cooled to 23 °C, stirred with sat. aqueous KF-sol. (5 mL) for 45 min, filtered through celite, washed with ether and the filtrate was dried over MgSO₄. Removal of the solvent in vacuum left a brown oil, which was purified by silica gel column chromatography with hexane/EtOAc to give the title compound.

Example E1

4-(4-tert.-Butoxycarbonylamino-3-nitro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert.-butyl ester.

Prepared from (2-nitro-4-tributylstannanyl-phenyl)-carbamic acid tert.-butyl ester (Example D2) (3.18 g, 6.06 mmol) and 4-trifluoromethylsulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid tert.-butyl ester (1.99 g, 6.0 mmol) [prepared from Boc-4-piperidone by treatment with LDA in THF at -78 °C followed by reaction with N-phenyl-bis(trifluoromethanesulfonimide) according to Wustrow et al. *Synthesis*, 1991, 1993] according to the general procedure E. Obtained as an orange solid (1.304 g, 52 %).

MS (ISP) 420 [(M+H)⁺], 442 [(M+Na)⁺] and 458 [(M+K)⁺]; mp 85-87 °C.

Example E2

(2-Nitro-4-thiazol-2-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (2-nitro-4-tributylstannanyl-phenyl)-carbamic acid tert.-butyl ester (Example D2) (1.0 g, 1.9 mmol) and 2-bromothiazole (0.56 mL, 6.27 mmol) according to the general procedure E. Obtained as a yellow solid (160 mg).

MS (EI) 321 (M⁺).

Example E3

[4-(6-Benzoyloxy-pyridin-3-yl)-2-nitro-phenyl]-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (728 mg, 2.0 mmol) and 2-(phenylmethoxy)-5-(trimethylstannyl)-pyridine (766 mg, 2.2 mmol) [CAS-No. [188881-22-3], WO 9709311] according to the general procedure E. Obtained as a yellow solid (876 mg).

MS (ISP) 422 [(M+H)⁺]; mp 119-122 °C.

General procedure F(Synthetic Scheme E):

Preparation of (4-alkynyl-2-nitro-phenyl)-carbamic acid tert.-butyl esters by Sonogashira-coupling of (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl esters with acetylenic compounds; also Sonogashira-coupling of (4-ethynyl-2-nitro-phenyl)-carbamic acid tert.-butyl esters with aryl halides; and Sonogashira-coupling of 8-iodo-4-aryl-1,3-dihydro-benzo[b][1,4]diazepin-2-ones with acetylenic compounds.

A mixture of the halide (3.0-4.5 mmol), acetylenic compound (3.0-4.5 mmol), Et₃N (13.5 mmol), PdCl₂(PPh₃)₂ (5 mol%) and PPh₃ (2.5 mol%) in THF (12 mL) [with very insoluble material DMF (up to 12 mL) could be added] was stirred for 20 min at 23 °C while being purged with Argon. CuI (1.2 mol%) was added and stirring was continued at 60 °C under Argon atmosphere until tlc indicated complete conversion of the minor component [cf. J. Org. Chem. 1998, 63, 8551]. The mixture was transferred into a separating funnel, 5% citric acid (50 mL) was added and the product was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with sat. NaHCO₃-sol. (50 mL) and brine (50 mL), followed by drying over MgSO₄. Removal of the solvent left a yellow residue, which was purified by silica gel column chromatography with hexane/EtOAc and/or triturated with hexane or aqueous EtOH to give the title compound.

Example F1

(2-Nitro-4-trimethylsilylanylethynyl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (3.64 g, 10 mmol) and trimethylsilylacetylene (4.2 mL, 30 mmol) according to the general procedure F. Obtained as a green oil (3.6 g).

MS (EI) 334 (M⁺).

Example F2

(4-Ethynyl-2-nitro-phenyl)-carbamic acid tert.-butyl ester.

To a solution of (2-nitro-4-trimethylsilanylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example F1) (3.54 g, 10.6 mmol) in MeOH (10 mL) and THF (20 mL) at 0 °C was added 1N NaOH (13 mL) and stirring was continued at 23 °C for 30 min. Poured into cold 5% citric acid, extracted with EtOAc (300 mL), washed with sat. NaHCO₃-sol. and brine, dried over MgSO₄. Removal of the solvent in vacuum left a dark brown oil, which was purified by silica gel column chromatography with hexane/EtOAc 19:1. Obtained as a yellow solid (2.4 g).

MS (EI) 262 (M⁺); mp 102 °C.

10 Example F3

(2-Nitro-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (5.64 g, 15 mmol) and phenylacetylene (2.47 mL, 22.5 mmol) according to the general procedure F. Obtained as a yellow solid (4.96 g).

15 MS (EI) 338 (M⁺); mp 146-148 °C.

Example F4

(2-Nitro-4-p-tolyethynyl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (728 mg, 2.0 mmol) and 4-tolylacetylene (349 mg, 3.0 mmol) according to the general procedure F. Obtained as a yellow solid (632 mg).

20 MS (EI) 352 (M⁺); mp 164-165 °C.

Example F5

[4-(2-Chloro-phenylethynyl)-2-nitro-phenyl]-carbamic acid tert.-butyl ester

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (1.82 g, 5.0 mmol) and 2-chlorophenylacetylene (1.02 g, 7.5 mmol) according to the general procedure F. Obtained as a yellow solid (1.8 g).

25 MS (ISN) 371 [(M-H)-] and 373 [(M+2-H)-]; mp 152-155 °C.

Example F6

[4-(4-Chloro-phenylethynyl)-2-nitro-phenyl]-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (728 mg, 2.0 mmol) and 4-chlorophenylacetylene (416 mg, 3.0 mmol) according to the general
5 procedure F. Obtained as a yellow solid (658 mg).

MS (EI) 372 (M^+) and 374 [$(M+2)^+$]; mp 213-218 °C.

Example F7

(2-Nitro-4-thiazol-2-ylethynyl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-ethynyl-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example F2)
10 (262 mg, 1.00 mmol) and 2-bromothiazole (0.14 mL, 1.50 mmol) according to the general procedure F. Obtained as a yellow solid (215 mg).

MS (ISN) 344 [$(M-H)^+$]; mp 137 °C.

Example F8

(2-Nitro-4-pyridin-2-ylethynyl-phenyl)-carbamic acid tert.-butyl ester.

15 Prepared from (4-ethynyl-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example F2) (262 mg, 1.0 mmol) and 2-bromopyridine (0.15 mL, 1.6 mmol) according to the general procedure F. Obtained as a yellow solid (293 mg).

MS (ISP) 340 [$(M+H)^+$]; mp 142-144 °C.

General procedure G (Synthetic Scheme E)

20 Preparation of the (2-amino-phenyl)-carbamic acid tert.-butyl esters by reduction of (2-nitro-phenyl)-carbamic acid tert.-butyl esters; Also preparation of 4-aryl-1,3-dihydro-benzo[b][1,4]diazepin-2-ones by reduction and concomitant cyclization of 3-aryl-N-(2-nitro-phenyl)-3-oxo-propionamides.

Method a: Catalytic hydrogenation

25 A mixture of the nitro compound (1.0 mmol) in MeOH or EtOH and THF (1:1 ca. 20 mL) and 10% Palladium on carbon (20 mg) or Raney-Ni (20 mg) was stirred vigorously at 23°C under hydrogen atmosphere until tlc indicated complete conversion. The catalyst was

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filtered off, washed thoroughly with MeOH or EtOH and THF (1:1), the solvent was removed in vacuum to give the title compound, which was generally pure enough for further transformations.

Method b: Reduction with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$

- 5 A mixture of the nitro compound (1.0 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (5.0 mmol) in EtOH (30 mL) was stirred at 70-80°C under Argon atmosphere until tlc indicated complete conversion [cf. *Tetr. Lett.*, 1984, 25, 839]. The reaction mixture was brought to pH 8 by addition of sat. NaHCO_3 -sol. and extracted with EtOAc (2 x 100 mL). The combined organic layer were washed with brine and dried over Na_2SO_4 . Removal of the solvent left a
10 yellow solid, which - if necessary - can be purified by silica gel column chromatography.

Method c: Reduction with Zn and NH_4Cl

- To a mixture of the nitro compound (1.0 mmol) in EtOH/THF/sat. NH_4Cl -sol. (1:1:1, 30 mL) was added Zinc dust (3.0 mmol) and the mixture was stirred at 70 °C under Argon atmosphere until tlc indicated complete conversion. Aqueous workup as described in
15 method b.

Method d: Reduction with Fe and HOAc

To a mixture of the nitro compound (1.0 mmol) in THF/ H_2O (4:1, 10-50 mL) was added Fe powder (6.0 mmol) and the mixture was stirred at 70 °C under Argon atmosphere until tlc indicated complete conversion. Aqueous workup as described in method b.

20 **Example G1**

(2-Amino-4-iodo-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-iodo-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example A1) (2.18 g, 6.0 mmol) by reduction with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (6.77 g, 30 mmol) according to the general procedure G (method b). Obtained as a brown-yellow solid (2.0 g).

- 25 MS (EI) 334 (M^+); mp 127-130 °C.

Example G2

(2-Amino-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester

34 Prepared from (2-nitro-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example F3) (403 mg, 1.19 mmol) by reduction with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.34 g, 5.96 mmol) according to the general procedure G (method b). Obtained as an orange solid (237 mg).

MS (ISP) 309 $[(\text{M}+\text{H})^+]$; mp 177-178 °C.

5 Example G3

(2-Amino-4-p-tolyethynyl-phenyl)-carbamic acid tert.-butyl ester

Prepared from (2-nitro-4-p-tolyethynyl-phenyl)-carbamic acid tert.-butyl ester (Example F4) (640 mg, 1.82 mmol) by reduction with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.0 g, 9.1 mmol) according to the general procedure G (method b). Obtained as a beige solid (569 mg).

10 MS (ISP) 323 $[(\text{M}+\text{H})^+]$; mp 175 °C.

Example G4

[2-Amino-4-(2-chloro-phenylethynyl)-phenyl]-carbamic acid tert.-butyl ester.

Prepared from (4-(2-chloro-phenylethynyl)-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example F5) (1.61 g, 4.3 mmol) by reduction with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (5.3 g, 23.5 mmol) according to the general procedure G (method b). Obtained as a light brown solid (1.1 g).

MS (EI) 342 (M^+) and 344 $[(\text{M}+2)^+]$; mp 120-122 °C.

Example G5

(3-Amino-4'-methoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4'-methoxy-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example B1) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white solid (77 mg).

MS (ISP) 315 $[(\text{M}+\text{H})^+]$ and 337 $[(\text{M}+\text{Na})^+]$.

Example G6

25 (2-Amino-4-thiophen-3-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (2-nitro-4-thiophen-3-yl-phenyl)-carbamic acid tert.-butyl ester (Example B2) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white solid (278 mg).

MS (ISP) 291 [(M+H)⁺].

5 Example G7

(2-Amino-4-furan-2-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-furan-2-yl-2-nitrophenyl)-carbamic acid tert.-butyl ester (Example B3) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a grey powder (212 mg).

10 MS (EI) 274 (M⁺).

Example G8

(3-Amino-4'-ethyl-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4'-ethyl-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example B4) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white solid (311 mg).

MS (ISP) 313 [(M+H)⁺] and 335 [(M+Na)⁺].

Example G9

(3-Amino-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example B5) (100 mg, 0.32 mmol) by catalytic hydrogenation with Pd/C according to the general procedure G (method a). Obtained as a white solid (85 mg).

MS (ISP) 285 [(M+H)⁺]; mp 137 °C.

Example G10

(3-Amino-2'-methoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (2'-methoxy-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example C1) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white solid (169 mg).

MS (ISP) 315 [(M+H)⁺].

5 Example G11

(2-Amino-4-furan-3-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-furan-3-yl-2-nitrophenyl)-carbamic acid tert.-butyl ester (Example B6) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a light brown solid. (744 mg).

10 MS (ISP) 275 [(M+H)⁺] and 297 [(M+Na)⁺]; mp 158-161 °C (dec.).

Example G12

(3-Amino-4'-chloro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4'-chloro-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example C2) by reduction with Zn/NH₄Cl according to the general procedure G (method c).

15 Obtained as a green solid (162 mg).

MS (EI) 318 (M⁺).

Example G13

[2-Amino-4-(4-chloro-phenylethynyl)-phenyl]-carbamic acid tert.-butyl ester.

20 Prepared from (4-(4-chloro-phenylethynyl)-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example F6) (606 mg, 1.63 mmol) by reduction with SnCl₂·2H₂O (1.83 g, 8.1 mmol) according to the general procedure G (method b). Obtained as a beige solid (406 mg).

MS (ISP) 343 [(M+H)⁺] and 345 [(M+2+H)⁺]; mp 170-173 °C.

Example G14

(2-Amino-4-naphthalen-1-yl-phenyl)-carbamic acid tert.-butyl ester.

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Prepared from (4-naphthalen-1-yl-2-nitro-phenyl)-carbamic acid tert-butyl ester (Example B7) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white solid (226 mg).

MS (EI) 334 (M^+).

5 Example G15

(2-Amino-4-thiazol-2-ylethynyl-phenyl)-carbamic acid tert.-butyl ester

Prepared from (2-nitro-4-thiazol-2-ylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example F7) (205 mg, 0.59 mmol) by reduction with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (668 mg, 2.95 mmol) according to the general procedure G (method b). Obtained as a yellow solid (108 mg).

10 MS (ISP) 316 [$(M+H)^+$]; mp 182 °C.

Example G16

(3-Amino-4'-methyl-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (4'-methyl-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example C4) by catalytic hydrogenation with Pd/C according to the general procedure G (method
15 a). Obtained as a white solid (125 mg).

MS (ISP) 299 [$(M+H)^+$], 321 [$(M+Na)^+$] and 337 [$(M+K)^+$].

Example G17

(2-Amino-4-pyridin-2-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (2-nitro-4-pyridin-2-yl-phenyl)-carbamic acid tert.-butyl ester (Example
20 C5) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a light brown solid (339 mg).

MS (ISP) 286 [$(M+H)^+$] and 308 [$(M+Na)^+$].

Example G18

(2-Amino-4-thiophen-2-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (2-nitro-4-thiophen-2-yl-phenyl)-carbamic acid tert.-butyl ester (Example C3) by catalytic hydrogenation with Pd/C according to the general procedure G (method a). Obtained as a beige powder (151 mg).

MS (ISP) 291 [(M+H)⁺].

5 Example G19

(2-Amino-4-pyridin-2-ylethynyl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (2-nitro-4-pyridin-2-ylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example F8) (262 mg, 0.772 mmol) by reduction with SnCl₂·2H₂O (871 mg, 3.86 mmol) according to the general procedure G (method b). Obtained as a light brown solid (130
10 mg).

MS (EI) 309 (M⁺); mp 178 °C.

Example G20

(3-Amino-3'-methyl-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (3'-methyl-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example
15 C6) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white powder (212 mg).

MS (EI) 298 (M⁺).

Example G21

(3-Amino-3',4'-dichloro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

20 Prepared from (3',4'-dichloro-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example C7) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white solid (485 mg).

MS (ISP) 353 (M⁺); mp 168-171 °C.

Example G22

25 (3-Amino-2'-chloro-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (2'-chloro-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example C8) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white solid (180 mg).

MS (ISP) 319 [(M+H)⁺], 341 [(M+Na)⁺] and 357 [(M+K)⁺].

5 Example G23

(3-Amino-2'-methyl-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (2'-methyl-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example C9) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white powder (281 mg).

10 MS (ISP) 299 [(M+H)⁺], 321 [(M+Na)⁺] and 337 [(M+K)⁺].

Example G24

(2-Amino-4-benzoyl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (4-benzoyl-2-nitro-phenyl)-carbamic acid tert.-butyl ester (Example D1) (280 mg, 0.82 mmol) by catalytic hydrogenation with Raney-Ni according to the general
15 procedure G (method a). Obtained as a yellow foam (269 mg).

MS (ISP) 313 [(M+H)⁺].

Example G25

(3-Amino-3'-methoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (3'-methoxy-3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester
20 (Example B8) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white solid (165 mg).

MS (ISP) 315 [(M+H)⁺].

Example G26

(2-Amino-4-pyridin-3-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (2-nitro-4-pyridin-3-yl-phenyl)-carbamic acid tert.-butyl ester (Example C10) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a grey powder (200 mg).

MS (ISP) 286 [(M+H)⁺].

5 Example G27

(3-Amino-4'-trifluoromethoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester.

Prepared from (3-nitro-4'-trifluoromethoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example B9) by catalytic hydrogenation with Raney-Ni according to the general procedure G (method a). Obtained as a white solid (371 mg).

10 MS (ISP) 369 [(M+H)⁺] and 391 [(M+Na)⁺].

Example G28

(2-Amino-4-pyridin-4-yl-phenyl)-carbamic acid tert.-butyl ester.

Prepared from (2-nitro-4-pyridin-4-yl-phenyl)-carbamic acid tert.-butyl ester (Example C11) by catalytic hydrogenation with Raney-Ni according to the general procedure G

15 (method a). Obtained as a light grey powder (305 mg).

MS (ISP) 286 [(M+H)⁺].

Example G29

4-(3-Amino-4-tert.-butoxycarbonylamino-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert.-butyl ester.

20 Prepared from 4-(4-tert.-butoxycarbonylamino-3-nitro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert.-butyl ester (Example E1) (256 mg, 0.61 mmol) by reduction with Zn/NH₄Cl according to the general procedure G (method c). Obtained as an orange foam (75 mg).

MS (EI) 389 (M⁺).

25 Example G30

[2-Amino-4-(6-benzyloxy-pyridin-3-yl)-phenyl]-carbamic acid tert.-butyl ester

Prepared from [4-(6-benzyloxy-pyridin-3-yl)-2-nitro-phenyl]-carbamic acid tert.-butyl ester (Example E3) (768 mg, 1.82 mmol) by reduction with Zn/NH₄Cl according to the general procedure G (method c). Obtained as a light brown solid (678 mg).

MS (ISP) 392 [(M+H)⁺]; mp 176-177 °C.

5 Example G31

[2-Amino-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-carbamic acid tert.-butyl ester

Prepared from [2-amino-4-(6-benzyloxy-pyridin-3-yl)-phenyl]-carbamic acid tert.-butyl ester (Example G30) (160 mg, 0.409 mmol) by catalytic hydrogenation with Pd/C according to the general procedure G (method a). Obtained as an off-white solid (136 mg).

10 MS (ISP) 302 [(M+H)⁺]; mp 120-124 °C (dec.).

General procedure H (Synthetic Scheme G)

Preparation of 3-aryl-3-oxo-propionic acids

The 3-aryl-3-oxo-propionic acids were prepared from the aryl acid chlorides and
15 bis(trimethylsilyl)malonate with Et₃N and LiBr in CH₃CN at 0 °C according to *Synth. Commun.* 1985, 15, 1039 (method a) or with n-BuLi in ether at -60 °C to 0 °C according to *Synthesis* 1979, 787 (method b).

General procedure I (Synthetic Scheme G)

Preparation of 6-aryl-2,2-dimethyl-[1,3]dioxin-4-ones

20 The 6-aryl-2,2-dimethyl-[1,3]dioxin-4-ones were prepared from 3-aryl-3-oxo-propionic acids and catalytic amount of conc. H₂SO₄ or TFA in isopropenyl acetate at 23 °C according to *Chem. Pharm. Bull.* 1983, 31, 1896. The final products were purified by silica gel column chromatography with hexane/EtOAc.

Example H1

25 2,2-Dimethyl-6-thiophen-2-yl-[1,3]dioxin-4-one.

The 3-oxo-3-thiophen-2-yl-propionic acid was prepared from thiophene-2-carbonyl chloride (5.3 mL, 50 mmol) and bis(trimethylsilyl)malonate (25.6 mL, 100 mmol) with n-

BuLi (1.6M in hexane, 62.5 mL) in ether at -60 °C to 0 °C according to the general procedure H (method b). The crude material (7.88 g) was transformed into the title compound by stirring in isopropenyl acetate and TFA according to the general procedure J. Obtained as a yellow solid (4.09 g).

5 MS (EI) 210 (M^+); mp 42 °C (dec.).

Example H2

6-(3-Chloro-thiophen-2-yl)-2,2-dimethyl-[1,3]dioxin-4-one.

10 The 3-(3-chloro-thiophen-2-yl)-3-oxo-propionic acid was prepared from 3-chloro-thiophene-2-carbonyl chloride (7.82 g, 43.2 mmol) and bis(trimethylsilyl)malonate (11.6 mL, 45.4 mmol) with Et_3N (12.65 mL, 90.7 mmol) and LiBr (3.53 g, 47.5 mmol) in CH_3CN at 0 °C according to general procedure H (method a). The crude material (5.69 g) was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure J. Obtained as an orange solid (2.3 g).

MS (EI) 244 (M^+) and 246 [$(M+2)^+$]; mp 88-89 °C (dec.).

15 Example H3

6-(3-Cyano-thiophen-2-yl)-2,2-dimethyl-[1,3]dioxin-4-one.

20 The 3-(3-cyano-thiophen-2-yl)-3-oxo-propionic acid was prepared from 3-cyano-thiophene-2-carbonyl chloride (24.33 g, 140.6 mmol) and bis(trimethylsilyl)malonate (38.0 mL, 147.7 mmol) with Et_3N (41 mL, 295.4 mmol) and LiBr (13.5 g, 154.7 mmol) in CH_3CN at 0 °C according to general procedure H (method a). The crude material (24.8 g) was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure J. Obtained as an orange solid (5.6 g).

MS (EI) 235 (M^+); mp 116-120 °C (dec.).

Example H4

25 3-(2,2-Dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile.

The 3-(3-cyano-phenyl)-3-oxo-propionic acid was prepared from 3-cyanobenzoyl chloride (828 mg, 5 mmol) and bis(trimethylsilyl)malonate (2.56 mL, 10 mmol) with n-BuLi (1.6M in hexane, 6.25 mL) in ether at -60 °C to 0 °C according to general procedure H (method b). The crude material (1.04 g) was transformed into the title compound by

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stirring in isopropenyl acetate and TFA according to general procedure J. Obtained as a light yellow solid (0.8 g).

MS (EI) 229 (M^+); mp 138 °C (dec.).

Example H5

5 2,2-Dimethyl-6-(3-trifluoromethyl-phenyl)-[1,3]dioxin-4-one.

The 3-oxo-3-(3-trifluoromethyl-phenyl)-propionic acid was prepared from 3-trifluoromethylbenzoyl chloride (10 mL, 67.6 mmol) and bis(trimethylsilyl)malonate (18.2 mL, 71 mmol) with Et_3N (20 mL, 142 mmol) and LiBr (6.46 g, 74.4 mmol) in CH_3CN at 0 °C according to general procedure H (method a). The crude material (7.0 g of the obtained 10 15.4 g) was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure J. Obtained as a light yellow solid (5.3 g).

MS (EI) 272 (M^+); mp 77-78 °C (dec.).

Example H6

6-(3-Chloro-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one.

15 The 3-(3-chloro-phenyl)-3-oxo-propionic acid was prepared from 3-chlorobenzoyl chloride (11 mL, 85.7 mmol) and bis(trimethylsilyl)malonate (23.0 mL, 90.0 mmol) with Et_3N (25 mL, 180 mmol) and LiBr (8.19 g, 94.3 mmol) in CH_3CN at 0 °C according to general procedure H (method a). The crude material (17.1 g) was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general 20 procedure J. Obtained as a yellow-brown solid (8.0 g).

MS (EI) 238 (M^+) and 240 [$(M+2)^+$]; mp 87-88 °C (dec.).

Example H7

6-(3-Iodo-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one.

25 The 3-(3-iodo-phenyl)-3-oxo-propionic acid was prepared from 3-iodobenzoyl chloride (21.0 g, 78.8 mmol) and bis(trimethylsilyl)malonate (21.0 mL, 82.8 mmol) with Et_3N (23 mL, 165.5 mmol) and LiBr (7.54 g, 86.7 mmol) in CH_3CN at 0 °C according to general procedure H (method a). The crude material (21.9 g) was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure J. Obtained as a yellow solid (9.6 g).

MS (EI) 330 (M^+); mp 79-80 °C (dec.).

Example H8

2,2-Dimethyl-6-(3-trifluoromethoxy-phenyl)-[1,3]dioxin-4-one.

The 3-oxo-3-(3-trifluoromethoxy-phenyl)-propionic acid was prepared from 3-trifluoromethoxybenzoyl chloride and bis(trimethylsilyl)malonate with Et_3N and $LiBr$ in CH_3CN at 0 °C according to general procedure H (method a). The crude material was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure J. Obtained as an orange solid (2.27 g).

MS (EI) 288 (M^+); mp 49-54 °C (dec.).

10 **Example H9**

2,2-Dimethyl-6-pyridin-4-yl-[1,3]dioxin-4-one.

Prepared from 3-oxo-3-pyridin-4-yl-propionic acid [prepared from 4-acetylpyridine, magnesium methylcarbonate and CO_2 in DMF at 120 °C according to *Journal of Antibiotics* 1978, 31, 1245] by treatment with acetone, TFA and TFAA at -78 °C to 23 °C. Obtained as a white solid (1.3 g).

MS (EI) 205 (M^+)

Example H10

6-(3-Imidazol-1-yl-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one.

The 3-(3-imidazol-1-yl-phenyl)-3-oxo-propionic acid was prepared from 3-(1H-imidazol-1-yl)benzoyl chloride hydrochloride [prepared by treatment of 3-(1H-imidazol-1-yl)benzoic acid (*J. Med. Chem.* 1987, 30, 1342; CAS-No. [108035-47-8] with $SOCl_2$) and bis(trimethylsilyl)malonate with Et_3N and $LiBr$ in CH_3CN at 0 °C according to general procedure H (method a). The crude material was transformed into the title compound by stirring in isopropenyl acetate and conc. H_2SO_4 according to general procedure J. Obtained as an orange semisolid (617 g).

MS (EI) 270 (M^+).

Example H11

2,2-Dimethyl-6-(3-methoxy-phenyl)-[1,3]dioxin-4-one.

The 3-(3-methoxy-phenyl)-3-oxo-propionic acid was prepared from 3-methoxybenzoyl chloride (10.3 g, 60.4 mmol) and bis(trimethylsilyl)malonate (16.2 mL, 63.4 mmol) with Et₃N (17.7 mL, 127 mmol) and LiBr (5.77 g, 66.4 mmol) in CH₃CN at 0 °C according to general procedure H (method a). The crude material (6.38 g) was transformed into the title compound by stirring in isopropenyl acetate and conc. H₂SO₄ according to general procedure J. Obtained as a yellow oil (640 mg).

MS (ISP) 235 [(M+H)⁺] and 252 [(M+NH₄)⁺].

General procedure K (Synthetic Scheme B)

Preparation of {2-[3-aryl-3-oxo-propionylamino]-4-aryl-phenyl}-carbamic acid tert-butyl ester by reaction of (2-amino-4-aryl-phenyl)-carbamic acid tert-butyl esters with ethyl 3-aryl-3-oxo-propionates or 6-aryl-2,2-dimethyl-[1,3]dioxin-4-ones; also 3-aryl-N-(2-nitro-4-aryl-phenyl)-3-oxo-propionamides by reaction of 2-nitro-4-aryl-phenylamines with 6-aryl-2,2-dimethyl-[1,3]dioxin-4-ones.

A mixture of the (2-amino-4-aryl-phenyl)-carbamic acid tert-butyl ester or 2-nitro-4-aryl-phenylamine (1.0 mmol) and excess (1.2-1.5 mmol) of the ethyl 3-aryl-3-oxo-propionate [prepared from the aryl acid chloride and ethyl malonate potassium salt with Et₃N and MgCl₂ in CH₃CN at 23 °C according to *Synthesis* 1993, 290] or 6-aryl-2,2-dimethyl-[1,3]dioxin-4-one was refluxed in toluene (8 mL) until thin layer chromatography indicated complete consumption of the amine. The solution was allowed to cool to 23 °C, whereupon the product generally crystallized (in cases where crystallization failed to appear it was induced by addition of hexane). The solid was filtered off, washed with ether or mixtures of ether/hexane and dried in vacuum to give the {2-[3-aryl-3-oxo-propionylamino]-4-aryl-phenyl}-carbamic acid tert-butyl esters or 3-aryl-N-(2-nitro-4-aryl-phenyl)-3-oxo-propionamides, which was used directly in the following step or - if necessary - was purified by recrystallization or by silica gel column chromatography.

Example K1

{2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-iodo-phenyl}-carbamic acid tert.-butyl ester.

Prepared from (2-amino-4-iodo-phenyl)-carbamic acid tert.-butyl ester (Example G1) (900 mg, 2.7 mmol) and 3-(3-cyano-phenyl)-3-oxo-propionic acid ethyl ester (880 mg, 4.1 mmol) according to the general procedure K. Obtained as a yellow solid (1.2 g).

MS (ISP) 506 [(M+H)⁺] and 528 [(M+Na)⁺]; mp 182-183 °C.

Example K2

{2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-phenylethynyl-phenyl}-carbamic acid tert.-butyl ester.

Prepared from (2-amino-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example G2) (214 mg, 0.7 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (250 mg, 1.1 mmol) according to the general procedure K. Obtained as a light yellow solid (260 mg).

MS (ISP) 480 [(M+H)⁺], 497 [(M+NH₄)⁺] and 502 [(M+Na)⁺]; mp 168-170 °C (dec.).

Example K3

{3-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4'-methoxy-biphenyl-4-yl}-carbamic acid tert.-butyl ester.

Prepared from (3-amino-4'-methoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G5) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. Obtained as a light brown solid (207 mg).

MS (ISP) 486 [(M+H)⁺], 508 [(M+Na)⁺] and 524 [(M+K)⁺]

Example K4

{2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-thiophen-3-yl-phenyl}-carbamic acid tert.-butyl ester.

Prepared from (2-amino-4-thiophen-3-yl-phenyl)-carbamic acid tert.-butyl ester (Example G6) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example

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H4) according to the general procedure K. Obtained as a brown solid (104 mg) and used crude in the next step (Example 7).

Example K5

- 5 {2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-furan-2-yl-phenyl}-carbamic acid tert.-butyl ester.

Prepared from (2-amino-4-furan-2-yl-phenyl)-carbamic acid tert.-butyl ester (Example G7) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. Obtained as a beige powder (271 mg).

- 10 MS (ISP) 446 [(M+H)⁺], 468 [(M+Na)⁺] and 484 [(M+K)⁺]

Example K6

{3-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-biphenyl-4-yl}-carbamic acid tert.-butyl ester.

- 15 Prepared from (3-amino-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G9) (250 mg, 0.88 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (243 mg, 1.06 mmol) according to the general procedure K. Obtained as a white solid (324 mg).

MS (ISP) 456 [(M+H)⁺]; mp 168 °C (dec.)

Example K7

- 20 {2-[3-(3-Iodo-phenyl)-3-oxo-propionylamino]-4-phenylethynyl-phenyl}-carbamic acid tert.-butyl ester.

- Prepared from (2-amino-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example G2) (1.0 g, 3.24 mmol) and 6-(3-iodo-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H7) (1.78 g, 3.57 mmol) according to the general procedure K. Obtained as a
25 light yellow solid (1.9 g).

MS (ISP) 581 [(M+H)⁺] and 603 [(M+Na)⁺]; mp 193-195 °C (dec.)

Example K8

{3-[3-(3-Azido-phenyl)-3-oxo-propionylamino]-biphenyl-4-yl}-carbamic acid tert.-butyl ester.

Prepared (3-amino-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G9) (569 mg, 2 mmol) and 3-(3-azido-phenyl)-3-oxo-propionic acid ethyl ester (700 mg, 3 mmol;

- 5 prepared from 3-azido-benzoyl chloride (*Bioorg. Chem* 1986, 134) using the procedure described in *Synthesis*, 1993, 290, method A; MS (EI) 233 (M^+) according to the general procedure K. Obtained as an orange solid (367 mg).
MS (ISP) 472 [$(M+H)^+$] and 494 [$(M+Na)^+$]

Example K9

- 10 {2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-furan-3-yl-phenyl}-carbamic acid tert.-butyl ester.

Prepared from (2-amino-4-furan-3-yl-phenyl)-carbamic acid tert.-butyl ester (Example G11) and 3-(3-cyano-phenyl)-3-oxo-propionic acid ethyl ester (*Pol. J. Chem.* 1978, 25) according to the general procedure K. Obtained as an orange solid (460 mg).

- 15 MS (ISP) 446 [$(M+H)^+$], 463 [$(M+NH_4)^+$] and 468 [$(M+Na)^+$]

Example K10

{2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-naphthalen-1-yl-phenyl}-carbamic acid tert.-butyl ester.

- Prepared from (2-amino-4-naphthalen-1-yl-phenyl)-carbamic acid tert.-butyl ester
20 (Example G14) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. Obtained as an off-white solid (92 mg) and used crude in the next step (Example 20).

Example K11

- 25 {2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-thiazol-2-ylethynyl-phenyl}-carbamic acid tert.-butyl ester.

Prepared from (2-amino-4-thiazol-2-ylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example G11) (89 mg, 0.28 mmol) and 3-(3-cyano-phenyl)-3-oxo-propionic acid ethyl ester (*Pol. J. Chem.* 1978, 25) (74 mg, 0.34 mmol) according to the general procedure K. Obtained as a light yellow solid (129 mg).

MS (ISP) 487 [(M+H)⁺]; mp 131 °C

Example K12

{2-[3-(3-Chloro-thiophen-2-yl)-3-oxo-propionylamino]-4-pyridin-2-yl-phenyl}-carbamic acid tert.-butyl ester.

- 5 Prepared from (2-amino-4-pyridin-2-yl-phenyl)-carbamic acid tert.-butyl ester (Example G17) and 6-(3-chloro-thiophen-2-yl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H2) according to the general procedure K. Obtained as an amorphous brown solid (145 mg).

MS (ISP) 472 [(M+H)⁺] and 494 [(M+Na)⁺]

Example K13

- 10 {2-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4-pyridin-2-yl-phenyl}-carbamic acid tert.-butyl ester.

Prepared from (2-amino-4-pyridin-2-yl-phenyl)-carbamic acid tert.-butyl ester (Example G17) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. Obtained as a light brown solid (90 mg).

- 15 MS (ISP) 457 [(M+H)⁺] and 479 [(M+Na)⁺].

Example K14

[3-(3-Oxo-3-thiophen-3-yl-propionylamino)-biphenyl-4-yl]-carbamic acid tert.-butyl ester

- 20 Prepared from (3-amino-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G9) (144 mg, 0.51 mmol) and 3-oxo-3-thiophen-3-yl-propionic acid ethyl ester (FR 7191887) (151 mg, 0.76 mmol) according to the general procedure K. Obtained as a yellow foam (181 mg).

MS (ISN) 435 [(M+H)⁺].

Example K15

- 25 {3-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-3'-methyl-biphenyl-4-yl}-carbamic acid tert.-butyl ester.

Prepared from (3-amino-3'-methyl-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G20) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. Obtained as a viscous orange oil (290 mg).

MS (ISP) 470 [(M+H)⁺], 492 [(M+Na)⁺] and 508 [(M+K)⁺].

5 Example K16

{3-[3-(3-Chloro-thiophen-2-yl)-3-oxo-propionylamino]-2'-methyl-biphenyl-4-yl}-carbamic acid tert.-butyl ester.

Prepared from (3-amino-2'-methyl-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G23) and 6-(3-chloro-thiophen-2-yl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H2) according to the general procedure K. Obtained as a viscous brown oil (154 mg).

MS (ISP) 485 [(M+H)⁺], 507 [(M+Na)⁺] and 523 [(M+K)⁺].

Example K17

{4-Benzoyl-2-[3-(3-chloro-phenyl)-3-oxo-propionylamino]-phenyl}-carbamic acid tert.-butyl ester.

15 Prepared from (2-amino-4-benzoyl-phenyl)-carbamic acid tert.-butyl ester (Example G24) (205 mg, 0.66 mmol) and 6-(3-chloro-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H6) (174 mg, 0.73 mmol) according to the general procedure K. Obtained as a brown foam (232 mg).

MS (ISP) 493 [(M+H)⁺].

20 Example K18

{4-Benzoyl-2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-phenyl}-carbamic acid tert.-butyl ester.

Prepared from (2-amino-4-benzoyl-phenyl)-carbamic acid tert.-butyl ester (Example G24) (375 mg, 1.20 mmol) and 3-(3-cyano-phenyl)-3-oxo-propionic acid ethyl ester (Pol. J.

25 Chem.1978, 25) (313 mg, 1.44 mmol) according to the general procedure K. Obtained as a light yellow solid (170 mg).

MS (ISP) 484 [(M+H)⁺], 501 [(M+NH₄)⁺] and 506 [(M+Na)⁺]; mp 168 °C (dec.)

Example K19

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[4-Benzoyl-2-(3-oxo-3-thiophen-2-yl-propionylamino)-phenyl]-carbamic acid tert.-butyl ester.

Prepared from (2-amino-4-benzoyl-phenyl)-carbamic acid tert.-butyl ester (Example G24) (259 mg, 0.5 mmol) and 2,2-dimethyl-6-thiophen-2-yl-[1,3]dioxin-4-one (Example H1) (135 mg, 0.55 mmol) according to the general procedure K. Obtained as a light yellow solid (60 mg).

MS (ISP) 465 [(M+H)⁺]

Example K20

{3-[3-(3-Chloro-thiophen-2-yl)-3-oxo-propionylamino]-biphenyl-4-yl}-carbamic acid tert.-butyl ester.

Prepared from (3-amino-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G9) (100 mg, 0.35 mmol) and 6-(3-chloro-thiophen-2-yl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H2) (95 mg, 0.39 mmol) according to the general procedure K. Obtained as a white solid (127 mg).

MS (ISP) 471 [(M+H)⁺]; mp 165 °C.

Example K21

{3-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-3'-methoxy-biphenyl-4-yl}-carbamic acid tert.-butyl ester.

Prepared from (3-amino-3'-methoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G25) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. Obtained as a beige solid (238 mg).

MS (ISP) 486 [(M+H)⁺], 508 [(M+Na)⁺] and 524 [(M+K)⁺].

Example K22

{5-(6-Oxo-1,6-dihydro-pyridin-3-yl)-2-(3-oxo-3-thiophen-2-yl-propionylamino)-phenyl}-carbamic acid tert.-butyl ester

Prepared from [2-amino-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-carbamic acid tert.-butyl ester (Example G31) (200 mg, 0.664 mmol) and 2,2-dimethyl-6-thiophen-2-yl-

[1,3]dioxin-4-one (Example H1) (140 mg, 0.665 mmol) according to the general procedure K. Obtained as a beige solid (235 mg).

MS (ISP) 454 [(M+H)⁺]

Example K23

- 5 {4-(6-Benzyloxy-pyridin-3-yl)-2-[3-oxo-3-(3-trifluoromethyl-phenyl)-propionylamino]-phenyl}-carbamic acid tert.-butyl ester.

Prepared from [2-amino-4-(6-benzyloxy-pyridin-3-yl)-phenyl]-carbamic acid tert.-butyl ester (Example G30) (203 mg, 0.52 mmol) and 2,2-dimethyl-6-(3-trifluoromethyl-phenyl)-[1,3]dioxin-4-one (Example H5) (150 mg, 0.55 mmol) according to the general procedure K. Obtained as an off-white solid (213 mg).

MS (ISP) 606 [(M+H)⁺]; mp 190 °C (dec.).

Example K24

{3-[3-(3-Cyano-phenyl)-3-oxo-propionylamino]-4'-trifluoromethoxy-biphenyl-4-yl}-carbamic acid tert.-butyl ester.

- 15 Prepared from (3-amino-4'-trifluoromethoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G27) and 3-(3-cyano-phenyl)-3-oxo-propionic acid ethyl ester (*Pol. J. Chem.* 1978, 25) according to the general procedure K. Obtained as a brown semisolid (94 mg).

MS (ISP) 540 [(M+H)⁺], 557 [(M+NH₄)⁺] and 562 [(M+Na)⁺].

20 Example K25

4-[4-tert.-Butoxycarbonylamino-3-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert.-butyl ester

- Prepared from 4-(3-amino-4-tert.-butoxycarbonylamino-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert.-butyl ester (Example G29) (544 mg, 1.4 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (336 mg, 1.5 mmol) according to the general procedure K. Obtained as an orange solid (722 mg).

MS (ISP) 561 [(M+H)⁺]; mp 75-79 °C (dec.).

Example K26

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{4-(6-Benzyloxy-pyridin-3-yl)-2-[3-(3-chloro-thiophen-2-yl)-3-oxo-propionylamino]-phenyl}-carbamic acid tert.-butyl ester

Prepared from [2-amino-4-(6-benzyloxy-pyridin-3-yl)-phenyl]-carbamic acid tert.-butyl ester (Example G30) (216 mg, 0.55 mmol) and 6-(3-chloro-thiophen-2-yl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H2) (142 mg, 0.58 mmol) according to the general procedure K. Obtained as a beige solid (172 mg).

MS (ISP) 578 [(M+H)⁺]; mp 158-159 °C (dec.).

Example K27

{2-[3-(3-Imidazol-1-yl-phenyl)-3-oxo-propionylamino]-4-phenylethynyl-phenyl}-carbamic acid tert.-butyl ester

Prepared from (2-amino-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example G2) (154 mg, 0.5 mmol) and 6-(3-imidazol-1-yl-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H10) (135 mg, 0.5 mmol) according to the general procedure K. Obtained as an orange oil (179 mg).

MS (ISN) 519 [(M-H)⁻].

General procedure M (Synthetic Scheme B)

Preparation of 4,8-diaryl-1,3-dihydro-benzo[b][1,4]diazepin-2-ones, 4-aryl-8-aryl-1,3-dihydro-benzo[b][1,4]diazepin-2-ones or 4-aryl-8-arylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-ones

A suspension of the {2-[3-aryl-3-oxo-propionylamino]-4-aryl-phenyl}-carbamic acid tert-butyl ester or {2-[3-aryl-3-oxo-propionylamino]-4-arylethynyl-phenyl}-carbamic acid tert-butyl ester (1.0 mmol) in CH₂Cl₂ (5 mL) [anisole or thioanisole (5 mmol) can be added if necessary] was treated with TFA (0.5-5.0 mL) at 0 °C and stirring was continued at 23 °C until tlc indicated complete consumption of the starting material. The solvent was removed in vacuum, the residue treated with little ether, whereupon it crystallized. The solid was stirred with sat. NaHCO₃-sol., filtered, washed with H₂O and ether or mixtures of ether/hexane and was dried to give the title compound, which if necessary can be purified by crystallization from THF/CH₂Cl₂/ether/hexane.

Example 1

3-(7-Iodo-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from 2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-iodo-phenyl]-carbamic acid tert.-butyl ester (Example K1) (1.15 g, 2.3 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a yellow solid (880 mg).

MS (EI) 387 (M^+); mp 198-200 °C (dec.)

5 Example 2

3-(4-Oxo-7-phenylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from 2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-phenylethynyl-phenyl]-carbamic acid tert.-butyl ester (Example K2) (230 mg, 0.48 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow solid (135 mg).

MS (EI) 361 (M^+); mp 245 °C (dec.)

Example 3

3-(4-Oxo-7-p-tolyethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from (2-amino-4-p-tolyethynyl-phenyl)-carbamic acid tert.-butyl ester Example G3) (161 mg, 0.5 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (183 mg, 0.6 mmol) according to the general procedure K. Obtained as a light yellow solid (228 mg). This material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow solid (86 mg).

MS (EI) 375 (M^+); mp 236-239 °C (dec.).

Example 4

3-[7-(2-Chloro-phenylethynyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from [2-amino-4-(2-chloro-phenylethynyl)-phenyl]-carbamic acid tert.-butyl ester (Example G4) (172 mg, 0.5 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (230 mg, 0.75 mmol, 75% pure) according to the general procedure K. Obtained as a yellow solid (321 mg). This material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow solid (148 mg).

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MS (EI) 395 (M^+) and 397 [$(M+2)^+$]; mp 239-240 °C (dec.).

Example 5

4-(3-Chloro-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from (2-amino-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester

- 5 (Example G2) and 6-(3-chloro-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H6) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as an orange solid (155 mg).

MS (EI): 370 (M^+)

10 Example 6

3-[7-(4-Methoxy-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from {3-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4'-methoxy-biphenyl-4-yl}-carbamic acid tert.-butyl ester (Example K3) by treatment with TFA in CH_2Cl_2

- 15 according to the general procedure M. Obtained as a light yellow powder (122 mg).

MS (ISP) 368 [$(M+H)^+$]; mp 236-237 °C (dec.).

Example 7

3-(4-Oxo-7-thiophen-3-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from {2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-thiophen-3-yl-phenyl}-carbamic acid tert.-butyl ester (Example K4) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a beige solid (54 mg).

- 20

MS (EI) 343 (M^+); mp 238-243 °C (dec.).

Example 8

3-(7-Furan-2-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

- 25 Prepared from {2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-furan-2-yl-phenyl}-carbamic acid tert.-butyl ester (Example K5) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a brown powder (73 mg).

MS (EI) 327 (M^+); mp 205-210 °C (dec.).

Example 9

3-[7-(4-Ethyl-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from (3-amino-4'-ethyl-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G8) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a beige solid (67 mg).

MS (EI) 365 (M^+); mp 225-229 °C (dec.).

10 **Example 10**

3-(4-Oxo-7-phenyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from (3-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example K6) (268 mg, 0.59 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a white solid (188 mg).

15 MS (EI) 337 (M^+); mp 238-240 °C (dec.).

Example 11

4-(3-Iodo-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from {2-[3-(3-iodo-phenyl)-3-oxo-propionylamino]-4-phenylethynyl-phenyl}-carbamic acid tert.-butyl ester (Example K7) (871 mg, 1.5 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow solid (542 mg).

MS (EI) 462 (M^+); mp 227-229 °C (dec.).

Example 12

4-(3-Azido-phenyl)-8-phenyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

25 Prepared from {3-[3-(3-azido-phenyl)-3-oxo-propionylamino]-biphenyl-4-yl}-carbamic acid tert.-butyl ester (Example K8) (360 mg, 0.763 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a beige solid (106 mg).

MS (EI) 353 (M^+).

Example 13

3-[7-(2-Methoxy-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

- 5 Prepared from (3-amino-2'-methoxy-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G10) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light green powder (30 mg).

10 MS (EI) 367 (M^+)

Example 14

3-(7-Furan-3-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

- Prepared from {2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-furan-3-yl-phenyl}-carbamic acid tert.-butyl ester (Example K9) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow powder (73 mg).
- 15

MS (EI) 327 (M^+); mp 228-233 °C (dec.).

Example 15

3-[7-(4-Chloro-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

- Prepared from (3-amino-4'-chloro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G12) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a yellow powder (79 mg).
- 20

MS (EI) 371 (M^+); mp 244-250 °C (dec.).

25 **Example 16**

3-[7-(4-Chloro-phenylethynyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from [2-amino-4-(4-chloro-phenylethynyl)-phenyl]-carbamic acid tert.-butyl ester (Example G13) (187 mg, 0.5 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (184 mg, 0.6 mmol) according to the general procedure K. The obtained material (234 mg) was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow powder (93 mg).

MS (EI) 395 (M^+) and 397 [$(\text{M}+2)^+$]; mp 237-240 °C (dec.).

Example 17

8-Phenyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from (3-amino-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G9) (69 mg, 0.243 mmol) and 2,2-dimethyl-6-thiophen-2-yl-[1,3]dioxin-4-one (Example H1) (54 mg, 0.257 mmol) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a brown solid (46 mg).

MS (ISP) 319 [$(\text{M}+\text{H})^+$].

Example 18

8-Phenylethynyl-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from (2-amino-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example G2) and 2,2-dimethyl-6-(3-trifluoromethoxy-phenyl)-[1,3]dioxin-4-one (Example H8) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a yellow solid (157 mg).

MS (EI) 404 (M^+).

Example 19

4-(3-Chloro-phenyl)-8-phenyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from (3-amino-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G9) (284 mg, 1.0 mmol) and 6-(3-Chloro-phenyl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H6) (358 mg, 1.2 mmol) according to the general procedure K. The obtained material (339 mg) was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a yellow solid (188 mg).

MS (EI) 346 (M^+) and 348 [$(M+2)^+$]; mp 208 °C (dec.).

Example 20

3-(7-Naphthalen-1-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from {2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-naphthalen-1-yl-phenyl}-carbamic acid tert.-butyl ester (Example K10) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow powder (41 mg).

MS (ISP) 388 [$(M+H)^+$]; mp 240-245 °C (dec.)

Example 21

3-(4-Oxo-7-thiazol-2-ylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from {2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-thiazol-2-ylethynyl-phenyl}-carbamic acid tert.-butyl ester (Example K11) (119 mg, 0.24 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a yellow solid (36 mg).

MS (EI) 368 (M^+); mp 230 °C (dec.).

Example 22

3-(4-Oxo-7-p-tolyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from (3-amino-4'-methyl-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G16) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a white solid (76 mg).

MS (ISP) 352 [$(M+H)^+$]; mp 242-245 °C (dec.).

Example 23

4-(3-Chloro-thiophen-2-yl)-8-pyridin-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from {2-[3-(3-chloro-thiophen-2-yl)-3-oxo-propionylamino]-4-pyridin-2-yl-phenyl}-carbamic acid tert.-butyl ester (Example K12) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light brown powder (51 mg).

MS (EI) 353 (M^+); mp 220-225 °C (dec.).

Example 24

3-(4-Oxo-7-thiophen-2-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from (2-amino-4-thiophen-2-yl-phenyl)-carbamic acid tert.-butyl ester

- 5 (Example G18) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow solid (108 mg).

MS (EI) 343 (M^+); mp >250 °C (dec.).

10 **Example 25**

8-Iodo-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from (2-amino-4-iodo-phenyl)-carbamic acid tert.-butyl ester (Example G1) and 2,2-dimethyl-6-thiophen-2-yl-[1,3]dioxin-4-one (Example H1) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA

- 15 in CH_2Cl_2 according to the general procedure M. Obtained as a yellow solid (30 mg).

MS (EI) 368 (M^+); mp >260 °C.

Example 26

3-(4-Oxo-7-pyridin-2-ylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

- 20 Prepared from (2-amino-4-pyridin-2-ylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example G19) (124 mg, 0.4 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (147 mg, 0.48 mmol) according to the general procedure K. The obtained material (199 mg) was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a yellow solid (124 mg).

- 25 MS (EI) 362 (M^+); mp 229-231 °C (dec.).

Example 27

4-(3-Methoxy-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

251

Prepared from (2-amino-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example G2) and 2,2-dimethyl-6-(3-methoxy-phenyl)-[1,3]dioxin-4-one (Example H11) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a
5 light yellow solid (131 mg).

MS (EI) 366 (M⁺).

Example 28

3-(4-Oxo-7-pyridin-2-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from {2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4-pyridin-2-yl-phenyl}-
10 carbamic acid tert.-butyl ester (Example K13) by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a brown powder (29 mg).

MS (EI) 338 (M⁺); mp 243-244 °C (dec.).

Example 29

8-Phenyl-4-thiophen-3-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

15 Prepared from [3-(3-oxo-3-thiophen-3-yl-propionylamino)-biphenyl-4-yl]-carbamic acid tert.-butyl ester (Example K14) (110 mg, 0.25 mmol) by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a light yellow solid (53 mg).

MS (EI) 318 (M⁺); mp 233 °C (dec.).

Example 30

20 3-(4-Oxo-7-m-tolyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from {3-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-3'-methyl-biphenyl-4-yl}-carbamic acid tert.-butyl ester (Example K15) by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a light yellow powder (145 mg).

MS (ISP) 352 [(M+H)⁺]; mp 248-251 °C (dec.).

Example 31

3-[7-(3,4-Dichloro-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from (3-amino-3',4'-dichloro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G21) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a light yellow solid (150 mg).

MS (EI) 405 (M⁺); mp 252-255 °C (dec.).

Example 32

8-Phenyl-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from (3-amino-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G9) (284 mg, 1.0 mmol) and 2,2-dimethyl-6-(3-trifluoromethyl-phenyl)-[1,3]dioxin-4-one (Example H5) (408 mg, 1.2 mmol) according to the general procedure K. The obtained material (392 mg) was deprotected and cyclized by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a yellow solid (238 mg).

MS (EI) 380 (M⁺); mp 210 °C (dec.).

Example 33

3-[7-(2-Chloro-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from (3-amino-2'-chloro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example G22) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a white powder (43 mg).

MS (ISP) 372 [(M+H)⁺]; mp 240-244 °C (dec.).

Example 34

4-(3-Chloro-thiophen-2-yl)-8-o-tolyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from {3-[3-(3-chloro-thiophen-2-yl)-3-oxo-propionylamino]-2'-methyl-biphenyl-4-yl}-carbamic acid tert.-butyl ester (Example K16) by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a light yellow powder (60 mg).

MS (ISP) 366 (M⁺) and 368 [(M+2)⁺]; mp 247-248 °C (dec.).

Example 35

8-Benzoyl-4-(3-chloro-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from {4-benzoyl-2-[3-(3-chloro-phenyl)-3-oxo-propionylamino]-phenyl}-
carbamic acid tert.-butyl ester (Example K17) (193 mg, 0.39 mmol) by treatment with TFA
5 in CH₂Cl₂ according to the general procedure M. Obtained as a light yellow solid (93 mg).

MS (EI) 374 (M⁺) and 376 [(M+2)⁺]; mp 199-202 °C (dec.).

Example 36

3-(7-Benzoyl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from {4-benzoyl-2-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-phenyl}-
10 carbamic acid tert.-butyl ester (Example K18) (263 mg, 0.54 mmol) by treatment with TFA
in CH₂Cl₂ according to the general procedure M. Obtained as an orange solid (77 mg).

MS (EI) 365 (M⁺); mp 207 °C (dec.).

Example 37

8-Benzoyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

15 Prepared from [4-benzoyl-2-(3-oxo-3-thiophen-2-yl-propionylamino)-phenyl]-carbamic
acid tert.-butyl ester (Example K19) (54 mg, 0.12 mmol) by treatment with TFA in CH₂Cl₂
according to the general procedure M. Obtained as a yellow solid (8 mg).

MS (EI) 346 (M⁺).

Example 38

20 **4-(3-Chloro-thiophen-2-yl)-8-phenyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one**

Prepared from {3-[3-(3-chloro-thiophen-2-yl)-3-oxo-propionylamino]-biphenyl-4-yl}-
carbamic acid tert.-butyl ester (Example K20) (100 mg, 0.21 mmol) by treatment with
TFA in CH₂Cl₂ according to the general procedure M. Obtained as a yellow solid (93 mg).

MS (EI) 352 (M⁺) and 354 [(M+2)⁺]; mp 228 °C (dec.).

25 **Example 39**

3-[7-(3-Methoxy-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from {3-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-3'-methoxy-biphenyl-4-yl}-carbamic acid tert.-butyl ester (Example K21) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow powder (118 mg).

MS (ISP) 368 $[(M+H)^+]$; mp 240-243 °C (dec.).

Example 40

3-(4-Oxo-7-pyridin-3-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from (2-amino-4-pyridin-3-yl-phenyl)-carbamic acid tert.-butyl ester (Example G26) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a beige powder (161 mg).

MS (EI) 338 (M^+); mp 210-214 °C (dec.).

Example 41

8-(6-Oxo-1,6-dihydro-pyridin-3-yl)-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from [5-(6-oxo-1,6-dihydro-pyridin-3-yl)-2-(3-oxo-3-thiophen-2-yl-propionylamino)-phenyl]-carbamic acid tert.-butyl ester (Example K22) (127 mg, 0.28 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a yellow solid (57 mg).

MS (ISP) 336 $[(M+H)^+]$; mp >250 °C.

Example 42

8-(6-Benzyloxy-pyridin-3-yl)-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from {4-(6-benzyloxy-pyridin-3-yl)-2-[3-oxo-3-(3-trifluoromethyl-phenyl)-propionylamino]-phenyl}-carbamic acid tert.-butyl ester (Example K 23) (198 mg, 0.33

mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a yellow solid (49 mg).

MS (ISP) 488 $[(\text{M}+\text{H})^+]$; mp 195 °C (dec.).

Example 43

- 5 3-[4-Oxo-7-(4-trifluoromethoxy-phenyl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from {3-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-4'-trifluoromethoxy-biphenyl-4-yl}-carbamic acid tert.-butyl ester (Example K24) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a light yellow powder (23 mg).

- 10 MS (EI) 421 (M^+) ; mp 237-241 °C (dec.).

Example 44

3-(4-Oxo-7-pyridin-4-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

- Prepared from (2-amino-4-pyridin-4-yl-phenyl)-carbamic acid tert.-butyl ester (Example G28) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a red-brown solid (25 mg).

MS (EI) 338 (M^+) ; mp >200 °C (dec.).

Example 45

- 20 3-[4-Oxo-7-(1,2,3,6-tetrahydro-pyridin-4-yl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

- Prepared from 4-{4-tert.-butoxycarbonylamino-3-[3-(3-cyano-phenyl)-3-oxo-propionylamino]-phenyl}-3,6-dihydro-2H-pyridine-1-carboxylic acid tert.-butyl ester (Example K25) (690 mg, 1.23 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a brown solid (309 mg).

MS (EI) 342 (M^+) ; mp 162-165 °C (dec.).

Example 46

3-[7-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from 3-[4-oxo-7-(1,2,3,6-tetrahydro-pyridin-4-yl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile (Example 45) (60 mg, 0.175 mmol),

5 methanesulfonyl chloride (0.014 mL, 0.175 mmol) and Et₃N (0.025 mL, 0.175 mmol) in THF (3 mL) at 23 °C. Obtained as an orange solid (35 mg).

MS (ISP) 421 [(M+H)⁺]; mp 211-213 °C (dec.).

Example 47

10 3-[7-(1-Acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from 3-[4-oxo-7-(1,2,3,6-tetrahydro-pyridin-4-yl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile (Example 45) (54 mg, 0.158 mmol) and Ac₂O (0.017 mL, 0.173 mmol) in THF (3 mL) at 23 °C. Obtained as an orange solid (65 mg).

MS (EI) 384 (M⁺); mp 220-222 °C (dec.).

15 Example 48

8-(6-Benzyloxy-pyridin-3-yl)-4-(3-chloro-thiophen-2-yl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from {4-(6-benzyloxy-pyridin-3-yl)-2-[3-(3-chloro-thiophen-2-yl)-3-oxo-propionylamino]-phenyl}-carbamic acid tert.-butyl ester (Example K26) (172 mg, 0.3 mmol) by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a yellow solid (38 mg).

MS (ISP) 460 [(M+H)⁺]; mp 213-215 °C (dec.).

Example 49

25 3-[7-(4-Methoxy-phenylethynyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile

Prepared from 3-(7-iodo-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile (Example 1) (290 mg, 0.75 mmol) and 4-methoxy-phenylacetylene (350 mg, 1.57 mmol) according to the general procedure F. Obtained as a light yellow solid (172 mg).

MS (EI) 391 (M^+); mp 234-235 °C (dec.).

Example 50

3-(4-Oxo-7-thiophen-2-ylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

- 5 Prepared from 3-(7-iodo-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile (Example 50) (185 mg, 0.48 mmol) and 2-ethynylthiophene (78 mg, 0.72 mmol) [prepared from 2-thiophenecarboxaldehyde according to *J. Org. Chem.* 1982, 47, 2201-2204] according to the general procedure F. Obtained as a light yellow solid (146 mg).

MS (EI) 367 (M^+); mp 235-238 °C (dec.).

10

The following examples relate to the palladium-catalyzed carbonylation of the 4-(3-iodophenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one in the presence of secondary amines leads directly to the corresponding amides as shown in synthetic scheme H.

15 **General procedure N**

Preparation of 4-[3-(Amino-4-carbonyl)-phenyl]-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-ones by Pd-catalyzed carbonylative amination of 4-(3-iodophenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

- 20 A solution of 4-(3-iodophenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 11) (1.0 mmol), the secondary amine (5.0 mmol), PPh_3 (6 mol%) or dppp (3 mol%), $Pd(OAc)_2$ (3 mol%) and Et_3N (2.0 mmol) in DMF (4 mL) was stirred at 23 °C under CO-atmosphere until tlc indicated complete consumption of the iodide. After dilution with EtOAc, washing with sat. $NaHCO_3$ -sol. and brine, the organic phase was dried over Na_2SO_4 . Removal of the solvent left a brown oil, which was purified by silica gel
25 column chromatography with hexane/EtOAc to give the title compound.

Example 51

4-[3-(Morpholine-4-carbonyl)-phenyl]-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from 4-(3-iodophenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 11) (471 mg, 1.02 mmol) and morpholine (0.44 mL, 5.09 mmol) according to the general procedure N. Obtained as a light yellow solid (324 mg).

MS (ISP) 450 [(M+H)⁺]; mp 142-145 °C (dec.).

5 **Example 52**

4-[3-(4-Methyl-piperazine-1-carbonyl)-phenyl]-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from 4-(3-iodophenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 11) (231 mg, 0.5 mmol) and N-methylpiperazine (0.28 mL, 2.5 mmol) according to the general procedure N. Obtained as a light yellow solid (65 mg).

MS (ISP) 463 [(M+H)⁺]; mp 168-172 °C (dec.).

Example 53

3-(4-Oxo-7-phenylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzamide

Prepared from 4-(3-iodophenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one (Example 11) (231 mg, 0.5 mmol) and hexamethyldisilazane (0.52 mL, 2.5 mmol) according to the general procedure N. Obtained as a yellow solid (104 mg).

MS (EI) 379 (M⁺); mp >250 °C (dec.).

The following examples relate to the preparation of the 4,7-diaryl-1,3-dihydro-benzo[b][1,4]diazepin-2-ones (Synthetic Scheme F):

20 **Example P1**

3-Nitro-biphenyl-4-ylamine

Prepared from (3-nitro-biphenyl-4-yl)-carbamic acid tert.-butyl ester (Example B5) by treatment with TFA in CH₂Cl₂ according to the general procedure P. Obtained as an orange solid (26 mg).

25 MS (EI) 214 (M⁺); mp 163 °C (dec.).

Example P2

2-Nitro-4-thiophen-2-yl-phenylamine

Prepared from (2-nitro-4-thiophen-2-yl-phenyl)-carbamic acid tert.-butyl ester (Example C3) by treatment with TFA in CH_2Cl_2 according to the general procedure P. Obtained as a red solid (134 mg).

5 MS (EI) 220 (M^+); mp 148 °C.

Example P3**2-Nitro-4-pyridin-2-yl-phenylamine**

Prepared from (2-nitro-4-pyridin-2-yl-phenyl)-carbamic acid tert.-butyl ester (Example C5) by treatment with TFA in CH_2Cl_2 according to the general procedure P. Obtained as an orange solid (240 mg).

10

MS (EI) 215 (M^+); mp 143 °C.

Example P4**2-Nitro-4-thiazol-2-yl-phenylamine**

Prepared from (2-nitro-4-thiazol-2-yl-phenyl)-carbamic acid tert.-butyl ester (Example E2) by treatment with TFA in CH_2Cl_2 according to the general procedure P. Obtained as a red solid (104 mg).

15

MS (EI) 221 (M^+); mp 187 °C (dec.).

Example P5**N-(5-Chloro-2-nitro-phenyl)-3-(3-cyano-phenyl)-3-oxo-propionamide**

20 Prepared from 5-chloro-2-nitroaniline (84 mg, 0.485 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (95 mg, 0.5 mmol) according to the general procedure K. Obtained as a yellow solid (116 mg).

MS (EI) 343 (M^+); mp 215 °C (dec.).

Example P6

25 N-(5-Chloro-2-nitro-phenyl)-3-(3-chloro-thiophen-2-yl)-3-oxo-propionamide

Prepared from 5-chloro-2-nitroaniline and 6-(3-chloro-thiophen-2-yl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H2) according to the general procedure K. Obtained as a yellow solid (165 mg).

MS (ISP) 359 [(M+H)⁺], 361 [(M+2+H)⁺] and 363 [(M+4+H)⁺]; mp 118-126 °C.

5 Example P7

N-(5-Chloro-2-nitro-phenyl)-3-(3-cyano-thiophen-2-yl)-3-oxo-propionamide

Prepared from 5-chloro-2-nitroaniline (173 mg, 1 mmol) and 6-(3-cyano-thiophen-2-yl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H3) (247 mg, 1.05 mmol) according to the general procedure K. Obtained as a yellow solid (279 mg).

10 MS (EI) 349 (M⁺) and 351 [(M+2)⁺]; mp 172-173 °C.

Example P8

3-(3-Cyano-phenyl)-N-(2-nitro-4-thiophen-2-yl-phenyl)-3-oxo-propionamide

Prepared from 2-nitro-4-thiophen-2-yl-phenylamine (Example P2) (70 mg, 0.32 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (88 mg, 0.38 mmol) according to the general procedure K. Obtained as an orange solid (162 mg).

MS (EI) 391 (M⁺); mp 209 °C (dec.).

Example P9

N-(4-Chloro-2-nitro-phenyl)-3-(3-cyano-phenyl)-3-oxo-propionamide

Prepared from 4-chloro-2-nitroaniline (84 mg, 0.485 mmol) and 3-(2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-yl)-benzonitrile (Example H4) (95 mg, 0.5 mmol) according to the general procedure K. Obtained as a yellow solid (96 mg).

MS (EI) 343 (M⁺) and 345 [(M+2)⁺]; mp 212 °C.

Example P10

N-(4-Cyano-2-nitro-phenyl)-3-oxo-3-thiophen-2-yl-propionamide

259

256

Prepared from 4-amino-3-nitrobenzonitrile (326 mg, 2 mmol) and 2,2-dimethyl-6-thiophen-2-yl-[1,3]dioxin-4-one (Example H1) (433 mg, 2 mmol) according to the general procedure K. Obtained as a yellow solid (608 mg).

MS (EI) 315 (M^+); mp 155 °C.

5 **Example P11**

N-(4-Methyl-2-nitro-phenyl)-3-oxo-3-thiophen-2-yl-propionamide

Prepared from 4-methyl-3-nitroaniline and 2,2-dimethyl-6-thiophen-2-yl-[1,3]dioxin-4-one (Example H1) according to the general procedure K. Obtained as a red solid (392 mg).

MS (EI) 304 (M^+); mp 113-115 °C.

10 **Example P12**

N-(3-Nitro-biphenyl-4-yl)-3-oxo-3-thiophen-2-yl-propionamide

Prepared from 3-nitro-biphenyl-4-ylamine RO-66-8886/000 (150 mg, 0.72 mmol) and 2,2-dimethyl-6-thiophen-2-yl-[1,3]dioxin-4-one (Example P1) (152 mg, 0.72 mmol) according to the general procedure K. Obtained as a yellow solid (230 mg).

15 MS (EI) 366 (M^+); mp 152 °C.

Example P13

N-(4-Chloro-2-nitro-phenyl)-3-oxo-3-(3-trifluoromethyl-phenyl)-propionamide

Prepared from 4-chloro-2-nitroaniline and 2,2-dimethyl-6-(3-trifluoromethyl-phenyl)-[1,3]dioxin-4-one (Example H5) according to the general procedure K. Obtained as a
20 yellow powder (553 mg).

MS (ISP) 387 [$(M+H)^+$], 404 [$(M+NH_4)^+$], 409 [$(M+Na)^+$] and 425 [$(M+K)^+$]; mp 156-158 °C.

Example P14

25 **N-(4-Iodo-2-nitro-phenyl)-3-oxo-3-thiophen-2-yl-propionamide**

Prepared from 4-iodo-2-nitroaniline (264 mg, 1.0 mmol; Wilson, J. Gerald; Hunt, Frederick C. Aust. *J. Chem.* 1983, 36, 2317-25) and 2,2-dimethyl-6-thiophen-2-yl-[1,3]dioxin-4-one (Example H1) (330 mg, 1.1 mmol) according to the general procedure K. Obtained as a yellow solid (340 mg).

5 MS (EI) 416 (M⁺); mp 133-136 °C.

Example P15

N-(4-Chloro-2-nitro-phenyl)-3-(3-chloro-thiophen-2-yl)-3-oxo-propionamide

Prepared from 4-chloro-2-nitroaniline and 6-(3-chloro-thiophen-2-yl)-2,2-dimethyl-[1,3]dioxin-4-one (Example H2) according to the general procedure K. Obtained as an orange solid (100 mg).

MS (ISP) 359 [(M+H)⁺], 361 [(M+2+H)⁺] and 363 [(M+4+H)⁺]; mp 130-132 °C.

Example P16

N-(5-Methyl-2-nitro-phenyl)-3-oxo-3-thiophen-2-yl-propionamide

Prepared from 5-methyl-2-nitroaniline and 2,2-dimethyl-6-thiophen-2-yl-[1,3]dioxin-4-one (Example H1) according to the general procedure K. Obtained as a yellow powder (390 mg).

MS (ISP) 305 [(M+H)⁺], 322 [(M+NH₄)⁺], 327 [(M+Na)⁺] and 343 [(M+K)⁺]; mp 127-129 °C.

Example 54

20 **3-(7-Chloro-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile**

Prepared from N-(5-chloro-2-nitro-phenyl)-3-(3-cyano-phenyl)-3-oxo-propionamide (Example P5) (222 mg, 0.65 mmol) by reduction and cyclization with SnCl₂·H₂O (733 mg, 3.25 mmol) according to the general procedure G (method b). Obtained as a yellow solid (142 mg).

25 MS (EI) 295 (M⁺) and 297 [(M+2)⁺]; mp 105 °C (dec.).

Example 55

8-Chloro-4-(3-chloro-thiophen-2-yl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one

258

257

Prepared from N-(5-chloro-2-nitro-phenyl)-3-(3-chloro-thiophen-2-yl)-3-oxo-propionamide (Example P6) (145 mg, 0.4 mmol) by reduction and cyclization with Fe (134 mg, 2.4 mmol) in EtOH (3.2 mL), H₂O (0.8 mL) and HOAc (3 drops) according to the general procedure G (method d). Obtained as a yellow solid (70 mg).

- 5 MS (EI) 310 (M⁺), 312 [(M+2)⁺] and 314 [(M+4)⁺]; mp 210 °C (dec.).

Example 56

2-(7-Chloro-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-thiophene-3-carbonitrile

Prepared from N-(5-chloro-2-nitro-phenyl)-3-(3-cyano-thiophen-2-yl)-3-oxo-propionamide (Example P7) (258 mg, 0.74 mmol) by reduction and cyclization with
10 SnCl₂·2H₂O (832 mg, 3.69 mmol) according to the general procedure G (method b).
Obtained as a yellow solid (169 mg).

MS (EI) 301 (M⁺) and 303 [(M+2)⁺]; mp 237-241 °C (dec.).

Example 57

3-(4-Oxo-8-thiophen-2-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

- 15 Prepared from 3-(3-cyano-phenyl)-N-(2-nitro-4-thiophen-2-yl-phenyl)-3-oxo-propionamide (Example P8) (70 mg, 0.18 mmol) by reduction and cyclization with
SnCl₂·2H₂O (203 mg, 0.90 mmol) according to the general procedure G (method b).
Obtained as a yellow solid (66 mg).

MS (EI) 343 (M⁺); mp 215 °C (dec.).

20 Example 58

3-(8-Chloro-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile

Prepared from N-(4-chloro-2-nitro-phenyl)-3-(3-cyano-phenyl)-3-oxo-propionamide
(Example P9) (82 mg, 0.24 mmol) by reduction and cyclization with SnCl₂·2H₂O (270 mg,
1.19 mmol) according to the general procedure G (method b). Obtained as a light yellow
25 solid (50 mg).

MS (EI) 295 (M⁺) and 297 [(M+2)⁺]; mp 246-247 °C (dec.).

Example 59

2-Oxo-4-thiophen-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine-7-carbonitrile

Prepared from N-(4-cyano-2-nitro-phenyl)-3-oxo-3-thiophen-2-yl-propionamide (Example P10) (558 mg, 1.77 mmol) by reduction and cyclization with Fe (593 mg, 10.62 mmol) in EtOH (14.4 mL), H₂O (3.6 mL) and HOAc (1.2 mL) according to the general procedure G (method d). Obtained as a green solid (275 mg).

MS (EI) 267 (M⁺); mp 254 °C (dec.).

Example 60**7-Methyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one**

Prepared from N-(4-methyl-2-nitro-phenyl)-3-oxo-3-thiophen-2-yl-propionamide (Example P11) (149 mg, 0.49 mmol) by reduction and cyclization with Fe (164 mg, 2.94 mmol) in THF (8 mL), H₂O (8 mL) and HOAc (5 drops) according to the general procedure G (method d). Obtained as a light brown solid (103 mg).

MS (EI) 256 (M⁺); mp 215-216 °C (dec.).

Example 61**7-Phenyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one**

Prepared from N-(3-nitro-biphenyl-4-yl)-3-oxo-3-thiophen-2-yl-propionamide (Example P12) (189 mg, 0.52 mmol) by reduction and cyclization with Fe (174 mg, 3.12 mmol) in EtOH (4 mL), H₂O (1 mL) and HOAc (3 drops) according to the general procedure G (method d). Obtained as a light yellow solid (44 mg).

MS (EI) 318 (M⁺); mp 250 °C (dec.).

Example 62**7-Chloro-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one**

Prepared from N-(4-chloro-2-nitro-phenyl)-3-oxo-3-(3-trifluoromethyl-phenyl)-propionamide (Example P13) by reduction and cyclization with Fe (6 eq.) in THF/H₂O (1:1) and HOAc (catalytic amount) according to the general procedure G (method d). Obtained as a beige powder (362 mg).

MS (EI) 338 (M⁺) and 340 [(M+2)⁺]; mp 233-236 °C (dec.).

Example 63

7-Iodo-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from N-(3-nitro-biphenyl-4-yl)-3-oxo-3-thiophen-2-yl-propionamide (Example P14) (208 mg, 0.5 mmol) by reduction and cyclization with Fe (168 mg, 3.0 mmol) in EtOH (4 mL), H₂O (1 mL) and HOAc (3 drops) according to the general procedure G (method d). Obtained as an off-white solid (56 mg).

MS (ISP) 369 [(M+H)⁺]; mp >250 °C.

Example 64

7-Chloro-4-(3-chloro-thiophen-2-yl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from N-(4-chloro-2-nitro-phenyl)-3-(3-chloro-thiophen-2-yl)-3-oxo-propionamide (Example P15) (77 mg, 0.21 mmol) by reduction and cyclization with Fe (70 mg, 1.26 mmol) in EtOH (1.6 mL), H₂O (0.4 mL) and HOAc (3 drops) according to the general procedure G (method d). Obtained as a light brown solid (34 mg).

MS (EI) 310 (M⁺), 312 [(M+2)⁺] and 314 [(M+4)⁺]; mp 203 °C (dec.).

Example 65

8-Methyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from N-(5-methyl-2-nitro-phenyl)-3-oxo-3-thiophen-2-yl-propionamide (Example P16) by reduction and cyclization with Fe (6 eq.) in THF/H₂O (1:1) and HOAc (catalytic amount) according to the general procedure G (method d). Obtained as a beige solid (58 mg).

MS (EI) 256 (M⁺); mp >265 °C (dec.).

Example 66

8-Phenylethynyl-4-pyridin-4-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from (2-amino-4-phenylethynyl-phenyl)-carbamic acid tert.-butyl ester (Example G2) and 2,2-dimethyl-6-pyridin-4-yl-[1,3]dioxin-4-one (Example H9) according to the general procedure K. The obtained material was deprotected and cyclized by treatment with TFA in CH₂Cl₂ according to the general procedure M. Obtained as a brown solid (50 mg).

MS (EI) 337 (M^+); mp 198-200 °C (dec.).

Example 67

4-(3-Imidazol-1-yl-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one

Prepared from {2-[3-(3-imidazol-1-yl-phenyl)-3-oxo-propionylamino]-4-phenylethynyl-phenyl}-carbamic acid tert.-butyl ester (Example K27) (170 mg, 0.33 mmol) by treatment with TFA in CH_2Cl_2 according to the general procedure M. Obtained as a brown solid (64 mg).

MS (EI) 402 (M^+); mp 193-196 °C.

10 **Example I**

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
Active ingredient	100
15 Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
20	Tablet weight 250

Example II

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
25 Active ingredient	200
Powdered. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12

262

259

Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

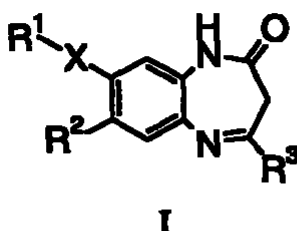
Example III

5 Capsules of the following composition are produced:

	<u>mg/Capsule</u>
Active ingredient	50
Crystalline lactose	60
10 Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

- 15 The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatin capsules of suitable size.

1. Compounds of general formula



5 wherein

X is a single bond or an ethynediyl group, wherein,

in case X is a single bond,

10 R^1 is hydrogen; halogen; nitro; lower alkyl; lower halo-alkyl; lower cycloalkyl, optionally substituted with oxygen; benzoyl, optionally substituted with lower alkyl, lower halo-alkyl, halogen; phenyl, optionally substituted with halogen, lower alkyl, lower halo-alkyl, lower cycloalkyl, lower alkoxy, lower halo-alkoxy; 5 or 6 membered heterocyclic ring, optionally substituted with oxo, benzyloxy, benzoyl, methanesulfonyl, benzenesulfonyl, acetyl; naphthyl;

in case X is an ethynediyl group,

15 R^1 is hydrogen; lower alkyl; lower halo-alkyl; lower cycloalkyl, optionally substituted with lower alkyl, lower halo-alkyl, lower alkoxy; lower halo-alkoxy, halogen; lower cycloalkenyl, optionally substituted with lower alkyl, lower halo-alkyl, lower alkoxy, lower halo-alkoxy, halogen; lower alkenyl; phenyl, optionally substituted with halogen, lower alkyl, lower halo-alkyl, lower cycloalkyl, lower alkoxy, lower halo-alkoxy; 5 or 6 membered heterocyclic
20 ring, optionally substituted with lower alkyl, halogen, oxo, benzyloxy, benzoyl, methanesulfonyl, benzenesulfonyl, acetyl;

R^2 is hydrogen, lower alkyl; halogen; cyano; benzoyl optionally substituted with lower alkyl, lower halo-alkyl, halogen; phenyl optionally substituted with halogen, lower alkyl, lower halo-alkyl, lower cycloalkyl, lower alkoxy, lower halo-alkoxy; phenoxy optionally
25 substituted with halogen, lower alkyl, lower halo-alkyl, lower cycloalkyl, lower alkoxy,

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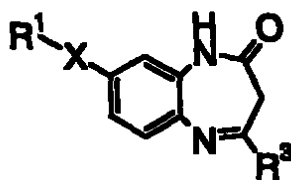
lower halo-alkoxy; 5 or 6 membered heterocyclic ring, optionally substituted with lower alkyl, halogen, hydroxy

R^3 is phenyl substituted in meta position with halogen, cyano, lower alkyl, lower alkoxy, lower halo-alkyl, azido, ethynyl, nitro, morpholine-4-carbonyl, 4-lower alkyl-piperazine-1-carbonyl; aminocarbonyl; mono-lower alkylaminocarbonyl; di-lower alkylaminocarbonyl; trimethylsilyl-ethynyl; imidazolyl optionally substituted with lower alkyl, halogen; thiophenyl, optionally substituted with halogen, hydroxy, lower alkoxy, lower alkyl, cyano; pyridinyl, optionally substituted with lower alkyl, halogen,

with the proviso that, if X is a single bond, R^3 is pyridinyl and R^2 is hydrogen, R^1 is not hydrogen and methyl.

and their pharmaceutically acceptable acid addition salts.

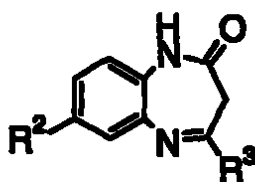
Compounds according to claim 1, being



Ia

wherein X, R^1 and R^3 have the same meaning as in claim 1.

3. Compounds according to claim 1, being



Ib

wherein R^2 and R^3 have the same meaning as in claim 1.

4. Compounds according to claim 1, wherein R^3 is phenyl substituted in meta position by ciano, halogen, azido, lower halo-alkyl, lower alkyl, lower alkoxy, lower cycloalkyl,

lower halo-alkoxy; imidazolyl, morpholine-4-carbonyl; 4-methyl-piperazine-1-carbonyl; 3-carboxy-amino-phenyl.

5. Compounds according to claim 1, being

- 3-(7-Iodo-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 5 3-(4-Oxo-7-phenylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(4-Oxo-7-p-tolyethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-[7-(2-Chloro-phenylethynyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 4-(3-Chloro-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 10 4-(3-Imidazol-1-yl-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 3-[7-(4-Methoxy-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-(4-Oxo-7-thiophen-3-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(7-Furan-2-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 15 3-[7-(4-Ethyl-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-(4-Oxo-7-phenyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 4-(3-Iodo-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 4-(3-Azido-phenyl)-8-phenyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 3-[7-(2-Methoxy-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 20 3-(7-Furan-3-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-[7-(4-Chloro-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 3-[7-(4-Chloro-phenylethynyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
- 25 8-Phenylethynyl-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 4-(3-Chloro-phenyl)-8-phenyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 3-(7-Naphthalen-1-yl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(4-Oxo-7-thiazol-2-ylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 30 3-(4-Oxo-7-p-tolyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(4-Oxo-7-thiophen-2-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 3-(4-Oxo-7-pyridin-2-ylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
- 4-(3-Methoxy-phenyl)-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
- 35 3-(4-Oxo-7-pyridin-2-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;

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Luis A. Rodríguez Roldán
Secretario Oficial
del Min. de Justicia

- 3-(4-Oxo-7-m-tolyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
3-[7-(3,4-Dichloro-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
8-Phenyl-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
5 3-[7-(2-Chloro-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
8-Benzoyl-4-(3-chloro-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
3-(7-Benzoyl-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
~~3-[7-(3-Methoxy-phenyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;~~
~~3-(4-Oxo-7-pyridin-3-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;~~
~~8-(6-Benzoyloxy-pyridin-3-yl)-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;~~
3-[4-Oxo-7-(4-trifluoromethoxy-phenyl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
15 3-(4-Oxo-7-pyridin-4-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
3-[4-Oxo-7-(1,2,3,6-tetrahydro-pyridin-4-yl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
3-[7-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
20 3-[7-(1-Acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
3-[7-(4-Methoxy-phenylethynyl)-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-benzonitrile;
3-(4-Oxo-7-thiophen-2-ylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
25 4-[3-(Morpholine-4-carbonyl)-phenyl]-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
4-[3-(4-Methyl-piperazine-1-carbonyl)-phenyl]-8-phenylethynyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
30 3-(4-Oxo-7-phenylethynyl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzamide;
3-(7-Chloro-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
3-(4-Oxo-8-thiophen-2-yl-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile;
3-(8-Chloro-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-benzonitrile; and
7-Chloro-4-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one.

- 35 6. Compounds according to claim 1, wherein R³ is thiophen-2-yl, optionally substituted with halogen; ciano; thiophen-3-yl; pyridin-4-yl.

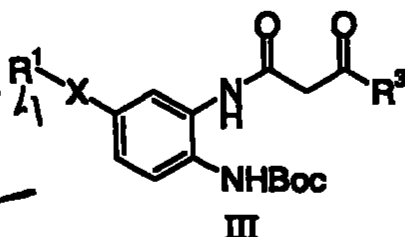
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7. Compounds according to claim 6, being
- 8-Phenyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
4-(3-Chloro-thiophen-2-yl)-8-pyridin-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
8-Iodo-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
5 8-Phenyl-4-thiophen-3-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
4-(3-Chloro-thiophen-2-yl)-8-o-tolyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
8-Benzoyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
4-(3-Chloro-thiophen-2-yl)-8-phenyl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
8-(6-Oxo-1,6-dihydro-pyridin-3-yl)-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
10 2-one;
8-(6-Benzyl-oxy-pyridin-3-yl)-4-(3-chloro-thiophen-2-yl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
8-Chloro-4-(3-chloro-thiophen-2-yl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
2-(7-Chloro-4-oxo-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl)-thiophene-3-
15 carbonitrile;
2-Oxo-4-thiophen-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine-7-carbonitrile;
7-Methyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
7-Phenyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
7-Iodo-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one;
20 7-Chloro-4-(3-chloro-thiophen-2-yl)-1,3-dihydro-benzo[b][1,4]diazepin-2-one
8-Methyl-4-thiophen-2-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one; and
8-Phenylethynyl-4-pyridin-4-yl-1,3-dihydro-benzo[b][1,4]diazepin-2-one.
8. A medicament containing one or more compounds of any one of claims 1 to 7 and/or one or more of their pharmaceutically acceptable acid addition salts.
- 25 9. A medicament according to claim 8 for the treatment or prevention of acute and/or chronic neurological disorders, such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia, acute and chronic
30 pain, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

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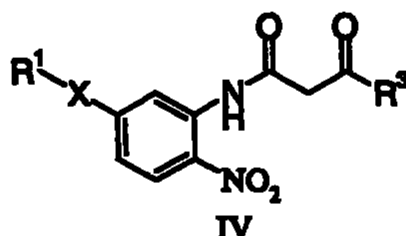
10. A process for preparing compounds of formula Ia as defined in claim 2, which process comprises:

a) cleaving the BOC protecting group in compounds of general formula III



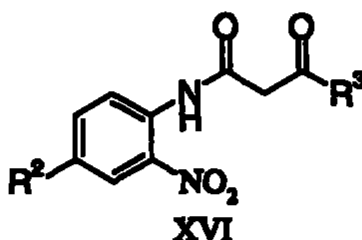
and subsequently cyclization of the deprotected compound; or

b) reducing the nitro group in compounds of general formula IV to the amino group



and subsequently heating the mixture to achieve cyclisation.

11. A process for preparing compounds of general formula Ib as defined in claim 3, which process comprises reducing the nitro group in compounds of general formula XVI to the amino group



and subsequently heating the mixture to achieve cyclisation.

12. The use of one or more compounds according to claims 1 to 7 and/or one or more of their pharmaceutically acceptable acid addition salts for the manufacture of medicaments for the treatment or prevention of diseases.

13. The use according to claim 12, for the treatment or prevention of acute and/or chronic neurological disorders, such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits, brain function caused by bypass operations

or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia, acute and chronic pain, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia and depression.

14. The invention as hereinbefore described.

5.764
Eduardo Rodríguez
Intérprete Oficial
nom. No. 0782 del Min. de Justicia

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 268

Radicación no 00-77374

Concepto Técnico no 1272

Clasificación Internacional de Patentes A61K 31/5513

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de Patente de Invención:

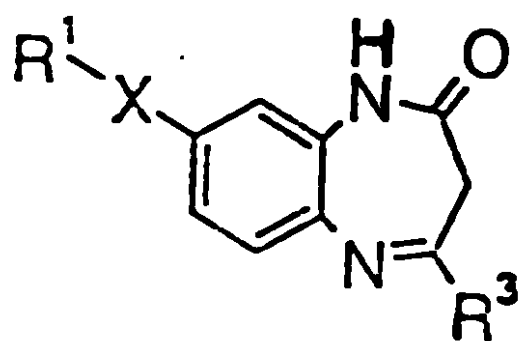
- SI ☒ NO ☐ Contiene un resumen de la invención (Art.26-e).
- SI ☒ NO ☐ Contiene el título o nombre de la invención (Art.27-d).
- SI ☒ NO ☐ Contiene la descripción de la invención (Art.26-b).
- SI ☒ NO ☐ NO ES APLICABLE ☐ Contiene los dibujos necesarios para comprender la invención (Art.26-d).
- SI ☒ NO ☐ Contiene una o más reivindicaciones. (Art.26-c).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-i).
- SI ☐ NO ☒ La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
- SI ☒ NO ☐ La prioridad coincide con la materia reivindicada.
- SI ☒ NO ☐ CUMPLE LOS REQUISITOS TÉCNICOS

OBSERVACIONES Y OTROS: SI ☒ NO ☐ ver hoja(s) anexa(s)

Se anexan los artes finales

EXAMINADOR TÉCNICO
202048

Bogotá D. C., 09 de septiembre del 2002.



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Folio 266

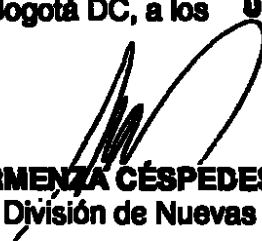
2020
Bogotá DC

Doctor(a)
JOSE ANTONIO LLOREDA
Apoderado(a)

REFERENCIA:	Radicación No.	00-77374
	Trámite	002
	Evento	001
	Actuación	418
	Oficio No.	1845
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá DC, a los **08 NOV. 2002**


ALIX CARMEN CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Nº 525.

202048