1/3

Industria y Comercio

SUPERINTENDENCIA

Organización y Digitalizacion CSA Ltda

CSA716454

INVENTARIO

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-1709

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE ISOINDOLINA PARA EL TRATAMIENTO DE ARRITMIAS

SOLICITANTE: ASTRAZENECA AB

DIRECCIÓN: Sodertalje S-SE-151 85, Suecia

APODERADO: J. IAN RAISBECK

BOGOTÁ 08 de Enero de 2009

202099

P2008/000238

OlarteRaisbeck

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

PETITORIO - FORMULARIO UNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2008/000238**

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: **ASTRAZENECA AB**
Dirección: S-151 85 Södertalje
Nacionalidad o Domicilio: Suecia
Lugar de Constitución: Suecia
Teléfono: **Fax:**
E-mail:

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número

REPRESENTANTE O APODERADO

Nombre: J. IAN RAISBECK
Dirección: World Trade Center, Torre A, Calle 100 No. 8A-37 Piso 10.
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número 79.376.996
TP 135.799

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA DJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/SE2007/000683 Fecha Julio 12, 2007

Publicación Internacional No. WO 2008/008022 Fecha Enero 17, 2008

(6) **Título (54)** **DERIVADOS DE ISOINDOLINA PARA EL TRATAMIENTO DE ARRITMIAS**

Clasificación Internacional (51) C07D 209/46, A61K 31/40, A6K 31/4035, A61K 31/41, A61K 31/435, A61K 31/495, A61P 9/04, A61P 9/06, C07D 401/00, C07D 403/00, C07D 43/00

Prioridad
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Julio 12, 2006	60/830,243
US	Abril 23, 2007	60/913,367

(9) **Comprobante de pago No.** 09-151 **Fecha** Enero 5 de 2009

(10) **ANEXOS**

X	Comprobante de pago de la tasa de presentación de la solicitud.
X	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
X	Poderes, si fuere el caso. Adjunto copia autentica.
	Documento de cesión del inventor al solicitante o a su causante.
	Declaraciones.
X	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
X	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
	Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA). (IPRP)
	Traducción del examen preliminar internacional efectuado por la IPEA.
	De ser el caso, copia del contrato de acceso.
	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
	De ser el caso, certificado de depósito del material biológico.
	Arte final 12 x 12.
	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
X	De ser el caso, modificaciones efectuadas a la solicitud internacional.
X	Otros. Búsqueda Internacional.

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK

FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

LISTA DE INVENTORES

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   Nacionalidad: Sueco

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   Suecia
   Nacionalidad: Sueco

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Nacionalidad: Sueco

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Nacionalidad: Sueco

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Suecia
Nacionalidad: Sueco

12 **Zhong-Qing YUAN,**
AstraZeneca R & D Mólndal,
S-431 83 Mölndal
Suecia
Nacionalidad: China

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 151
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 214
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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RECIBO OFICIAL DE CAJA : 09 - 215
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 216
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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FECHA : ENERO 5 DE 2009

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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 DTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

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***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 220
FECHA : ENERO 5 DE 2009

[redacted]

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

[redacted]

RESPONSABLE : _____

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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

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***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

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1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT: 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 202 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 371 -ASENACIONALI
Act. 411 PRESENTACION Folio: 389

RECIBO OFICIAL DE CAJA : 09 - 225
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

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RECIBO OFICIAL DE CAJA : 09 - 226
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
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***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
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***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 229
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 230
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 589

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 231
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 232
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 233
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
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Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 234
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2 . -

RECIBO OFICIAL DE CAJA : 09 - 235
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha. 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 236
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
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Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 237
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 238
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 239
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

32

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 240
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 589

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 241
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 242
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 243
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 244
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 245
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 246
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : .800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 247
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 80017(

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEI .II Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 248
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : .800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001709- -00000-0000
Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 249
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 250
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 251
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

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RECIBO OFICIAL DE CAJA : 09 - 252
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RECIBO OFICIAL DE CAJA : 09 - 254
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RECIBO OFICIAL DE CAJA : 09 - 255
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RECIBO OFICIAL DE CAJA : 09 - 257
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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RECIBO OFICIAL DE CAJA : 09 - 258
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
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RECIBO OFICIAL DE CAJA : 09 - 259
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

52

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
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RECIBO OFICIAL DE CAJA : 09 - 260
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

53

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

No. 09-001709- -00000-0000

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RECIBO OFICIAL DE CAJA : 09 - 261
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

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RESPONSABLE : _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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RECIBO OFICIAL DE CAJA : 09 - 263
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

56

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

RECIBO OFICIAL DE CAJA : 09 - 264
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	25,000.00
			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

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FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
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			TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

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RECIBO OFICIAL DE CAJA : 09 - 266
FECHA : ENERO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14445465	05/01/2009	6,976,000.00

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CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial de un documento cuyo original está en inglés

No. 11426

El Ministerio de Relaciones Exteriores en Estocolmo certifica por el presente documento que Mrs. Anna-Karin Östin, de la Oficina de Registro de Compañías de Suecia, Sundsvall, ha expedido y firmado la anterior certificación en su calidad oficial.

En Estocolmo, este día 14 de Agosto de 2007.

(Firmado)

Hay un sello del Ministerio de Relaciones Exteriores de Suecia.

Hay un sello firmado de la Embajada de Sudán en Estocolmo.

Firma de Agneta S...

Y sello de ...

Firma: Mohamed Hussein.

Fecha: 20 de Agosto de 2007.

Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Certificación Notarial

Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anders Burén, debidamente autorizado para firmar en nombre de Astrazeneca AB ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex oficio:

(Firmado) Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Traductor Oficial
JORGE E. SIERRA REYES
Licencia [illegible] - 1993 Minjusti

60

Apostilla adjunta:

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

1. País:	Suecia
	El presente documento público
2. Ha sido firmado por:	Anne-Marie Bonde
3. Actuando en calidad de:	Notario Público
4. Lleva el sello / estampilla de:	Notario Público de Estocolmo.
	Certificado
5. En:	Estocolmo
6. El:	Día 26 de Octubre de 2007
7. Por:	Björn Sandin, Notario Público
8. Bajo el No.	4071
9. Sello / estampilla:	Björn Sandin, Notario Público de Estocolmo.
10. Firma:	(Firmado)

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Cert.Min. Rel."

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 10-054

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

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APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country : Sweden

This public document

2. has been signed by Anne-Marie Bonde

3. acting in the capacity of Notary Public

4. bears the seal/stamp of

Notary Public in Stockholm

Certified

5. at Stockholm **6. the** 26.10.2007

7. by Björn Sandin

Notary Public

8. No 4071

9. Seal/stamp: **10. Signature:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

62

Carlos R. Olart
J. Ian Raisbec
Ana María Frie
Juan Guillermo Mour
Natalia Castr

Zayde Chahí
Simón Salina
Alexander Agudel
Camilo A. Rodrígue
Lina Mosquer
Catalina Barbastefan

Of Couns
Guillermo Chahí
Graciela Mel
Jacqueline Chaparr
Cruz E. de Moncalean

Power of Attorney

Poder

The undersigned,

El suscrito,

AstraZeneca AB

domiciled in

domiciliado en

Vastra Malarehamnen 9 S-151 85 Södertälje, Sweden

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications, collect refunds, desist, settle, conciliate or negotiate. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: Anders Burén
Authorized Signatory

Date/Fecha: 24 OCTOBER 2007

City,Country/Ciudad,País: SÖDERTÄLJE

NOTARIS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm
hereby certify that
ANDERS BURÉN
duly authorized to sign for
ASTRAZENECA AB
has issued and signed the foregoing document.

Fee 340:- Crowns

Stockholm 2007-10-26

Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

Anders Burén
Authorised Signatory

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MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	Certificación Notarial
On this date,	En esta fecha,
The undersigned Notary Public certifies:	el Notario Público suscrito certifica:
1. That	1. Que
of legal age and domiciled in	mayor de edad y domiciliado
signed the foregoing document.	suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as DULY AUTHORISED SIGNATORY of ASTRAZENECA AB	2. Que el otorgante ha suscrito el referido documento en su carácter de de
3. That ASTRAZENECA AB having its principal place of business located in SODERTALJE, SWEDEN is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.	4. Que con sede principal ubicada en está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.
4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):	5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):
1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB	
2. AUTHORISATION IN FAVOUR OF SIGNATORY	

NOTARY PUBLIC (Signature):
Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)
SEAL (optional)

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

851 81 Sund... Tel. 060-18 40 00 – Fax: 060 129840.
bolagsverket@bolagsverket (llegible)

Certificado de Existencia

Yo, Anna-Karin Östin, de Bolagsverket, la Oficina de Registro de Compañías de Suecia, certifico por medio del presente documento que

AstraZeneca AB

Registro No. 556011-7482

es una compañía debidamente constituida según las leyes de Suecia, vigente y con existencia corporativa legal hasta donde muestran los registros de esta oficina en la fecha que se indica más adelante.

En testimonio de lo anterior, he puesto mi firma y estampado el sello oficial de Bolagsverket en Sundsvall, este día 8 de Agosto del año 2007.

(Firmado) Anna-Karin Östin.

Hay un sello de Bolagsverket

Bolagsverket, la Oficina de registro de Compañías de Suecia, es el Registrador Oficial de las Compañías Limitadas y otras formas de empresas comerciales en Suecia. Antes de que se expida un Certificado de existencia, los registros radicados en esta oficina se examinan para tener la seguridad de que la compañía en cuestión llena los siguientes requerimientos:

- La compañía tiene una Junta Directiva competente
- La compañía tiene un Auditor titulado calificado.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Ministerio

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- La compañía ha llenado sus obligaciones con respecto a la radicación correcta de su informe anual.
- La compañía no es el sujeto de acciones legales de división de compañías, terminación o bancarrota.
- La compañía no ha sido disuelta como resultado de una fusión y no ha salido del registro por ninguna otra razón.

El Certificado está firmado por un funcionario autorizado para expedir estos y similares documentos en nombre de Bolagsverket, la Oficina de Registro de Compañías de Suecia.

Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Certificación Notarial

Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anna-Karin Östin, debidamente autorizada para firmar en nombre de la Oficina de Registro de Compañías de Suecia, ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex oficio:

(Firmado) Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Apostilla adjunta:

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

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APOSTILLE
(Convention du La Haye du 5 octobre 1961)

1. País:	Suecia
	El presente documento público
2. Ha sido firmado por:	Anne-Marie Bonde
3. Actuando en calidad de:	Notario Público
4. Lleva el sello / estampilla de:	Notario Público de Estocolmo.
	Certificado
5. En:	Estocolmo
6. El:	Día 26 de Octubre de 2007
7. Por:	Björn Sandin, Notario Público
8. Bajo el No.	4070
9. Sello / estampilla:	Björn Sandin, Notario Público de Estocolmo.
10. Firma:	(Firmado)

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Cert.Bolagsverket"

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 10-053

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Ministerio

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country : Sweden

This public document

2. has been signed by Anne-Marie Bonde

3. acting in the capacity of Notary Public

4. bears the seal/stamp of

Notary Public in Stockholm

Certified

5. at Stockholm **6. the** 26.10.2007

7. by Björn Sandin

Notary Public

8. No 4070

9. Seal/stamp: **10. Signature:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

Bolagsverket

851 81 Sundsvall
Besökare: Badhusparken
Tel: 060-18 40 00 • Fax: 060-12 98 40
bolagsverket@bolagsverket.se • bolagsverket.se

Certificate of Good Standing

I, Anna-Karin Östin, of Bolagsverket, the Swedish Companies Registration Office, do hereby certify that

AstraZeneca AB
registration number: **556011-7482**

is a duly incorporated company under the laws of Sweden and is in good standing and has a legal corporate existence as far as the records of this office show as of the date stated below.

In testimony hereof, I have hereunto set my hand and the official seal of Bolagsverket at Sundsvall, this 8th day of August in the year of two thousand and seven.

Anna-Karin Östin

Bolagsverket, the Swedish Companies Registration Office, is the official registrar of limited companies and other forms of business enterprise in Sweden. Before a Certificate of Good Standing is issued, the records kept by this office are examined to ensure that the following requirements are fulfilled for the company in question:

- the company has a registered competent board of directors
- the company has a registered qualified auditor
- the company has fulfilled its obligations regarding the correct filing of its annual report
- the company is not the subject of company division, winding up or bankruptcy proceedings
- the company has not been dissolved as the result of a merger and has not been struck off the register for any other reason.

The Certificate is signed by an official authorized to issue these and similar documents on behalf of Bolagsverket, the Swedish Companies Registration Office.

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm

hereby certify that

ANNA-KARIN ÖSTIN

duly authorized to sign for

THE SWEDISH COMPANIES REGISTRATION OFFICE

has issued and signed the foregoing document in original of which this is a true copy.

Fee 340:- Crowns

Stockholm 2007-10-26

Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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No. 11426
The Ministry for Foreign Affairs in Stockholm, hereby certifies that
Mrs. Anna-Karin Bohn

Swedish Companies Registration Office, Sundsvall

has issued and signed the foregoing attestation in ~~his~~ her official capacity

Fee Stockholm this 14th day of August 2007
Kr 60/- PAID

Agneta Söderlund

MINISTRY FOR FOREIGN AFFAIRS

STOCKHOLM

SIGNATURE OF Agneta Söderlund
AND STAMP OF: Sr. MFA
SIGNATURE: Mohamed Husseini
DATE: 20-08-07

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2008 (17.01.2008)

PCT

(10) International Publication Number
WO 2008/008022 A1

(51) International Patent Classification:
C07D 209/46 (2006.01) *A61P 9/04* (2006.01)
A61K 31/40 (2006.01) *A61P 9/06* (2006.01)
A61K 31/4035 (2006.01) *C07D 401/00* (2006.01)
A61K 31/41 (2006.01) *C07D 403/00* (2006.01)
A61K 31/435 (2006.01) *C07D 413/00* (2006.01)
A61K 31/495 (2006.01)

(21) International Application Number:
PCT/SE2007/000683

(22) International Filing Date: 12 July 2007 (12.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/830,243 12 July 2006 (12.07.2006) US
60/913,367 23 April 2007 (23.04.2007) US

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(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, S-151 85 Södertälje (SE).

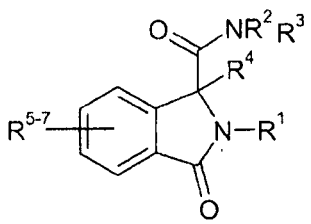
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:
— *with international search report*

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

(54) Title: ISOINDOLINE DERIVATIVES FOR THE TREATMENT OF ARRHYTHMIAS



(I)

(57) Abstract: There is provided compounds of formula I, wherein R^1 to R^7 have meanings given in the description, which are useful in the prophylaxis and in the treatment of arrhythmias, in particular atrial and ventricular arrhythmias.

WO 2008/008022 A1

Isoindoline derivatives for the treatment of arrhythmias

Field of the Invention

This invention relates to novel pharmaceutically useful 3-oxoisoindoline-1-carboxamide compounds, in particular compounds that are useful in the treatment of cardiac arrhythmias.

Background

Cardiac arrhythmias may be defined as abnormalities in the rate, regularity, or site of origin of the cardiac impulse or as disturbances in conduction which causes an abnormal sequence of activation. Arrhythmias may be classified clinically by means of the presumed site of origin (i.e. as supraventricular, including atrial and atrioventricular, arrhythmias and ventricular arrhythmias) and/or by means of rate (i.e. bradyarrhythmias (slow) and tachyarrhythmias (fast)).

In the treatment of cardiac arrhythmias, the negative outcome in clinical trials (see, for example, the outcome of the Cardiac Arrhythmia Suppression Trial (CAST) reported in New England Journal of Medicine, 321, 406 (1989)) with "traditional" antiarrhythmic drugs, which act primarily by slowing the conduction velocity (class I antiarrhythmic drugs), has prompted drug development towards compounds which selectively delay cardiac repolarization, thus prolonging the QT interval. Class III antiarrhythmic drugs may be defined as drugs which prolong the trans-membrane action potential duration (which can be caused by a block of outward K^+ currents or from an increase of inward ion currents) and refractoriness, without affecting cardiac conduction. The rapidly and slow activating delayed rectifier potassium currents I_{Kr} and I_{Ks} , respectively, are the main currents involved in the overall repolarisation process during the action potential plateau and most class III agents predominantly block I_{Kr} One of the key disadvantages of hitherto known drugs which act by delaying repolarization by a block of I_{Kr} (class III or otherwise) is that almost all are known to exhibit a unique form of ventricular proarrhythmia known as *torsades de pointes* (turning of points), which may, on occasion be fatal. From the point of view of safety, the minimisation of this phenomenon (which has also been shown to be exhibited as a result of administration of non-cardiac drugs

such as phenothiazines, tricyclic antidepressants, antihistamines and antibiotics) is a key problem to be solved in the provision of effective antiarrhythmic drugs.

In human atrial myocytes, an ultra-rapidly activating delayed rectifier potassium current, I_{Kur} also known as I_{so} or $I_{sus,}$ has been identified. The gene most likely coding the I_{Kur} channel protein has been identified, and is termed Kv1.5 (Wang et al (1993) Circ Res73:1061-0176, Feng et al (1997) Circ Res 80:572-579). Due to the slow inactivation of the current, I_{Kur} persists during the plateau phase and contributes significantly to action potential repolarisation in atrial myocytes. Most interestingly, voltage clamp studies investigating repolarising currents have failed to demonstrate the presence of I_{Kur} in human ventricular myocytes (Amos et al J Physiol (1996) 491(1):31-50). Thus, a selective blocker of I_{Kur} , that is a compound which block Kv1.5, is of great interest for the therapy of atrial arrhythmia, since such an agent should delay repolarisation in human atrial myocardium only, circumventing ventricular proarrhythmias (i.e. *torsades de pointes*,) associated with delayed ventricular repolarisation.

Kv1.5 blockers exhibiting these properties have been described (Peukert et al J Med Chem (2003) 46:486-498; Knobloch et al Naunyn-Schmiedeberg's Arch Pharmacol (2002) 366:482-487).

Some 3-oxoisoindoline-1-carboxamide derivatives are known. 3-oxoisoindoline-1-carboxamide derivatives are an ideal target for multicomponent reactions (MCRs). Tetrahedron Letters (1998), 39(18), 2725-2728 discloses some 3-oxoisoindoline-1-carboxamide derivatives prepared by so-called Ugi reactions (N-tert-butyl-3-oxo-2-propylisoindoline-1-carboxamide; N-tert-butyl-1-methyl-3-oxo-2-propylisoindoline-1-carboxamide; N,1-dimethyl-3-oxo-2-propylisoindoline-1-carboxamide; N-cyclohexyl-3-oxo-2-propylisoindoline-1-carboxamide; 2-benzyl-N-tert-butyl-3-oxoisoindoline-1-carboxamide; 2-benzyl-N,1-dimethyl-3-oxoisoindoline-1-carboxamide; 2-benzyl-N-tert-butyl-1-methyl-3-oxoisoindoline-1-carboxamide; 2-benzyl-N,1-dimethyl-3-oxoisoindoline-1-carboxamide.

Also Journal of Organic Chemistry (1999), 64(3), 1074-1076 discloses such compounds (tert-butyl {4-[1-(tert-butylcarbamoyl)-3-oxo-1,3-dihydro-2H-isoindol-2-yl]butyl}carbamate; 2-benzyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide; 2-benzyl-N-butyl-3-

oxoisoindoline-1-carboxamide; 2-benzyl-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide; 2-(2-hydroxyethyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide; N-butyl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide; 2-(2-hydroxyethyl)-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide; 2-[3-(1H-imidazol-1-yl)propyl]-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide; N-butyl-2-[3-(1H-imidazol-1-yl)propyl]-3-oxoisoindoline-1-carboxamide; 2-[3-(1H-imidazol-1-yl)propyl]-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide; 2-cyclohexyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide; N-butyl-2-cyclohexyl-3-oxoisoindoline-1-carboxamide; 2-cyclohexyl-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide) and in Bioorganic & Medicinal Chemistry Letters (2002), 12(14), 1813-1816 (2-cyclohexyl-N-hexyl-3-oxoisoindoline-1-carboxamide; N,2-dihexyl-3-oxoisoindoline-1-carboxamide; N-hexyl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide; N-hexyl-2-(4-hydroxybutyl)-3-oxoisoindoline-1-carboxamide; N,2-dicyclohexyl-3-oxoisoindoline-1-carboxamide; N-cyclohexyl-2-hexyl-3-oxoisoindoline-1-carboxamide; N-cyclohexyl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide; N-cyclohexyl-2-(4-hydroxybutyl)-3-oxoisoindoline-1-carboxamide; tert-butyl {4-[1-(cyclohexylcarbamoyl)-3-oxo-1,3-dihydro-2H-isoindol-2-yl]butyl}carbamate; N-adamantan-1-yl-2-cyclohexyl-3-oxoisoindoline-1-carboxamide; N-adamantan-1-yl-2-hexyl-3-oxoisoindoline-1-carboxamide; N-adamantan-1-yl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide; N-adamantan-1-yl-2-(2-morpholin-4-ylethyl)-3-oxoisoindoline-1-carboxamide; N-(2,6-dimethylphenyl)-2-hexyl-3-oxoisoindoline-1-carboxamide). Also Tetrahedron, vol. 53, No. 19, 6653-6679 discloses 3-oxoisoindoline-1-carboxamide derivatives prepared by so-called Ugi reactions (6-{[(2-allyl-1-methyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbonyl]amino}hexanoic acid). No pharmaceutical use of the prepared compounds is contemplated in those references. Tetrahedron Letters (2002), 43(6), 943-946 discloses some 3-oxoisoindoline-1-carboxamide derivatives prepared by intramolecular Diels-Alder type reactions (N,2-dibenzyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide; N-benzyl-2-tert-butyl-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide; N-benzyl-2-tert-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide; N,2-dibenzyl-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide; N-benzyl-2-tert-butyl-5-hydroxy-3-oxoisoindoline-1-carboxamide). Also Journal of Organic Chemistry (2004), 69(4), 1207-1214 discloses the compound (N,2-

dibenzyl-5-{[(2-nitrophenyl)sulfonyl]amino}-3-oxoisoindoline-1-carboxamide). No pharmaceutical use of the prepared compounds is contemplated.

Journal of Heterocyclic Chemistry (1997), 34(4), 1371-1374 discloses some symmetrically substituted 3-oxoisoindoline-1-carboxamide derivatives prepared by carbonylative cyclization of 2-bromobenzaldehyde with primary amines (N,2-dibenzyl-3-oxoisoindoline-1-carboxamide; N,2-diethyl-3-oxoisoindoline-1-carboxamide; N,2-dibutyl-3-oxoisoindoline-1-carboxamide; N,2-didodecyl-3-oxoisoindoline-1-carboxamide; N,2-bis(4-methoxybenzyl)-3-oxoisoindoline-1-carboxamide; 3-oxo-N,2-dipropylisoindoline-1-carboxamide; N,2-diheptyl-3-oxoisoindoline-1-carboxamide; 3-oxo-N,2-diphenylisoindoline-1-carboxamide). No pharmaceutical use of the prepared compounds is contemplated. Some additional 3-oxoisoindoline-1-carboxamide derivatives are disclosed in Zhurnal Obshchei Khimii (1965), 1(7), 1292-7; Yakugaku Zasshi (1969), 89(3), 418-21; Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1980), (4), 846-8 (2-(4-nitrophenyl)-3-(pyrrolidin-1-ylcarbonyl)isoindolin-1-one); EP1566378 A1 (2-(3-fluorophenyl)-5,6-dimethyl-3-[(4-methylpiperazin-1-yl)-carbonyl]isoindolin-1-one); EP 1661898; CHEMCATS (Chemical Catalogs Online provided by STN) (N-[2-(3,4-dimethoxyphenyl)ethyl]-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide; N-cyclopentyl-2-(3-methoxybenzyl)-3-oxoisoindoline-1-carboxamide; 2-(1,3-benzodioxol-5-ylmethyl)-N-{[(4-methylphenyl)sulfonyl]methyl}-3-oxoisoindoline-1-carboxamide; N-cyclohexyl-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide; 2-benzyl-N-cyclohexyl-3-oxoisoindoline-1-carboxamide; N-{[(4-methylphenyl)sulfonyl]methyl}-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide; 2-(4-chlorobenzyl)-N-{[(4-methylphenyl)sulfonyl]methyl}-3-oxoisoindoline-1-carboxamide; N-cyclohexyl-2-(2-furylmethyl)-3-oxoisoindoline-1-carboxamide; 2-(4-chlorobenzyl)-N-cyclohexyl-3-oxoisoindoline-1-carboxamide; WO03/040096 (tert-butyl {1-benzyl-2-hydroxy-3-[(2-hydroxy-3-{[(3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbonyl]amino}-4-phenylbutyl)amino]propyl}carbamate); US5559256; Chemical & Pharmaceutical Bulletin (1988), 36(1), 190-201; Journal of the Chemical Society (1972-1999), (1972), (6), 835-840; Justus Liebigs Annalen Der Chemie (1978), vol 2, 283-288 (1-hydroxy-2-methyl-3-oxo-N-(pyridin-2-ylmethyl)isoindoline-1-carboxamide; N-[3-(dimethylamino)propyl]-1-hydroxy-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide; N-(3-azepan-1-ylpropyl)-1-

hydroxy-3-oxo-2-phenylisoindoline-1-carboxamide, 1-hydroxy-2-methyl-3-oxoisoinoline-1-carbohydrazide; 1-hydroxy-3-oxo-phenylisoindoline-1-carbohydrazide); Zeitschrift for Naturforschung. B, 1993, vol 48:8, 1094-1104 (2-benzoyl-1-hydroxy-3-oxo-N-phenylisoindoline-1-carboxamide); J. Prakt. Chem. 2, 159, 1941, 241, 244, 254; Heterocycles Vol 38; No 8; 1994, 1828-1838; J. Org. Chem. 17, 1952, 4, 8, 1-13; Tetrahedron, EN, 53, 19, 1997, 6653-6680; Tetrahedron Letters, vol 38, No 3, 1997, 359-362 (6-{[(2-allyl-1-methyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbonyl]amino}hexanoic acid and 6-{[(1-methyl-2-octyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbonyl]amino} hexanoic acid). EP1566378 A1 discloses isoindoline derivatives having anestetic effect, EP 1661898 A1 isoindoline derivatives to be used in treatment of cancer, and EP 1749817 A1 isoindoline derivatives controlling neturophatic pain.. US 2007/0099930 discloses substituted dihydroisoindolones having an effect as glucokinase modulators. Further isoindoline derivatives are described in SYNTHESIS 2006, No 23, pp 4046-4052 (methyl [1-(tert-butylcarbamoyl)-3-oxo-1,3-dihydro-2H-isoindol-2-yl]acetate); and in J. Org. Chem 2006, 71, 9544-9547 (N1-cyclopentyl-N4-(2,6-difluorophenyl)-2-(2,4-dimethylphenyl)-5-methyl-3-oxoisoindoline-1,4-dicarboxamide).

The compounds disclosed in the documents listed above are disclaimed from the compound claims of the present application by proviso b). Compounds of proviso c) did not demonstrate activity at the concentrations at which they were tested.

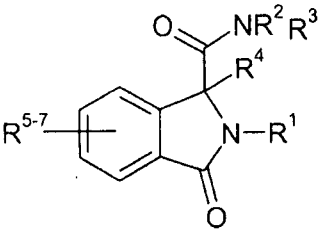
Copending case no US 60/830186 describes proviso a).

Further, the following compound is known in Chemical Abstracts but no reference is given: 3-oxo-N,2-diphenylisoindoline-1-carboxamide.

We have surprisingly found that a novel group of 3-oxoisoindoline-1-carboxamide compounds exhibit electrophysiological activity, preferably Kv1.5 blocking activity, and are therefore expected to be useful in the treatment of cardiac arrhythmias.

Disclosure of the Invention

According to the invention there is provided a compound of formula I,



I

or a pharmaceutically acceptable salt thereof

wherein

R^1 represents C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, $-OR^8$, $-COR^9$, $-SR^{10}$, $-COXR^{11}$, $-N(R^{12a})(R^{12b})$, $-N(R^{13a})C(O)OR^{13b}$, $-OC(O)N(R^{14a})(R^{14b})$, $-SO_2R^{15}$, aryl or Het^1); further R^1 represents aryl or Het^2;

R^8 to R^{11}, R^{13a}, R^{13b}, R^{15} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^9 (which C_1-C_6 alkyl, aryl and Het^9 groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{10});

R^{12a} and R^{12b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{11} (which C_1-C_6 alkyl, aryl and Het^{11} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{12}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{14a} and R^{14b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{13} (which C_1-C_6 alkyl, aryl and Het^{13} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{14}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^2 represents C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, $-OR^{16}$, $-COR^{17}$, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, trialkylsilyl, $-COXR^{18}$, aryl or Het^3);
further R^2 represents $-(CH_2)_kN(R^{19a})(R^{19b})$, $-(CH_2)_kNR^{20a}C(O)N(R^{20b})(R^{20c})$, $-(CH_2)_nNR^{21a}SO_2R^{21b}$, $-(CH_2)_nSO_2R^{22}$, $-(CH_2)_kN(R^{23a})C(O)OR^{23b}$, $-OC(O)N(R^{24a})(R^{24b})$, C_3-C_8 cycloalkyl, aryl or Het^4;

R^{16} to R^{18}, R^{21}, R^{22}, R^{23a}, R^{23b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{15} (which C_1-C_6 alkyl, aryl and Het^{15} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{16});

R^{19a} and R^{19b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{19} (which C_1-C_6 alkyl, aryl and Het^{19} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{20}) or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{20a}, R^{20b} and R^{20c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{21} (which C_1-C_6 alkyl, aryl and Het^{21} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{22}); R^{20b} and R^{20c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^3 represents hydrogen, C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, $-OR^{25}$, $-COR^{26}$, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, trialkylsilyl, $-COXR^{27}$, aryl or Het^5);
further R^3 represents $-(CH_2)_kN(R^{28a})(R^{28b})$, $-(CH_2)_kN(R^{29a})C(O)N(R^{29b})(R^{29c})$, $-(CH_2)_nNR^{30a}SO_2R^{30b}$, $-(CH_2)_nSO_2R^{31}$, $-(CH_2)_kN(R^{32a})C(O)OR^{32b}$, $-OC(O)N(R^{33a})(R^{33b})$,

C_3-C_8 cycloalkyl, aryl or Het^6;

R^{25} to R^{27}, R^{30}, R^{31}, R^{32a}, R^{32b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{23} (which C_1-C_6 alkyl, aryl and Het^{23} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{24});

R^{28a} and R^{28b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{25} (which C_1-C_6 alkyl, aryl and Het^{25} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{26}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{33a} and R^{33b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{27} (which C_1-C_6 alkyl, aryl and Het^{27} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{28}) or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{29a}, R^{29b}, and R^{29c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{29} (which C_1-C_6 alkyl, aryl and Het^{29} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{30}); R^{29b} and R^{29c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^4 represents hydrogen, –OH, aryl, C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, hydroxy, C_2-C_4 alkenyl, trialkylsilyl), $-OR^{34}$, $-(CH_2)_mR^{35}$;

R^{34} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{31} (which C_1-C_6 alkyl, aryl and Het^{31} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{32});

R^{35} independently represent aryl or Het^{33} (which aryl and Het^{33} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{34});

R^5 to R^7 independently represent, at each occurence, hydrogen, -OH, halogen, cyano, nitro, C_{1-6} alkyl, $-OR^{36}$, $-N(R^{37a})(R^{37b})$, $-C(O)R^{38}$, $-C(O)OR^{39}$, $-C(O)N(R^{40a})(R^{40b})$, $-NC(O)OR^{41}$, $-OC(O)N(R^{42a})(R^{42b})$, $-N(R^{43a})C(O)R^{43b}$, $-N(R^{44a})S(O)_2R^{44b}$, $-S(O)_2R^{45}$, $-OS(O)_2R^{46}$, $-(CH_2)_nN(R^{47a})(R^{47b})$, $-(CH_2)_nNR^{48a}C(O)N(R^{48b})(R^{48c})$, $-(CH_2)_nNR^{49a}SO_2R^{49b}$, trialkylsilyl, aryl or Het^7;

R^{36}, R^{38}, R^{39}, R^{41}, R^{43}, R^{44a}, R^{44b}, R^{45}, R^{46}, R^{49a} and R^{49b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{35} (which C_1-C_6 alkyl, aryl and Het^{35} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{36});

R^{37a} and R^{37b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{37} (which C_1-C_6 alkyl, aryl and Het^{37} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{38}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{40a} and R^{40b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{39} (which C_1-C_6 alkyl, aryl and Het^{39} groups are optionally substituted with one or

more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{40}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{42a} and R^{42b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{41} (which C_1-C_6 alkyl, aryl and Het^{41} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{42}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{47a} and R^{47b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{43} (which C_1-C_6 alkyl, aryl and Het^{43} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{44}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{48a}, R^{48b} and R^{48c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{45} (which C_1-C_6 alkyl, aryl and Het^{45} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{46}); R^{48b} and R^{48c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

aryl is, at each occurrence, optionally substituted by –OH, halogen, cyano, nitro, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, aryl, Het^8, $-OR^{50}$, $-(CH_2)_mR^{51}$, $-SR^{52}$, $-C(O)R^{53}$, $-COXR^{54}$, $-N(R^{55a})(R^{55b})$, $-SO_2R^{56}$, $-OS(O)_2R^{57}$, $-(CH_2)_mN(R^{58a})(R^{58b})$, $-CH_2)_mNR^{59a}C(O)N(R^{59b})(R^{59c})$, $-C(O)OR^{60}$, $-C(O)N(R^{61a})(R^{61b})$, $-N(R^{62a}C(O)R^{62b}$, $-N(R^{63a})C(O)OR^{63b}$, $-OC(O)N(R^{64a})(R^{64b})$, $-N(R^{65a})S(O)_2R^{65b}$ and $OC(O)R^{66}$;

R^{50} to R^{54}, R^{56}, R^{57}, R^{60}, R^{62a}, R^{62b}, R^{63a}, R^{63b}, R^{65a}, R^{65b} and R^{66} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{47} (which C_1-C_6 alkyl, aryl and Het^{47} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{48});

R^{51} independently represent aryl or Het^{49} (which aryl and Het^{49} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{50});

R^{55a} and R^{55b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{51} (which C_1-C_6 alkyl, aryl and Het^{51} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{52}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{58a} and R^{58b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{53} (which C_1-C_6 alkyl, aryl and Het^{53} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{54}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{59a}, independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{55} (which C_1-C_6 alkyl, aryl and Het^{55} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{56}); R^{59b} and R^{59c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{61a} and R^{61b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{57} (which C_1-C_6 alkyl, aryl and Het^{57} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{58}); or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{64a} and R^{64b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{59} (which C_1-C_6 alkyl, aryl and Het^{59} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{60});

Het^{1} to Het^{60} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl, C_2-6 alkenyl, aryl, a further Het, $-OR^{67}$, $-(CH_2)_mR^{68}$, $-SR^{69}$, $-COXR^{70}$, $-N(R^{71a})(R^{71b})$, $-SO_2R^{72}$, $-(CH_2)_mN(R^{73a})(R^{73b})$, $-(CH_2)_mNR^{74a}C(O)N(R^{74b})(R^{74c})$, $-C(O)R^{75}$, $-C(O)OR^{76}$, $-C(O)N(R^{77a})(R^{77b})$, $-N(R^{78a})C(O)R^{78b}$, $-N(R^{79a})S(O)_2R^{79b}$, $OC(O)R^{80}$, $-NC(O)OR^{81}$, $-OC(O)N(R^{82a})(R^{82b})$;

R^{67}, R^{69}, R^{70}, R^{72}, R^{75}, R^{76}, R^{78a}, R^{78b}, R^{79a}, R^{79b}, R^{80} or R^{81} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{61} (which C_1-C_6 alkyl, aryl and Het^{61} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{62});

R^{68} represents aryl or Het^{63} (which aryl and Het^{63} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{64});

R^{71a} and R^{71b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{65} (which C_1-C_6 alkyl, aryl and Het^{65} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{66}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{73a} and R^{73b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{67} (which C_1-C_6 alkyl, aryl and Het^{67} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{68}); or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{74a}, R^{74b} and R^{74c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{69} (which C_1-C_6 alkyl, aryl and Het^{69} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{70}); R^{74b} and R^{74c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{77a}, and R^{77b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{71} (which C_1-C_6 alkyl, aryl and Het^{71} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{72}); or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{82a}, and R^{82b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{73} (which C_1-C_6 alkyl, aryl and Het^{73} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{74}) or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

Het^{61} to Het^{74} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl;

X represents a nitrogen or oxygen atom;

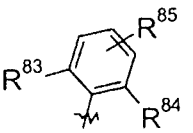
m is an integer of 0 to 10;

n is an integer of 0 to 4;

k is an integer of 1 to 5;

provided that

a) R^2 or R^3 does not represent a fragment of formula



wherein

R^{83} and R^{84} represent independently, at each occurrence, halogen, C_1-C_{12} alkyl, C_1-C_{12} alkoxy, C_1-C_{12} haloalkyl, C_1-C_{12} haloalkoxy, cyano, $-SR^{86}$, $-N(R^{87a})R^{87b}$, C_2-C_6 alkynyl, aryl or Het^{75};

R^{85} represents hydrogen, C_1-C_{12} alkyl group or C_1-C_{12} alkoxy group (which C_1-C_{12} alkyl and C_1-C_{12} alkoxy groups are optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, oxo, aryl, Het^{76}, $-OR^{88}$, $-SR^{89}$, $-COXR^{90}$, $-N(R^{91a})R^{91b}$, $-SO_2R^{92}$);

Het^{75} to Het^{76} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryloxy, $-N(R^{93a})R^{93b}$, $-C(O)R^{93c}$, $-C(O)OR^{93d}$, $-C(O)N(R^{93e})R^{93f}$, $-N(R^{93g})C(O)R^{93h}$ and $-N(R^{93i})S(O)_2R^{93j}$, $OC(O)R^{93k}$ and a further Het;

R^{86} to R^{93} represent independently, at each occurrence, hydrogen or C_{1-6} alkyl;

X represent O or N;

b) the compound is not:

2-(4-nitrophenyl)-3-(pyrrolidin-1-ylcarbonyl)isoindolin-1-one;

N,2-dibenzyl-3-oxoisoindoline-1-carboxamide;

N,2-diethyl-3-oxoisoindoline-1-carboxamide;

N,2-dibutyl-3-oxoisoindoline-1-carboxamide;

N,2-didodecyl-3-oxoisoindoline-1-carboxamide;

N,2-bis(4-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;

3-oxo-N,2-dipropylisoindoline-1-carboxamide;

N,2-diheptyl-3-oxoisoindoline-1-carboxamide;

3-oxo-N,2-diphenylisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-propylisoindoline-1-carboxamide;

N-(tert-butyl)-1-methyl-3-oxo-2-propyl-isoindoline-1-carboxamide;

N,1-dimethyl-3-oxo-2-propylisoindoline-1-carboxamide;

N-cyclohexyl-3-oxo-2-propylisoindoline-1-carboxamide;

N-(phenyl)-3-oxo-2-propylisoindoline-1-carboxamide;

2-benzyl-N-tert-butyl-3-oxoisoindoline-1-carboxamide:

2-benzyl-N,1-dimethyl-3-oxoisoindoline-1-carboxamide;

2-benzyl-N-tert-butyl-1-methyl-3-oxoisoindoline-1-carboxamide;

2-benzyl-N,1-dimethyl-3-oxoisoindoline-1-carboxamide;

tert-butyl (4-{1-[(tert-butylamino)carbonyl]-3-oxo-1,3-dihydro-2H-isoindol-2-yl}butyl)carbamate;

2-benzyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

2-benzyl-N-butyl-3-oxoisoindoline-1-carboxamide;

2-benzyl-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide;

2-(2-hydroxyethyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-butyl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide;

2-(2-hydroxyethyl)-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide;

2-(3-(1H-imidazol-1-yl)propyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-butyl-2-[3-(1H-imidazol-1-yl)propyl]-3-oxoisoindoline-1-carboxamide;

2-[3-(1H-imidazol-1-yl)propyl]-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide

2-(cyclohexyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-butyl-2-cyclohexyl-3-oxoisoindoline-1-carboxamide;

2-cyclohexyl-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide;

N,2-dibenzyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-tert-butyl-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide;

N-benzyl-2-tert-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N,2-dibenzyl-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide;

N-benzyl-2-tert-butyl-5-hydroxy-3-oxoisoindoline-1-carboxamide;

2-cyclohexyl-N-hexyl-3-oxoisoindoline-1-carboxamide;

N,2-dihexyl-3-oxoisoindoline-1-carboxamide;

N-hexyl-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide;

N-hexyl-2-(4-hydroxybutyl)-3-oxoisoindoline-1-carboxamide;

N,2-dicyclohexyl-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-2-hexyl-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-2-(4-hydroxybutyl)-3-oxoisoindoline-1-carboxamide;

tert-butyl (4-{1-[(cyclohexylamino)carbonyl]-3-oxo-1,3-dihydro-2H-isoindol-2-yl}butyl)carbamate;

N-adamantan-1-yl-2-cyclohexyl-3-oxoisoindoline-1-carboxamide;

N-adamantan-1-yl-2-hexyl-3-oxoisoindoline-1-carboxamide;

N-adamantan-1-yl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide ;

N-adamantan-1-yl-2-(2-morpholin-4-ylethyl)-3-oxoisoindoline-1-carboxamide;

N,2-dibenzyl-5-{[(2-nitrophenyl)sulfonyl]amino}-3-oxoisoindoline-1-carboxamide;

ethyl [1-(tert-butylcarbamoyl)-3-oxo-1,3-dihydro-2H-isoindol-2-yl]acetate;

N-[2-(3,4-dimethoxyphenyl)ethyl]-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide

N-cyclopentyl-2-(3-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;

2-(1,3-benzodioxol-5-ylmethyl)-N-{[(4-methylphenyl)sulfonyl]methyl}-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide;

2-benzyl-N-cyclohexyl-3-oxoisoindoline-1-carboxamide;

N-{[(4-methylphenyl)sulfonyl]methyl}-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide;

2-(4-chlorobenzyl)-N-{[(4-methylphenyl)sulfonyl]methyl}-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-2-(2-furylmethyl)-3-oxoisoindoline-1-carboxamide;

2-(4-chlorobenzyl)-N-cyclohexyl-3-oxoisoindoline-1-carboxamide;

tert-butyl {1-benzyl-2-hydroxy-3-[(2-hydroxy-3-{[(3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbonyl]amino}-4-phenylbutyl)amino]propyl}carbamate;

1-hydroxy-2-methyl-3-oxo-N-(pyridin-2-ylmethyl)isoindoline-1-carboxamide;

N-[3-(dimethylamino)propyl]-1-hydroxy-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide;

N-(3-azepan-1-ylpropyl)-1-hydroxy-3-oxo-2-phenylisoindoline-1-carboxamide;

2-benzoyl-1-hydroxy-3-oxo-N-phenylisoindoline-1-carboxamide;

3-oxo-N,2-diphenylisoindoline-1-carboxamide;

6-{[(1-methyl-2-octyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbonyl]amino}hexanoic acid

N-(methyl)-2-benzoyl-1-hydroxy-3-oxoindoline-1-carboxamide;

N-(phenyl)-2-benzoyl-1-hydroxy-3-oxoisoindoline-1-carboxamide;

6-[(2-allyl-1-methyl-3-oxoisoindoline-1-carbonyl)-amino]-hexanoic acid;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-ethyl-3-oxoisoindoline-1-carboxamide;

N1-cyclopentyl-N4-(2,6-difluorophenyl)-2-(2,4-dimethylphenyl)-5-methyl-3-oxoisoindoline-1,4-dicarboxamide;

methyl [1-(tert-butylcarbamoyl)-3-oxo-1,3-dihydro-2H-isoindol-2-yl]acetate;

1-hydroxy-2-methyl-3-oxoisoinoline-1-carbohydrazide;

1-hydroxy-3-oxo-phenylisoindoline-1-carbohydrazide;

or a pharmaceutically acceptable derivative thereof;

c) the compound is not:

2-(2-ethoxyethyl)-N-isopropyl-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-(3-pyrrolidin-1-ylpropyl)isoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-(tetrahydrofuran-2-ylmethyl)isoindoline-1-carboxamide;

2-[1-(hydroxymethyl)butyl]-N-isopropyl-3-oxoisoindoline-1-carboxamide;

N-isopropyl-2-(3-methylbutyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-cyclohexyl-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-(3-methylbutyl)-3-oxoisoindoline-1-carboxamide;

methyl N-{[2-(3-methylbutyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;

tert-butyl N-({2-[1-(hydroxymethyl)butyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;

tert-butyl N-{[2-(3-methylbutyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;

N-(tert-butyl)-2-[1-(methoxymethyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(diethylamino)ethyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[1-(hydroxymethyl)butyl]-3-oxoisoindoline-1-carboxamide;

tert-butyl N-{[3-oxo-2-(2-thienylmethyl)-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;

tert-butyl N-({2-[2-(methylthio)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;
methyl N-{[2-(cyclopropylmethyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate; or
2-(2,2-dimethylpropyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide.
or a pharmaceutically acceptable derivative thereof.

The compounds of formula I as defined above are referred to hereinafter as "the compounds of the invention".

In one embodiment R^1 represents C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, -OR^8, -$COXR^{11}$, aryl or Het^1); further R^1 represents Het^2.

In one embodiment R^1 represents C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, -OR^8, -$COXR^{11}$, phenyl, naphthalenyl or Het^1).

In one embodiment R^1 represents
(1-benzylpyrrolidin-3-yl); (1-fluoro-3-phenyl-propan-2-yl); (1-methyl-5-phenyl-pyrazol-3-yl)methyl; (1-methylpyrrol-2-yl)methyl; (2,3-difluorophenyl)methyl; (2,4-difluorophenyl)methyl; (2,5-dimethoxyphenyl)methyl; (2,5-dimethylphenyl)methyl; (2-bromophenyl)methyl; (2-chloro-4-fluoro-phenyl)methyl; (2-chloro-6-phenoxy-phenyl)methyl; (2-chlorophenyl)methyl; (2-dimethylamino-2-phenyl-ethyl); (2-ethoxyphenyl)methyl; (2-fluorophenyl)methyl; (2-methoxyphenyl)methyl; (2-methyl-2-phenyl-propyl); (2-methylphenyl)methyl; (2-phenoxyphenyl)methyl; (2-phenylphenyl)methyl; (2-pyridin-3-ylphenyl)methyl; (3,4-dichlorophenyl)methyl; (3,4-difluorophenyl)methyl; (3,5-dimethoxyphenyl)methyl; (3-chlorophenyl)methyl; (3-cyano-4-fluoro-phenyl)methyl; (3-cyanophenyl)methyl; (3-fluorophenyl)methyl; (3-hydroxy-2,2-dimethyl-propyl); (3-methoxyphenyl)methyl; (3-phenyl1,2-oxazol-5-yl)methyl; (3-phenylphenyl)methyl; (3-pyrrol-1-ylphenyl)methyl; (4-chlorophenyl)methyl;

(4-dimethylaminophenyl)methyl; (4-fluorophenyl)methyl; (4-hydroxyphenyl)methyl; (4-methoxycarbonylphenyl)methyl; (4-phenoxyphenyl)methyl; (4-phenylphenyl)methyl; (5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl; (5-methyl-3-phenyl-1,2-oxazol-4-yl)methyl; (phenyl-pyridin-2-yl-methyl); [(1R)-1-(4-methoxyphenyl)ethyl]; [(1S)-1-phenylethyl]; [(1R)-1-phenylethyl]; [(1R)-2-(4-chlorophenyl)-1-(4,4,4- trifluorobutylcarbamoyl)ethyl]; [(1R)-2-(4-chlorophenyl)-1-methoxycarbonyl-ethyl]; [(1S)-1-naphthalen-1-ylethyl]; [(2R)-2-(4-chlorophenyl)propyl]; [(2S)-2-(4- chlorophenyl)propyl]; [(4-chlorophenyl)-pyridin-4-yl-methyl]; [(4-fluorophenyl)-pyridin-3-yl-methyl]; [(4-fluorophenyl)-pyridin-3-yl-methyl]; [(4-fluorophenyl)-pyridin-3-yl- methyl]; [2-(2,4-dichlorophenyl)phenyl]methyl; [2-(2,4-difluorophenyl)phenyl]methyl; [2-(2,5-difluorophenyl)phenyl]methyl; [2-(2-chlorophenyl)phenyl]methyl; [2-(3,4-dichlorophenyl)phenyl]methyl; [2-(3,4-difluorophenyl)phenyl]methyl; [2-(3-chloro-4-fluoro-phenyl)phenyl]methyl; [2-(3-fluorophenyl)phenyl]methyl; [2-(4-chloro-2-methyl-phenyl)-2,2-difluoro-ethyl]; [2-(4-chlorophenyl)phenyl]methyl; [2-(4-fluoro-2-methyl-phenyl)phenyl]methyl; [2-(4-fluorophenoxy)phenyl]methyl; [2-(4-fluorophenyl)phenyl]methyl; [2-(4-methoxyphenyl)-2-oxo-ethyl]; [2-(4-methoxyphenyl)phenyl]methyl; [2-(4-methylphenyl)phenyl]methyl; [2-(trifluoromethyl)phenyl]methyl; [2-[4-(trifluoromethyl)phenoxy]phenyl]methyl; [3-(difluoromethoxy)phenyl]methyl; [3,5-bis(trifluoromethyl)phenyl]methyl; [4-(difluoromethoxy)phenyl]methyl; [4-(trifluoromethyl)phenyl]methyl; 1-(1H-indol-3-yl)propan-2-yl; 1-(4-fluorophenyl)ethyl; 1-naphthalen-1-ylethyl; 1-naphthalen-2-ylethyl; 1-phenylethyl; 1-phenylpropyl; 2-(1-cyclohexenyl)ethyl; 2-(2-ethoxyphenyl)ethyl; 2-(2-methoxyphenyl)ethyl; 2-(2-phenoxyphenyl)ethyl; 2-(3,4-dichlorophenyl)ethyl; 2-(3,5-dimethoxyphenyl)ethyl; 2-(3-bromo-4-methoxy-phenyl)ethyl; 2-(3-fluorophenyl)ethyl; 2-(4-bromophenyl)ethyl; 2-(4-chlorophenyl)ethyl; 2-(4-chlorophenyl)propyl; 2-(4-fluorophenoxy)propyl; 2-(4-fluorophenyl)ethyl; 2-(4-fluorophenyl)propyl; 2-(4-phenoxyphenyl)ethyl; 2-(4-methoxyphenyl)ethyl; 2-(4-methoxyphenyl)ethyl; 2-(4-phenylphenyl)ethyl; 2-(5-bromo-2-methoxy-phenyl)ethyl; 2-(6-chloro-1H-indol-3-yl)ethyl; 2,2-dimethylpropyl; 2,2-diphenylethyl; 2-[2-(trifluoromethoxy)phenyl]ethyl; 2-[3-(trifluoromethyl)phenyl]ethyl; 2-[4-(diethylcarbamoyl)phenyl]ethyl; 2-[4-(trifluoromethyl)phenyl]ethyl; 2-benzo[1,3]dioxol-5-ylethyl; 2-methylbutyl; 2-methylpropyl; 2-naphthalen-1-ylpropyl; 2-phenoxypropyl; 2-phenylpropyl; 2-thiophen-2-ylethyl; 3,3-dimethylbutyl; 3-phenylpropyl; 3-pyrrolidin-1-ylpropyl; 4-phenylbutan-2-yl;

4-phenylbutyl; 9H-fluoren-9-yl; benzhydryl; benzyl; cycloheptyl; cyclohexyl; cyclohexylmethyl; naphthalen-1-ylmethyl; pentan-3-yl; phenethyl; thiophen-2-ylmethyl; 2-phenylpropan-2-yl; 1-phenylpropyl; [2-(4-chlorophenyl)-2-methyl-propyl]; [4-fluoro-2-(4-fluorophenyl)phenyl]methyl; (4-fluoro-2-phenyl-phenyl)methyl; [5-fluoro-2-(4-fluorophenyl)phenyl]methyl; (5-fluoro-2-phenyl-phenyl)methyl; 1-(4-fluorophenyl)ethyl; 2-(4-chlorophenyl)propan-2-yl; 2-(4-fluorophenyl)propan-2-yl or 1-(4-chlorophenyl)ethyl.

(The naming of the radicals was made using a program from Lexichem package from Openeye, version 4.)

In one embodiment R^2 represents C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, $-COR^{17}$, trimethylsilyl, $-COXR^{18}$, aryl or Het^3);
further R^2 represent aryl or Het^4.

In one embodiment R^2 represents
(1-benzylpyrrolidin-3-yl); (1-methylpyrrol-2-yl)methyl; (2,2-difluorobenzo[1,3]dioxol-5-yl)methyl; (2,3-dimethylcyclohexyl); (2,4-difluorophenyl)methyl; (2-chloro-4-methylsulfonyl-phenyl)methyl; (2-chlorophenyl)methyl; (2-fluoro-4-methylsulfonyl-phenyl)methyl; (2-hydroxyphenyl)methyl; (2-methylpropan-2-yl)oxycarbonylmethyl; (3,4-dichlorophenyl)methyl; (3,4-difluorophenyl)methyl; (3,4-imethoxyphenyl)methyl; (3-carbamoyl-4-fluoro-phenyl)methyl; (3-chlorophenyl)methyl; (3-cyano-4-fluoro-phenyl)methyl; (3-cyanophenyl)methyl; (3-methoxyphenyl); (3-methyl-5-phenyl-1,2-oxazol-4-yl)methyl; (4-amino-2-methyl-pyrimidin-5-yl)methyl; (4-carbamoylphenyl); (4-carbamoylphenyl)methyl; (4-cyano-2,6-difluoro-phenyl)methyl; (4-cyanophenyl); (4-cyanophenyl)methyl; (4-dimethylaminophenyl)methyl; (4-fluorophenyl)methyl; (4-hydroxyphenyl)methyl; (4-methylcyclohexyl); (4-methylsulfonylphenyl)methyl; (5-methyl-1,2-oxazol-3-yl)methyl; (5-methyl-2-furyl)methyl; (5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl; (5-methylpyrazin-2-yl)methyl; [2-(trifluoromethyl)phenyl]methyl; [3-(aminomethyl)-4-fluoro-phenyl]methyl; [3-(difluoromethoxy)phenyl]methyl; [3-(dimethylcarbamoyl)-4-fluoro-phenyl]methyl; [3-(trifluoromethyl)phenyl]methyl; [3,5-

bis(trifluoromethyl)phenyl]methyl; [3-[[(2,2-difluoroacetyl)amino]methyl]-4-fluoro-phenyl]methyl; [4-(acetamidomethyl)phenyl]methyl; [4-(aminomethyl)phenyl]; [4-(difluoromethoxy)phenyl]methyl; [4-(trifluoromethyl)phenyl]methyl; [4-[[(2,2-difluoroacetyl)amino]methyl]phenyl]; [4-[[(2-fluoroacetyl)amino]methyl]phenyl]methyl; [5-(2-furyl)1,2-oxazol-3-yl]methyl; [6-(trifluoromethyl)pyridin-3-yl]methyl; 1H-indol-3-ylmethyl; 1-pyridin-4-ylethyl; 2-(1H-indol-3-yl)ethyl; 2-(2,4-dichlorophenyl)ethyl; 2-(2,6-dichlorophenyl)ethyl; 2-(2-chlorophenyl)ethyl; 2-(3,4-dichlorophenyl)ethyl; 2-(3,4-dimethoxyphenyl)ethyl; 2-(3-chlorophenyl)ethyl; 2-(3-fluorophenyl)ethyl; 2-(4-benzoylpiperazin-1-yl)ethyl; 2-(4-chlorophenyl)ethyl; 2-(4-fluorophenyl)ethyl; 2-(4-methoxyphenyl)ethyl; 2-[3-(trifluoromethyl)phenyl]ethyl; 2-benzo[1,3]dioxol-5-ylethyl; 2-ethoxycarbonylethyl; 2-furylmethyl; 2-methoxyethyl; 2-pyridin-2-ylethyl; 2-pyridin-4-ylethyl; 2-thiophen-2-ylethyl; 3-imidazol-1-ylpropyl; 3-methoxypropyl; 4,4,4-trifluorobutyl; 4,4-difluorobutyl; benzo[1,3]dioxol-5-ylmethyl; benzotriazol-1-ylmethyl; benzyl; butyl; cyclohexyl; ethyl; methoxycarbonylmethyl; phenethyl; propan-2-yl; propyl; pyridin-3-ylmethyl; pyridin-4-ylmethyl; tert-butyl; trimethylsilylmethyl; (5-oxo-1-propan-2-yl-pyrrolidin-3-yl)methyl; propan-2-ylcarbamoylmethyl, (2-fluorophenyl)methyl; (3-fluorophenyl)methyl; 1-phenylethyl; 2-phenylpropan-2-yl; or 5-cyanopentyl.

(The naming of the radicals was made using a program from Lexichem package from Openeye, version 4.)

In one embodiment R^1 represents C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, -OR^8, -$COXR^{11}$, aryl or Het^1); further R^1 represents Het^2; and
R^2 represents C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_7 cycloalkyl, –COR^{17}, trimethylsilyl, –$COXR^{18}$, aryl or Het^3); further R^2 represents aryl or Het^4.

In one embodiment R^1 represents C_3-C_8 cycloalkyl (which cycloalkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, -OR^8, -$COXR^{11}$, aryl or Het^1); and

R^2 represents C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_7 cycloalkyl, –COR^{17}, trimethylsilyl, –$COXR^{18}$, aryl or Het^3); further R^2 represents aryl or Het^4.

In one embodiment R^3 represents hydrogen, C_1-C_4 alkyl (which alkyl group is optionally substituted by one or more groups selected from fluoro, C_2-C_6 alkenyl, trialkylsilyl, –$COXR^{27}$, aryl or Het^5).

In one embodiment R^3 represents hydrogen.

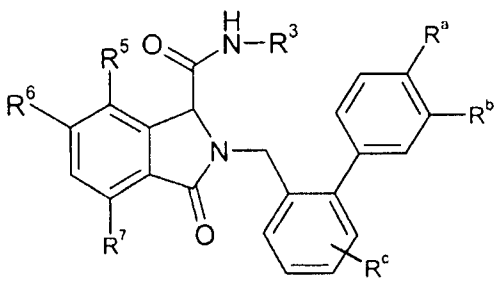
In one embodiment R^4 represents hydrogen.

In one embodiment R^5 to R^7 independently represent, at each occurence, hydrogen, -OH, halogen, cyano, C_{1-6} alkyl, -OR^{36}, -$C(O)N(R^{40a})(R^{40b})$, -$N(R^{44a})S(O)_2R^{44b}$.

In one embodiment aryl is, independently, at each occurrence, optionally substituted by –OH, halogen, cyano, nitro, C_1-C_6 alkyl, -OR^{50}, C_2-C_6 alkenyl, phenyl, Het^8; wherein R^{50} represents C_1-C_6 alkyl or aryl.

In one embodiment aryl is, at each occurrence, phenyl.

In an embodiment of this invention the compound of formula I is



in which R^a is hydrogen or fluoro;

R^b is hydrogen or fluoro;

R^c is hydrogen or fluoro;

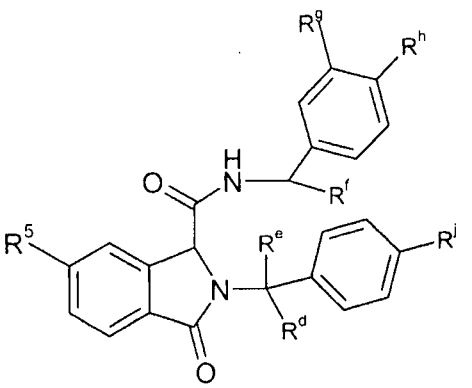
R^3 is C_{1-4} alkyl optionally terminally substituted by 1, 2 or 3 fluoro;

R^5 is hydrogen or C_{1-4} alkyl,

R^6 is hydrogen, OH, halo or C_{1-4}alkoxy;

R^7 is hydrogen or halo.

In an embodiment of this invention the compound of formula I is



in which

R^d is hydrogen or C_{1-4} alkyl;

R^e is hydrogen or C_{1-4} alkyl;

R^f is hydrogen or C_{1-4} alkyl;

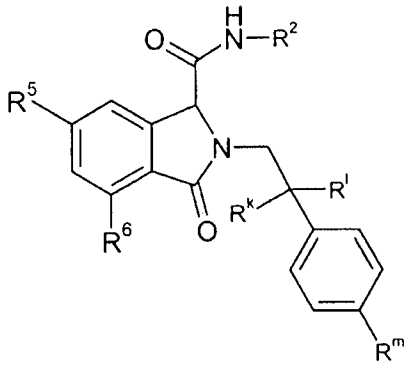
R^g is hydrogen or halo;

R^h is hydrogen or halo;

R^j is hydrogen or halo;

R^5 is hydrogen or halo.

In an embodiment of this invention the compound of formula I is



in which

R^k is hydrogen or C_{1-4} alkyl;

R^l is hydrogen or C_{1-4} alkyl;

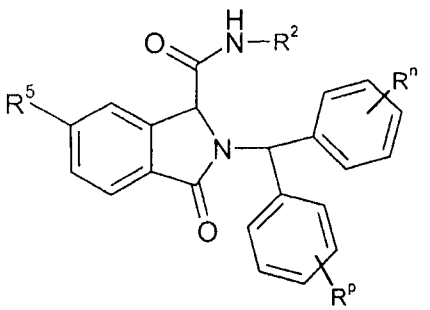
R^m is hydrogen or halo;

R^2 is C_{3-6} alkyl;

R^5 is hydrogen or halo;

R^6 is hydrogen or halo.

In an embodiment of this invention the compound of formula I is



in which

R^n is hydrogen or halo;

R^p is hydrogen or halo;

R^2 is C_{3-6} alkyl or benzyl, optionally substituted by halo in the phenyl ring;

R^5 is hydrogen or halo.

In an embodiment of this invention R^1 is (2-phenylphenyl)methyl (biphenylmethyl), optionally substituted by one to three fluoro;

R^2 is selected from ethyl, propyl, n-butyl, tert-butyl, 4,4,4-trifluorobutyl, 4,4-difluorobutyl, 4-fluorobutyl, benzo[1,3]dioxol-5-yl-methyl, (2,2-difluorobenzo[1,3]dioxol-5-yl)methyl, benzyl, (2-chlorophenyl)methyl, (4-fluorophenyl)methyl, (2-trifluoromethylphenyl)methyl, (3-cyanophenyl)methyl, (4-cyanophenyl)methyl, (3-cyano-4-fluorophenyl)methyl, (4-carbamoylphenyl)methyl, (5-methylpyrazin-2-yl)methyl, pyridin-3-ylmethyl, (4-amino-2-methyl-pyrimidin-5-yl)methyl, [6-(trifluoromethyl)pyridin-3-yl]methyl, pyridin-3-ylmethyl, [6-(trifluoromethyl)pyridin-3-yl]methyl, pyridin-4-ylmethyl, [4-[[(2,2-difluoroacetyl)amino]methyl]phenyl]methyl, [4-(acetamidomethyl)phenyl]methyl, [4-[[(2-fluoroacetyl)amino]methyl]phenyl]methyl, 2-phenylethyl or 2-(4-fluorophenyl)ethyl;

R^5 to R^7 are independently selected from –OH, methyl, methoxy, chloro, fluoro, cyano, methylsulfonylamino, fluoromethoxy, difluoromethoxy, trifluoromethanesulfonate;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to $R^7$are independently selected from hydrogen, –OH, methyl, methoxy, fluoro or chloro;

or an enantiomer thereof.

In an embodiment of this invention R^1 is benzhydryl (diphenylmethyl), optionally substituted by one or more substitutents selected from fluoro or chloro;

R^2 is selected from ethyl, propyl, butyl, tert-butyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, benzyl, (2-chloro-4-methylsulfonyl-phenyl)methyl, (4-methylsulfonylphenyl)methyl, (2-fluoro-4-methylsulfonyl-phenyl)methyl, (4-methylsulfonylphenyl)methyl, (2-hydroxyphenyl)methyl, [2-(trifluoromethyl)phenyl]methyl, (2,4-difluorophenyl)methyl, (2-chlorophenyl)methyl, 2-(4-fluorophenyl)ethyl

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to $R^7$are independently selected from hydrogen, –OH, methyl, methoxy, fluoro or chloro;

or an enantiomer thereof.

In an embodiment of this invention R^1 is 4-phenylbutan-2-yl, optionally substituted by one or more substitutents selected from fluoro or chloro;
R^2 is selected from (2-chlorophenyl)methyl, [2-(trifluoromethyl)phenyl]methyl, benzyl, 2-phenylethyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to $R^7$are independently selected from hydrogen, –OH, methyl, methoxy, fluoro or chloro;
or an enantiomer thereof.

In an embodiment of this invention R^1 is 3,3-dimethylbutyl;
R^2 is selected from [3-(difluoromethoxy)phenyl]methyl, [3-(trifluoromethoxy)phenyl]methyl, 2-(1H-indol-3-yl)ethyl, 1H-indol-3-ylmethyl, (3-chlorophenyl)methyl, (3,4-dichlorophenyl)methyl, [4-(difluoromethoxy)phenyl]methyl, 2-(3-fluorophenyl)ethyl, 2-benzo[1,3]dioxol-5-ylethyl, 2-[3-(trifluoromethyl)phenyl]ethyl, 2-(3,4-dichlorophenyl)ethyl, 2-(2,4-dichlorophenyl)ethyl, 2-(2,6-dichlorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(3-chlorophenyl)ethyl or 2-(2-chlorophenyl)ethyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to $R^7$are independently selected from hydrogen, –OH, methyl, methoxy, fluoro or chloro;
or an enantiomer thereof.

In an embodiment of this invention R^1 is benzyl (phenylmethyl), optionally substituted by one or more substiutents selected from fluoro, chloro, cyano;
R^2 is selected from ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, benzo[1,3]dioxol-5-yl-methyl, benzyl, 1-phenylethyl, 2-phenylethyl, cyclopentyl, which groups are optionally substituted by one or more substiutents selected from fluoro, chloro, cyano, trifluoromethyl;

further R^2 represents pyridin-3-ylmethyl, pyridin-4-ylmethyl, [3-[[(2,2-difluoroacetyl)amino]methyl]-4-fluoro-phenyl]methyl, [4-(difluoromethoxy)phenyl]methyl, (4-dimethylaminophenyl)methyl, [5-(2-furyl)1,2-oxazol-3-yl]methyl, [5-(2-furyl)1,2-oxazol-3-yl]methyl, 2-(3,4-dimethoxyphenyl)ethyl, butan-2-yl, cyclopentyl, (2,3-dimethylcyclohexyl), (4-hydroxyphenyl)methyl, [2-(trifluoromethyl)phenyl]methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to $R^7$are independently selected from hydrogen, –OH, methyl, methoxy, bromo, chloro, fluoro, trimethylsilyl;

or an enantiomer thereof.

In an embodiment of this invention R^1 is (2-cyclopentylphenyl)methyl;

R^7 is selected from 4,4-difluorobutyl, methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from bromo, fluoro, chloro or cyano;

or an enantiomer thereof.

In an embodiment of this invention R^1 is 1-phenylethyl, optionally substituted by one or more substiutents selected from fluoro, chloro, cyano, methoxy;

R^2 is selected from ethyl, propyl, tert-butyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, 4-methylsulfonyl, benzyl, which benzyl group is optionally substituted by one or more substituents selected from fluoro, chloro, cyano;

further R^2 represents pyridinmethyl, ((2,2-difluoroacetyl)amino)methyl, difluoromethoxy, dimethylamino, 5-(2-furyl)1,2-oxazol-3-yl-methyl, cyclopentyl

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from bromo, fluoro, chloro or cyano;

or an enantiomer thereof.

In an embodiment of this invention R^1 is 3-hydroxy-2,2-dimethylpropyl;

R^2 is selected from [3-(difluoromethoxy)phenyl]methyl, (3,4-dichlorophenyl)methyl, (3-chlorophenyl)methyl, [3-(trifluoromethyl)phenyl]methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, fluoro, chloro;

or an enantiomer thereof.

In an embodiment of this invention R^1 is 2-(4-chlorophenyl)propyl;

R^2 is selected from methyl, ethyl, n-propyl, propan-2-yl, butyl, (4-amino-2-methyl-pyrimidin-5-yl)methyl, (5-methylpyrazin-2-yl)methyl, pyridin-3-ylmethyl, [6-(trifluoromethyl)pyridin-3-yl]methyl, (4-amino-2-methyl-pyrimidin-5-yl)methyl, [6-(trifluoromethyl)pyridin-3-yl]methyl, (5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl, 4,4,4-trifluorobutyl, (4-methylsulfonylphenyl)methyl, benzyl (2,2-difluorobenzo[1,3]dioxol-5-yl)methyl, (4-methylsulfonylphenyl)methyl, butyl, 2-(1H-indol-3-yl)ethyl; (4-carbamoylphenyl)methyl, (4-cyanophenyl)methyl, [3-(dimethylcarbamoyl)-4-fluoro-phenyl]methyl, [3-(dimethylcarbamoyl)-4-fluoro-phenyl]methyl, [4-(aminomethyl)phenyl], [4-[[(2,2-difluoroacetyl)amino]methyl]phenyl], (4-carbamoylphenyl), pyridin-4-ylmethyl, 3-methoxypropyl, (3-cyano-4-fluoro-phenyl)methyl, [3-[[(2,2-difluoroacetyl)amino]methyl]-4-fluoro-phenyl]methyl, [3-(aminomethyl)-4-fluoro-phenyl]methyl, (3-carbamoyl-4-fluoro-phenyl)methyl, 2-pyridin-4-ylethyl, (1-methylpyrrol-2-yl)methyl, [4-(difluoromethoxy)phenyl]methyl, (1-benzylpyrrolidin-3-yl), 3-imidazol-1-ylpropyl, (4-dimethylaminophenyl)methyl, (4-methylsulfonylphenyl)methyl, 3-imethylaminopropyl, 1-pyridin-3-ylethyl, (3-methoxyphenyl), 1-pyridin-4-ylethyl, (4-cyanophenyl), 3-methoxypropyl, benzo[1,3]dioxol-5-ylmethyl, (3,4-dimethoxyphenyl)methyl, (3-methyl-5-phenyl-1,2-oxazol-4-yl)methyl, (5-methyl 1,2-oxazol-3-yl)methyl, [2-(trifluoromethyl)phenyl]methyl, (2-chlorophenyl)methyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-thiophen-2-ylethyl, 2-(4-methoxyphenyl)ethyl, 2-phenylethyl, 2-methoxyethyl, (4-fluorophenyl)methyl, methoxycarbonylmethyl or benzotriazol-1-ylmethyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro;

or an enantiomer thereof.

In an embodiment of this invention R1 is 2-(4-chlorophenyl)propyl;
R^2 represents tert-butyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, -OH, bromo, fluoro, chloro, methyl, $-OCH_3$, $-OCH_2F$, trimethylsilyl;
or an enantiomer thereof.

In an embodiment of this invention R^1 is 2-(4-fluorophenyl)propyl;
R^2 represents 4,4,4-trifluorobutyl, benzyl, tert-butyl, butyl,
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, -OH, bromo, fluoro, chloro, methoxy;
or an enantiomer thereof.

In an embodiment of this invention R^1 is 2,2-dimethylpropyl;
R^2 represents [3-(trifluoromethoxy)phenyl]methyl
[3-(difluoromethoxy)phenyl]methyl, (3,4-dichlorophenyl)methyl, 2-[3-(trifluoromethyl)phenyl]ethyl, 2-(1H-indol-3-yl)ethyl, (3-chlorophenyl)methyl, [4-(difluoromethoxy)phenyl]methyl, [3-(trifluoromethyl)phenyl]methyl, 2-(3-fluorophenyl)ethyl,
2-(2-chlorophenyl)ethyl, 2-(3-chlorophenyl)ethyl, 2-(2,4-dichlorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(2,6-dichlorophenyl)ethyl, benzo[1,3]dioxol-5-ylmethyl,
or benzyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro,
or an enantiomer thereof.

In an embodiment of this invention R^1 is 2-phenylpropan-2-yl;

R^2 represents benzyl, 1-phenylethyl, (4-fluorophenyl)methyl,4,4,4-trifluorobutyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro,
or an enantiomer thereof.

In an embodiment of this invention R^1 is 1-phenylpropyl;
R^2 is benzyl, (2-chlorophenyl)methyl, [2-(trifluoromethyl)phenyl]methyl or(4-dimethylaminophenyl)methyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro;
or an enantiomer thereof.

In an embodiment of this invention R^1 is [2-(4-chlorophenyl)-2-methyl-propyl];
R^2 represents n-butyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro or chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is (2-chlorophenyl)methyl;
R^1 represents benzhydryl, (2-pyridin-3-ylphenyl)methyl, (3,4-difluorophenyl)methyl 1-(1H-indol-3-yl)propan-2-yl, 2-(4-chlorophenyl)propyl, (2,5-dimethylphenyl)methyl, [(1R)-1-(4-methoxyphenyl)ethyl], 2-(1H-indol-3-yl)propyl, [(1R)-1-(3-methoxyphenyl)ethyl],
[(1S)-1-naphthalen-1-ylethyl], 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenethyl,
4-phenylbutan-2-yl, (2-phenylphenyl)methyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

In an embodiment of this invention R^2 is (3,4-dichlorophenyl)methyl;
R^1 is (3-hydroxy-2,2-dimethyl-propyl), 2,2-dimethylpropyl, 2-methylpropyl or 3,3-dimethylbutyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is (3-chlorophenyl)methyl;
R^1 represents (3-hydroxy-2,2-dimethyl-propyl), 2-methylpropyl, 2,2-dimethylpropyl, 3,3-dimethylbutyl, (4-hydroxyphenyl)methyl or (3-cyanophenyl)methyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is (3-cyano-4-fluoro-phenyl)methyl;
R^1 is (2-chloro-4-fluoro-phenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl, (3-cyano-4-fluoro-phenyl)methyl, 2-phenylethyl, benzyl, (3,4-difluorophenyl)methyl, (2-phenylphenyl)methyl or 2-(4-chlorophenyl)propyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is (3-cyanophenyl)methyl;
R^1 is (2-phenylphenyl)methyl, (3-chlorophenyl)methyl, (3,4-difluorophenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl or [4-(trifluoromethyl)phenyl]methyl;
R^3 is hydrogen;
R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is (4-fluorophenyl)methyl;
R^1 is [(4-chlorophenyl)-pyridin-4-yl-methyl], [(4-fluorophenyl)-pyridin-3-yl-methyl], (phenyl-pyridin-2-yl-methyl), 2-(4-methoxyphenyl)ethyl, (4-chlorophenyl)methyl, (2-phenylphenyl)methyl, benzhydryl, (2-pyridin-3-ylphenyl)methyl, (3,4-difluorophenyl)methyl, (1-fluoro-3-phenyl-propan-2-yl), (1-methylpyrrol-2-yl)methyl, (2-phenylphenyl)methyl, 2-(4-chlorophenyl)propyl, 1-(4-chlorophenyl)ethyl, 2-(4-chlorophenyl)propan-2-yl, 2-(4-fluorophenyl)propan-2-yl, 2-phenylpropan-2-yl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is (4-hydroxyphenyl)methyl;
R^1 is (3,4-difluorophenyl)methyl, (3-chlorophenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl or [4-(trifluoromethyl)phenyl]methyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is [2-trifluoromethyl)phenyl]methyl;
R^1 is (2-methoxyphenyl)methyl, (2-fluorophenyl)methyl, benzhydryl, 2-(4-chlorophenyl)ethyl, [4-(piperidine-1-carbonyl)phenyl]methyl, 2-(4-chlorophenyl)propyl, (2-phenylphenyl)methyl, 1-phenylpropyl, 2-phenylpropyl, 4-phenylbutan-2-yl, 2-phenylethyl,
3-phenylpropyl, 2-methylbutyl, cyclohexylmethyl, (3-fluorophenyl)methyl, (2-ethoxyphenyl)methyl, [4-(trifluoromethoxy)phenyl]methyl or (3,4-difluorophenyl)methyl
R^3 is hydrogen;
R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, methoxy or methyl;
or an enantiomer thereof.

In an embodiment of this invention R^2 is [3-difluoromethoxy)phenyl]methyl;
R^1 is 1-phenylethyl, (3-hydroxy-2,2-dimethyl-propyl), 3,3-dimethylbutyl or 2,2-dimethylpropyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is [3-trifluoromethoxy)phenyl]methyl;
R^1 represents 3,3-dimethylbutyl or 2,2-dimethylpropyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is [3-trifluoromethyl)phenyl]methyl;
R^1 is (3-hydroxy-2,2-dimethyl-propyl), 2-methylpropyl, 3,3-dimethylbutyl, 2,2-dimethylpropyl or (1-methylpyrrol-2-yl)methyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is [4-difluoromethoxy)phenyl]methyl;
R^1 is 2-methylpropyl, 3,3-dimethylbutyl, 2,2-dimethylpropyl, (2-chloro-4-fluoro-phenyl)methyl, 2-(4-chlorophenyl)propyl or [3,5-bis(trifluoromethyl)phenyl]methyl;
R^3 is hydrogen;
R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is [6-(trifluoromethyl)pyridin-3-yl]methyl;
R^1 is 2-(4-chlorophenyl)propyl or (2-phenylphenyl)methyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is 2-(1H-indol-3-yl)ethyl;
R^1 is 2-(4-chlorophenyl)propyl, 2-(2-phenoxyphenyl)ethyl, 2-[4-(diethylcarbamoyl)phenyl]ethyl, 2-(3-fluorophenyl)ethyl, 2-[2-(trifluoromethoxy)phenyl]ethyl, 2-(4-fluorophenyl)ethyl, 2-(3,5-dimethoxyphenyl)ethyl, 2-(4-phenylphenyl)ethyl, 2-(4-phenoxyphenyl)ethyl, 2-(2-ethoxyphenyl)ethyl or 2-benzo[1,3]dioxol-5-ylethyl, 2,2-dimethylpropyl, 3,3-dimethylbutyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is 2-(2,4-dichlorophenyl)ethyl;
R^1 is 2-methylpropyl, 3,3-dimethylbutyl or 2,2-dimethylpropyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is 2-(2,6-dichlorophenyl)ethyl;
R^1 is 2-methylpropyl, 3,3-dimethylbutyl or 2,2-dimethylpropyl;
R^3 is hydrogen;
R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is 4,4,4-trifluorobutyl;
R^1 is [2-(trifluoromethyl)phenyl]methyl, [(1R)-1-phenylethyl], benzhydryl, 2-(4-chlorophenyl)propyl, (2-phenylphenyl)methyl, (2-phenoxyphenyl)methyl, (2-phenylphenyl)methyl, 2-(4-chlorophenyl)ethyl, 2-(4-fluorophenyl)ethyl, 2-(4-fluorophenyl)propyl, 2-(4-chlorophenyl)propan-2-yl, 2-(4-fluorophenyl)propan-2-yl or 2-phenylpropan-2-yl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, –OH, methyl, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is 4,4-difluorobutyl;
R^1 is (2-cyclopentylphenyl)methyl, [2-(trifluoromethyl)phenyl]methyl, [(1R)-1-phenylethyl], (2-phenylphenyl)methyl, benzhydryl, 2-(4-chlorophenyl)propyl or (2-phenylphenyl)methyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;
or an enantiomer thereof.

In an embodiment of this invention R^2 is benzyl;
R^1 represents benzyl, benzhydryl, [2-(trifluoromethyl)phenyl]methyl, (2-pyridin-3-ylphenyl)methyl, (4-phenoxyphenyl)methyl, (2,4-difluorophenyl)methyl, [4-(difluoromethoxy)phenyl]methyl, [3-(difluoromethoxy)phenyl]methyl, (3-pyrrol-1-ylphenyl)methyl, (3-fluorophenyl)methyl, (4-cyanophenyl)methyl, (3,5-dimethoxyphenyl)methyl, (2-methoxyphenyl)methyl, (2-ethoxyphenyl)methyl, [4-(trifluoromethyl)phenyl]methyl, (3,4-difluorophenyl)methyl, (2,5-dimethylphenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl, (2-methylphenyl)methyl, (2,3-

difluorophenyl)methyl, (2-bromophenyl)methyl, [(4-fluorophenyl)-pyridin-3-yl-methyl], [(4-chlorophenyl)-pyridin-4-yl-methyl], (phenyl-pyridin-2-yl-methyl), (1-methyl-5-phenyl-pyrazol-3-yl)methyl, (5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl, (5-methyl-3-phenyl-1,2-oxazol-4-yl)methyl, (3-phenyl1,2-oxazol-5-yl)methyl, 2-(4-chlorophenyl)ethyl, 2-(4-fluorophenyl)ethyl, 2-[4-(trifluoromethyl)phenyl]ethyl, 2-(5-bromo-2-methoxy-phenyl)ethyl, 2-(3-bromo-4-methoxy-phenyl)ethyl, 2-(4-fluorophenyl)propyl, 2-(4-chlorophenyl)propyl, 4-phenylbutan-2-yl, [2-(4-chloro-2-methyl-phenyl)-2,2-difluoro-ethyl], 2-naphthalen-1-ylpropyl, (2-methyl-2-phenyl-propyl), 2-phenoxypropyl, 2-(4-fluorophenoxy)propyl, 2-phenylpropan-2-yl, cycloheptyl, 2-(2-methoxyphenyl)ethyl, 1-naphthalen-1-ylethyl, 2-[3-(trifluoromethyl)phenyl]ethyl, 2-(6-chloro-1H-indol-3-yl)ethyl, 2-(4-chlorophenyl)propyl, [(1R)-1-(4-methoxyphenyl)ethyl], [(1R)-1-(3-methoxyphenyl)ethyl], 4-phenylbutan-2-yl, 1-phenylethyl, 2-phenylethyl, 1-naphthalen-2-ylethyl, 2-(1-cyclohexenyl)ethyl, 1-(4-fluorophenyl)ethyl, 2-(4-fluorophenyl)propan-2-yl, 2-phenylpropan-2-yl, 1-phenylpropyl or (2-phenylphenyl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5- R^7 are independently selected from hydrogen, bromo, fluoro and chloro, -OH, methyl, or methoxy;

or an enantiomer thereof.

In an embodiment of this invention R^2 is n-butyl;

R^1 is (2-phenylphenyl)methyl, (2-phenoxyphenyl)methyl, [2-(4-fluorophenoxy)phenyl]methyl, 2-(3-fluorophenyl)ethyl, 2-(4-fluorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-[4-(trifluoromethyl)phenyl]ethyl, 2-(4-chlorophenyl)propyl, 2-(4-fluorophenyl)propyl, (2-phenylphenyl)methyl, 2-(4-phenylphenyl)ethyl, 2-naphthalen-1-ylpropyl,

2-(2-ethoxyphenyl)ethyl, 2-(2-phenoxyphenyl)ethyl, 2-(4-phenoxyphenyl)ethyl, 2-[2-(trifluoromethoxy)phenyl]ethyl, 2-(3,5-dimethoxyphenyl)ethyl, 2-benzo[1,3]dioxol-5-ylethyl,

(1-fluoro-3-phenyl-propan-2-yl), 2-(4-chlorophenyl)propyl, naphthalen-1-ylmethyl, 1-naphthalen-2-ylethyl, (2-phenylphenyl)methyl, [2-(4-chlorophenyl)-2-methyl-propyl];

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH, methyl, methoxy;

or an enantiomer thereof.

In an embodiment of this invention R^2 is ethyl;

R^1 is benzhydryl, (2-phenylphenyl)methyl or 2-(4-chlorophenyl)propyl

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH, methyl, methoxy;

or an enantiomer thereof.

In an embodiment of this invention R^2 is 2-phenylethyl;

R^1 is (2-phenylphenyl)methyl, 2-(4-methoxyphenyl)ethyl, (4-chlorophenyl)methyl, 2-(4-chlorophenyl)ethyl, 2-(3,4-dichlorophenyl)ethyl, (3,4-difluorophenyl)methyl, 2-(4-chlorophenyl)propyl, (2-chloro-4-fluoro-phenyl)methyl or 4-phenylbutan-2-yl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH, methyl, methoxy;

or an enantiomer thereof.

In an embodiment of this invention R^2 is propyl;

R^1 is (2-phenylphenyl)methyl, benzhydryl or 2-(4-chlorophenyl)propyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH, methyl, methoxy;

or an enantiomer thereof.

In an embodiment of this invention R^2 is pyridin-3-ylmethyl or pyridin-4-ylmethyl;
R^1 is (2-phenylphenyl)methyl, 2-(4-chlorophenyl)propyl, (3,4-difluorophenyl)methyl, (2-chloro-4-fluoro-phenyl)methyl or 1-(4-fluorophenyl)ethyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH;
or an enantiomer thereof.

In an embodiment of this invention R^2 is tert-butyl;
R^1 is (2-phenylphenyl)methyl, [2-(trifluoromethyl)phenyl]methyl, [4-(difluoromethoxy)phenyl]methyl, (2-chlorophenyl)methyl, (2-methoxyphenyl)methyl, (3,4-difluorophenyl)methyl, (3,4-difluorophenyl)methyl, (4-phenoxyphenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl, (4-fluoro-2-phenyl-phenyl)methyl, (5-fluoro-2-phenyl-phenyl)methyl, 1-phenylethyl, 2-(4-chlorophenyl)ethyl, 2-(2-phenoxyphenyl)ethyl, 2-[2-(trifluoromethoxy)phenyl]ethyl, 2,2-diphenylethyl, 2-(4-fluorophenyl)propyl, 2-(4-chlorophenyl)propyl, (2-phenylphenyl)methyl, 2-(4-phenylphenyl)ethyl, [2-(3-fluorophenyl)phenyl]methyl, [2-(4-fluorophenyl)phenyl]methyl, [2-(3,4-difluorophenyl)phenyl]methyl, [2-(2,4-difluorophenyl)phenyl]methyl, [2-(2,5-difluorophenyl)phenyl]methyl, [2-(2,4-dichlorophenyl)phenyl]methyl, [2-(3,4-dichlorophenyl)phenyl]methyl, [2-(2-chlorophenyl)phenyl]methyl, [2-(4-chlorophenyl)phenyl]methyl,
[2-(4-methylphenyl)phenyl]methyl, [2-(4-fluoro-2-methyl-phenyl)phenyl]methyl,
[2-(4-methoxyphenyl)phenyl]methyl, [4-fluoro-2-(4-fluorophenyl)phenyl]methyl,
[2-(3-chloro-4-fluoro-phenyl)phenyl]methyl, [2-(4-fluoro-2-methyl-phenyl)phenyl]methyl,
[5-fluoro-2-(4-fluorophenyl)phenyl]methyl, benzhydryl, [(1R)-2-(4-chlorophenyl)-1-(4,4,4-trifluorobutylcarbamoyl)ethyl], [3,5-bis(trifluoromethyl)phenyl]methyl, 9H-fluoren-9-yl,
[2-[4-(trifluoromethyl)phenoxy]phenyl]methyl, 2-naphthalen-1-ylpropyl, [(1R)-2-(4-chlorophenyl)-1-methoxycarbonyl-ethyl], (1-methyl-5-phenyl-pyrazol-3-yl)methyl or [2-(4-chloro-2-methyl-phenyl)-2,2-difluoro-ethyl], (3-phenylphenyl)methyl, (4-fluorophenyl)methyl, (4-phenylphenyl)methyl, [(4-chlorophenyl)-pyridin-4-yl-methyl], 2-(4-fluorophenyl)propyl, 2-(4-phenoxyphenyl)ethyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently –OH, bromo, chloro, fluoro, methyl, methoxy methylsulfonylamino, trimethylsilyl, cyano, $-OCHF_2$, $-OCH_2F$, $-OSO_2CF_3$,

or an enantiomer thereof.

In an embodiment of this invention R^2 is trimethylsilylmethyl;

R^1 is [3-(difluoromethoxy)phenyl]methyl, [4-(difluoromethoxy)phenyl]methyl, naphthalen-1-ylmethyl, 1-naphthalen-1-ylethyl, 2-(4-bromophenyl)ethyl, (2-chloro-6-phenoxy-phenyl)methyl or (3,4-dichlorophenyl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is R^7 are independently selected from hydrogen, bromo, fluoro, chloro;

or an enantiomer thereof.

In one embodiment of the invention the compound of the invention is according to formula I as defined above but also including proviso d), in addition to provisos a), b) and c), that when R^2 represents $-(CH_2)_kN(R^{19a})(R^{19b})$,wherein k represents 2; and R^{19a} and R^{19b} represent methyl;

or R^2 represents Het^4 selected from thiazolyl or pyridyl;

or R^2 represents phenyl substituted by dimethylamino;

and R^5-R^7 are selected from C_1-C_3 alkyl, $-OR^{36}$, wherein R^{36} is selected from C_1-C_3 alkyl;

then R^1 does not represent phenyl, benzyl, pyridyl, pyridylmethyl, pyrimidinyl, cyclohexyl, methylpiperazinyl, indanyl or naphthyl, optionally substituted by one to three substituents selected from halogen such as fluoro, chloro, bromo, iodo, hydroxy, C_1-C_4 alkyl such as methyl, ethyl, propyl, isopropyl, butyl, C_1-C_4 alkoxy such as methoxy, ethoxy, propoxy, isopropoxy and butoxy, trifluoromethyl, C_1-C_3 alkyl subtstituted by at least one fluorine atoms, such as trifluoromethoxy, trifluoroethoxy and trifluoropropoxy, amide, carboxy, cyano, C_1-C_4 alkylthio such as methylthio, ethylthio, propylthio and butylthio, nitro, amino, methylamino, dimethylamino, dimethylaminomethyl, dipropylaminomethyl,

methylenedioxy, phenoxy, benzyloxy, C_2-C_5 alkanoyloxy such as acetoxy, propionyloxy and butyryloxy, C_1-C_3 ω-hydroxyallkyl such as hydroxymethyl, hydroxyethyl, C_2-C_5 alkanoyloxy- C_1-C_3 alkyl such acetyloxymethyl, acetylocyethyl and propionyloxymethyl, C_2-C_5 alkanoylamino such as acetylamino and propionylamino; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl and butoxycarbonyl, phenoxycarbonyl and benzyloxycarbonyl.

Unless otherwise specified, alkyl groups and alkoxy groups as defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms be branched-chain, or cyclic. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such alkyl and alkoxy groups may also be part cyclic/acyclic. Unless otherwise specified, alkyl and alkoxy groups may also be substituted by one or more halogen atoms, and especially fluoro atoms. Unless otherwise specified the cyclic alkyl, for example C_3-C_8 cycloalkyl may optionally be substituted by one or more substituents selected from –OH, oxo, halo, cyano, nitro, amino, alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryloxy or a Het group.

Alkylene groups as defined herein are divalent and may be straight-chain or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms, be branched-chain. Unless otherwise specified, alkylene groups may also be substituted by one or more halogen atoms, and especially fluoro atoms.

The term "aryl", when used herein, includes C_{6-10} aryl groups such as phenyl, naphthyl and the like. The term "aryloxy", when used herein includes C_{6-10} aryloxy groups such as phenoxy, naphthoxy and the like. For the avoidance of doubt, aryloxy groups referred to herein are attached to the rest of the molecule *via* the O-atom of the oxy-group. Unless otherwise specified, aryl and aryloxy groups may be substituted by one or more substituents including -OH, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, sulfamoyl, methylsulfonyl, aryl, anilino and methylsulfinyl. When substituted, aryl and aryloxy groups are preferably substituted by between one and three substitutents.

The terms "halo" and "halogen", when used herein, include fluoro, chloro, bromo and iodo.

Het (Het[1]- Het[76]) groups that may be mentioned include those containing 1 to 4 heteroatoms (selected from the group oxygen, nitrogen and/or sulfur) and in which the total number of atoms in the ring system are between five and twelve. Het groups may be fully saturated, wholly aromatic, partly aromatic and/or bicyclic in character. Heterocyclic groups that may be mentioned include benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzimidazolyl, benzomorpholinyl, benzotriazol, benzoxazinonyl, benzothiophenyl, chromanyl, cinnolinyl, dioxanyl, dioxothiolanyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, indolyl, isoquinolinyl, isoxazolyl, morpholinyl, oxopyrrolidinyl, oxopiperidinyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimindinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrazole, thiazolyl, thienyl, thiochromanyl, triazolyl and the like. Substituents on Het groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of Het groups may be *via* any atom in the ring system including (where appropriate) a heteroatom, or an atom on any fused carbocyclic ring that may be present as part of the ring system. Het groups may also be in the N- or S-oxidised form.

Unless otherwise specified, the Het group may optionally be substituted by one or more substituents selected from –OH, oxo, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryloxy or a further Het group.

Further, the term "hydrocarbon" refers to any structure comprising only carbon and hydrogen atoms.

The term "hydrocarbon radical" or "hydrocarbyl" refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkenyl" refers to a monovalent straight or branched chain alkyl group having at least one carbon-carbon double bond. The double bond of an alkenyl can be unconjugated

or conjugated to another unsaturated group. Unless otherwise specified, alkenyl groups as defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms be branched-chain, or cyclic. Further, when there are a sufficient number (i.e. a minimum of four) of carbon atoms, such alkenyl group may also be part cyclic/acyclic. Unless otherwise specified, alkenyl groups may also be substituted by one or more halogen atoms, and especially fluoro atoms.

The term "heteroalkyl" refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O and S.

The compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

The compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric esters by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention. All enantiomers, and mixtures thereof, are included within the scope of the invention.

Abbreviations are listed at the end of this specification.

Illustrative examples of any substient, R group or any part of such groups include, but are not limited to:

C_1-C_6 alkyl: methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-

pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, and hexyl;

C_2-C_6 alkenyl: vinyl, allyl, butenyl, pentenyl, hexenyl, cyclohexenyl, butadienyl, pentadienyl, and hexadienyl;

C_3-C_8 cycloalkyl: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclooctyl;

Illustrative examples of substituent Het are benzodioxanyl, benzotriazol, furanyl, imidazolyl, indolyl, oxazolyl, piperazinyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimindinyl, pyrrolidinyl, pyrrolyl and thienyl.

Compounds of the invention that may be mentioned are those wherein R1 represents (2-phenylphenyl)methyl, (4-phenoxyphenyl)methyl, 2-phenoxyphenyl methyl, 2-(4-chlorophenyl)propyl, 2-(trifluoromethyl)phenylmethyl, 2,2-dimethylpropyl, benzhydryl, 1-phenylethyl or 2,2-dimethylpropyl, [2-(3,4)-difluorophenyl)phenyl]-methyl, [2-(4-chlorophenyl)-2-methyl-propyl], [4-fluoro-2-(4-fluorophenyl)phenyl]methyl, (4-fluoro-2-phenyl-phenyl)methyl, [5-fluoro-2-(4-fluorophenyl)phenyl]methyl, (5-fluoro-2-phenyl-phenyl)methyl, 1-(4-fluorophenyl)ethyl, 2-(4-chlorophenyl)propan-2-yl, 2-(4-fluorophenyl)propan-2-yl or 1-(4-chlorophenyl)ethyl.

Compounds of the invention that may be mentioned are those wherein R2 represents ethyl, propyl, butyl, tert-butyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, methoxycarbonylmethyl, benzyl, 3,4-dichlorophenylmethyl, (4-fluorophenyl)methyl, [3-(difluoromethoxy)phenyl]methyl, (5-oxo-1-propan-2-yl-pyrrolidin-3-yl)methyl, propan-2-ylcarbamoylmethyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, 1-phenylethyl, 2-phenylpropan-2-yl or 5-cyanopentyl.

Compounds of the invention that may be mentioned include those in which aryl is phenyl, optionally substituted by one or more of the following fluoro, chloro, hydroxy, methoxy, cyano, carbamoyl, dialkylamino, methylsulfonyl, trifluoromethyl, aminoalkyl, difluoromethoxy.

Compounds of the invention that may be mentioned are those where at least one of the substituents in R1 and R2 is an aryl.

Compounds of the invention that may be mentioned are those having R1 selected from bulky and branched sidechains, for example biphenyls, benzhydryls (diphenylmethyl), branched phenethyls and tertiary butyl groups; and R2 is selected from benzyl and lipophilic groups. Lipophilic groups are selected from, for example, tertiary butyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl and n-butyl.

In one embodiment the compound of the invention is according to formula I

wherein

R^1 represents C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, cyano, oxo, $-OR^8$, $-SR^{10}$, $-COXR^{11}$, $-N(R^{12a})(R^{12b})$, $-N(R^{13a})C(O)OR^{13b}$, $-OC(O)N(R^{14a})(R^{14b})$, $-SO_2R^{15}$, aryl or Het^1); further R^1 represents aryl or Het^2;

R^8, R^{10}, R^{11}, R^{13a}, R^{13b}, R^{15} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^9 (which C_1-C_6 alkyl, aryl and Het^9 groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{10});

R^{12a} and R^{12b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{11} (which C_1-C_6 alkyl, aryl and Het^{11} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{12});

R^{14a} and R^{14b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{13} (which C_1-C_6 alkyl, aryl and Het^{13} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{14});

R^2 represents C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, trialkylsilyl, $-COXR^{18}$, aryl or Het^3); further R^2 represents $-(CH_2)_kN(R^{19a})(R^{19b})$, $-(CH_2)_kNR^{20a}C(O)N(R^{20b})(R^{20c})$, $-(CH_2)_nNR^{21a}SO_2R^{21b}$, $-(CH_2)_nSO_2R^{22}$, $-OC(O)N(R^{24a})(R^{24b})$, aryl or Het^4;

R^{18}, R^{21}, R^{22} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{15} (which C_1-C_6 alkyl, aryl and Het^{15} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{16});

R^{19a} and R^{19b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{19} (which C_1-C_6 alkyl, aryl and Het^{19} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{20})

R^{20a}, R^{20b} and R^{20c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{21} (which C_1-C_6 alkyl, aryl and Het^{21} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{22});

R^3 represents hydrogen, C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, trialkylsilyl, $-COXR^{27}$, aryl or Het^5); further R^3 represents $-(CH_2)_kN(R^{28a})(R^{28b})$, $-(CH_2)_kN(R^{29a})C(O)N(R^{29b})(R^{29c})$, $-(CH_2)_nNR^{30a}SO_2R^{30b}$, $-(CH_2)_nSO_2R^{31}$, $-OC(O)N(R^{33a})(R^{33b})$, aryl or Het^6;

R^{27}, R^{30a}, R^{30b}, R^{31} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{23} (which C_1-C_6 alkyl, aryl and Het^{23} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{24});

R^{28a} and R^{28b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{25} (which C_1-C_6 alkyl, aryl and Het^{25} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{26});

R^{33a} and R^{33b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{27} (which C_1-C_6 alkyl, aryl and Het^{27} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{28}) ;

R^{29a}, R^{29b}, and R^{29c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{29} (which C_1-C_6 alkyl, aryl and Het^{29} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{30});

R^4 represents hydrogen, –OH, aryl, C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, hydroxy, C_2-C_4 alkenyl, trialkylsilyl), $-OR^{34}$, $-(CH_2)_mR^{35}$;

R^{34} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{31} (which C_1-C_6 alkyl, aryl and Het^{31} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{32});

R^{35} independently represent aryl or Het^{33}(which aryl and Het^{33} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{34});

R^5 to R^7 independently represent, at each occurence, hydrogen, -OH, halogen, cyano, nitro, C_{1-6} alkyl, $-OR^{36}$, $-N(R^{37a})(R^{37b})$, $-C(O)R^{38}$, $-C(O)OR^{39}$, $-C(O)N(R^{40a})(R^{40b})$, $-NC(O)OR^{41}$, $-OC(O)N(R^{42a})(R^{42b})$, $-N(R^{43a})C(O)R^{43b}$, $-N(R^{44a})S(O)_2R^{44b}$, $-S(O)_2R^{45}$, $-OS(O)_2R^{46}$, -

$(CH_2)_nN(R^{47a})(R^{47b})$, $-(CH_2)_nNR^{48a}C(O)N(R^{48b})(R^{48c})$, $-(CH_2)_nNR^{49a}SO_2R^{49b}$, trialkylsilyl, aryl or Het^7;

R^{36}, R^{38}, R^{39}, R^{41}, R^{43}, R^{44a}, R^{44b}, R^{45}, R^{46}, R^{49a} and R^{49b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{35} (which C_1-C_6 alkyl, aryl and Het^{35} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{36});

R^{37a} and R^{37b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{37} (which C_1-C_6 alkyl, aryl and Het^{37} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{38});

R^{40a} and R^{40b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{39} (which C_1-C_6 alkyl, aryl and Het^{39} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{40});

R^{42a} and R^{42b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{41} (which C_1-C_6 alkyl, aryl and Het^{41} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{42});

R^{47a} and R^{47b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{43} (which C_1-C_6 alkyl, aryl and Het^{43} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{44});

R^{48a}, R^{48b} and R^{48c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{45} (which C_1-C_6 alkyl, aryl and Het^{45} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{46});

aryl is, at each occurrence, optionally substituted by –OH, halogen, cyano, nitro, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, aryl, Het^8, $-OR^{50}$, $-(CH_2)_mR^{51}$, $-SR^{52}$, $-C(O)R^{53}$, $-COXR^{54}$, $-N(R^{55a})(R^{55b})$, $-SO_2R^{56}$, $-OS(O)_2R^{57}$, $-(CH_2)_mN(R^{58a})(R^{58b})$, $-CH_2)_mNR^{59a}C(O)N(R^{59b})(R^{59c})$, $-C(O)OR^{60}$, $-C(O)N(R^{61a})(R^{61b})$, $-N(R^{62a}C(O)R^{62b}$, $-N(R^{63a})C(O)OR^{63b}$, $-OC(O)N(R^{64a})(R^{64b})$, $-N(R^{65a})S(O)_2R^{65b}$ and $OC(O)R^{66}$;

R^{50} to R^{54}, R^{56}, R^{57}, R^{60}, R^{62a}, R^{62b}, R^{63a}, R^{63b}, R^{65a}, R^{65b} and R^{66} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{47} (which C_1-C_6 alkyl, aryl and Het^{47} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{48});

R^{51} independently represent aryl or Het^{49} (which aryl and Het^{49} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{50});

R^{55a} and R^{55b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{51} (which C_1-C_6 alkyl, aryl and Het^{51} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{52}),

R^{58a} and R^{58b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{53} (which C_1-C_6 alkyl, aryl and Het^{53} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{54}),

R^{59a}, independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{55} (which C_1-C_6 alkyl, aryl and Het^{55} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{56});

R^{61a} and R^{61b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{57} (which C_1-C_6 alkyl, aryl and Het^{57} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{58});

R^{64a} and R^{64b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{59} (which C_1-C_6 alkyl, aryl and Het^{59} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{60});

Het^{1} to Het^{60} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, a further Het, $-OR^{67}$, $-(CH_2)_mR^{68}$, $-SR^{69}$, $-COXR^{70}$, $-N(R^{71a})(R^{71b})$, $-SO_2R^{72}$, $-(CH_2)_mN(R^{73a})(R^{73b})$, $-(CH_2)_mNR^{74a}C(O)N(R^{74b})(R^{74c})$, $-C(O)R^{75}$, $-C(O)OR^{76}$, $-C(O)N(R^{77a})(R^{77b})$, $-N(R^{78a})C(O)R^{78b}$, $-N(R^{79a})S(O)_2R^{79b}$, $OC(O)R^{80}$, $-NC(O)OR^{81}$, $-OC(O)N(R^{82a})(R^{82b})$;

R^{67}, R^{69}, R^{70}, R^{72}, R^{75}, R^{76}, R^{78a}, R^{78b}, R^{79a}, R^{79b}, R^{80} or R^{81} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{61} (which C_1-C_6 alkyl, aryl and Het^{61} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{62});

R^{68} represents aryl or Het^{63} (which aryl and Het^{63} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{64});

R^{71a} and R^{71b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{65} (which C_1-C_6 alkyl, aryl and Het^{65} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{66}),

R^{73a} and R^{73b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{67} (which C_1-C_6 alkyl, aryl and Het^{67} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{68});

R^{74a}, R^{74b} and R^{74c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{69} (which C_1-C_6 alkyl, aryl and Het^{69} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{70});

R^{77a}, and R^{77b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{71} (which C_1-C_6 alkyl, aryl and Het^{71} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{72});

R^{82a}, and R^{82b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{73} (which C_1-C_6 alkyl, aryl and Het^{73} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{74})

Het^{61} to Het^{74} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl;

X represents a nitrogen or oxygen atom;
m is an integer of 0 to 10;
n is an integer of 0 to 4;
k is an integer of 1 to 5;
and with the provisos a), b) and c) as defined above.

In one embodiment the compound of the invention is according to formula I

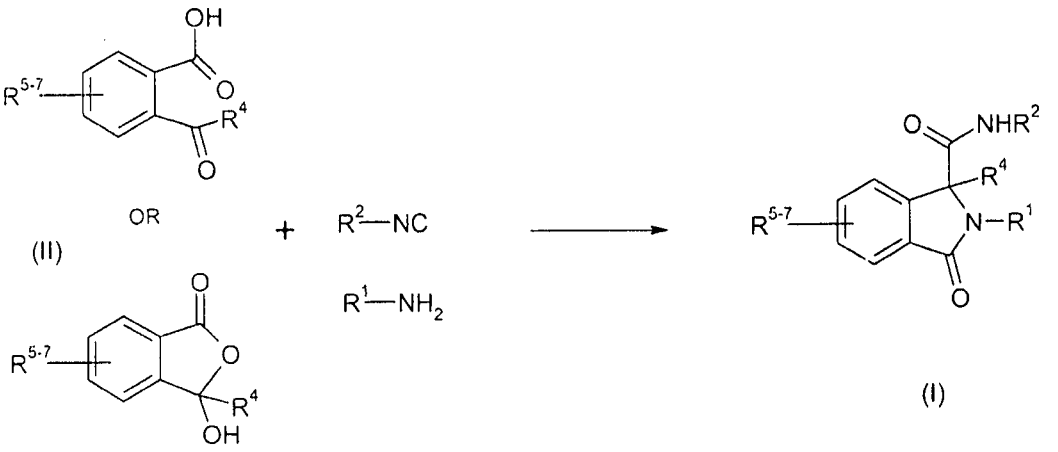
wherein

R^4 represents --OH, aryl, C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, hydroxy, C_2-C_4 alkenyl, trialkylsilyl), $-OR^{34}$, $-(CH_2)_mR^{35}$.

Preparation

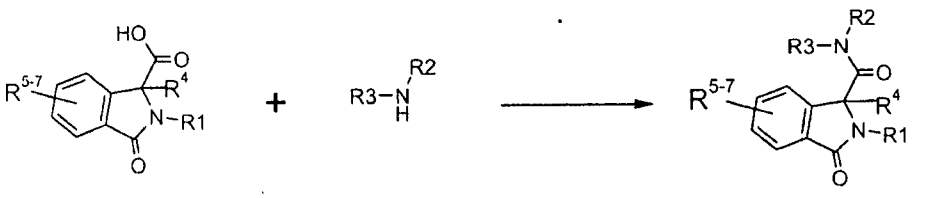
According to the invention there is also provided a process for the preparation of compounds of formula I which comprises:

reaction of a compound of formula II,



wherein R^3 to R^5 are as hereinbefore defined, with an amine R^1-NH_2 and an isonitrile R^2-NC under standard Ugi reaction conditions to give compounds of Formula I wherein R^1 to R^5 are as hereinbefore defined

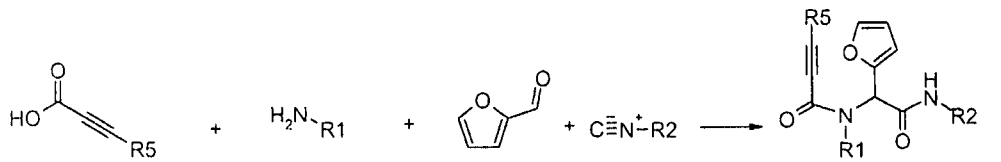
According to the invention there is also provided a process for the preparation of compounds of formula I which comprises reaction of a compound of formula III with an amine under standard amidecoupling reaction conditions.



(III)

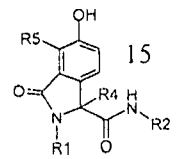
wherein R^1 to R^7 are as hereinbefore defined.

According to the invention there is also provided a process for the preparation of a compound of formula I which comprises a four-component UGI reaction with an amine, acid, aldehyde and isonitrile to the intermediate compound (IV)



(IV)

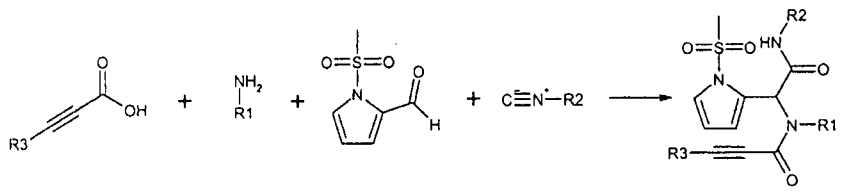
Compound (IV) is then undergoing intramolecular Diels-Alder reaction according to literature methods to give compounds of formula I.



R4=H (I)

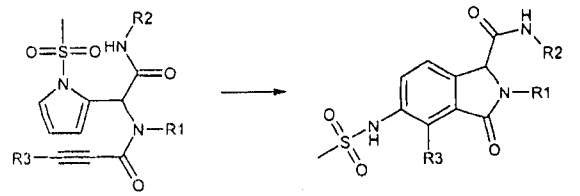
The synthetic sequence originated in a published procedure: D. L. Wright, C. V. Robotham and K. Aboud, *Tetrahedron Lett.* 2002, *43*, 943–946.

According to the invention there is also provided a process for the preparation of a compound of formula 1 which comprises a four-component UGI reaction with an amine, acid, aldehyde and isonitrile to the intermediate compound (V)



(V)

Compound (V) is then undergoing intramolecular Diels-Alder reaction according to literature methods to give compounds of formula I



A similar reaction is described in J. Org. Chem. 2004, *69*, 1207-1214.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

The prefixes *n-*, *s-*, *i-* *t-*, *tert-* have their usual meanings: normal, secondary, *iso* and tertiary.

The skilled person will also appreciate that various standard substituent or functional group interconversions and transformations within certain compounds of formula I will provide other compounds of formula I. For example, carbonyl may be reduced to hydroxy or alkylene, and hydroxy may be converted to halogen, and iodo, bromo and chloro may be converted to cyano.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the process described above, the functional groups of intermediate compounds may be, or may need to be, protected by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl and alkylcarbonyl groups (e.g. methyl- and ethylcarbonyl groups). Suitable protecting groups for amino include benzyl, sulfonamido (e.g. benzenesulfonamido), *tert*-butyloxycarbonyl, 9-fluorenyl-methoxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for amidino and guanidino include benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C_{1-6} alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art and as described hereinafter.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J.W.F. McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned herein may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those associated hereinbefore with a particular reaction). This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic

steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis.

It will also be appreciated by those skilled in the art that, although certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Moreover, certain compounds of formula I may act as prodrugs of other compounds of formula I.

All prodrugs of compounds of formula I are included within the scope of the invention.

Medical and pharmaceutical use

Compounds of the invention are useful because they possess pharmacological activity. They are therefore indicated as pharmaceuticals.

Thus, according to a further aspect of the invention there is provided the compounds of the invention for use as pharmaceuticals.

In particular, the compounds of the invention exhibit potassium channel inhibiting activity, especially Kv1.5 blocking activity, for example as demonstrated in the test described below.

The compounds of the invention are thus expected to be useful in both the prophylaxis and the treatment a condition which is effected or facilitated by Kv1.5 inhibition, in particular cardiac arrhythmias, eg.atrial fibrillation, atrial flutter, atrial arrhythmia, atrial tachycardia.

The compounds of the invention are thus indicated in the treatment or prophylaxis of cardiac diseases, or in indications related to cardiac diseases, in which arrhythmias, eg atrial fibrillation, atrial flutter, atrial arrhythmia and atrial tachycardia, are believed to play a major

role, including ischaemic heart disease, sudden heart attack, myocardial infarction, heart failure, cardiac surgery and thromboembolic events.

According to a further aspect of the invention, there is provided a method of treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

Pharmaceutical preparations

The compounds of the invention will normally be administered orally, subcutaneously, intravenously, intraarterially, transdermally, intranasally, by inhalation, or by any other parenteral route, in the form of pharmaceutical preparations comprising the active ingredient. In a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined with any other drugs useful in the treatment of arrhythmias and/or other cardiovascular disorders.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Suitable daily doses of the compounds of the invention in therapeutic treatment of humans are about 0.005 to 25.0 mg/kg body weight at oral administration and about 0.005 to 10.0 mg/kg body weight at parenteral administration. Examples of daily doses of the compounds of the invention in therapeutic treatment of humans are about 0.005 to 10.0 mg/kg body weight at oral administration and about 0.005 to 5.0 mg/kg body weight at parenteral administration.

The compounds of the invention have the advantage that they are effective against cardiac arrhythmias.

The compounds of the invention may also be combined with any other drugs useful in the treatment of arrhythmias and/or other cardiovascular disorders.

The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of the aforementioned disorders or other disorders, including: other antiarrhythmic agents such as Class I agents (e.g. propafenone), Class II agents (e.g., carvadiol and propranolol), Class III agents (e.g. sotalol, dofetilide, amiodarone, azimilide and ibutilide), Class IV agents (e.g. diltiazem and verapamil), 5 HT antagonists (e.g. sulamserol, serraline and trosetron), dronedarone, atrial selective compounds such as RSD1235, cardiac glycosides including digitalis and ouabain, calcium channel blockers (both L-type and T-type) such as diltiazem, verapamil, nifedipine, amlopdipine and mybefradil.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an antithrombotic agents for example anagrelide hydrochloride, bivalirudin, cilostazol, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, fluretofen, ifetroban, ifetroban sodium, lamifiban, lotrafiban hydrochloride, napsagatran, orbofiban acetate, roxifiban acetate, sibrafiban, tinzaparin sodium, trifenagrel, abciximab and zolimomab aritox or pharmaceutically acceptable derivative thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with other agents that act as or deliver a Factor IIa agonist for example 3DP-4815, AZD-0837, melagatran, ximelagatran, ART-123, lepirudin, AVE-5026, bivaluridin, dabigatran etexilate, E-4444, odiparcil, ardeparin sodium, pegmusirudin, LB-30870, dermatan sulfate, argatroban, MCC-977, desirudin, deligoparin sodium, PGX-100, idraparinux sodium, SR-123781, SSR-182289A, SCH-530348, TRIB50, TGN-167, TGN-255, and compounds described in WO94/29336, WO97/23499 and WO02/44145, which are incorporated hereby by reference.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a fibrinogen receptor antagonists for example roxifiban acetate, fradafiban, orbofiban, lotrafiban hydrochloride, tirofiban, xemilofiban, monoclonal antibody 7E3 and sibrafiban, or pharmaceutically acceptable derivative thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a platelet inhibitors for example cilostezol, clopidogrel bisulfate, epoprostenol, epoprostenol sodium, ticlopidine hydrochloride, aspirin, ibuprofen, naproxen, sulindae, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone and piroxicam, dipyridamole, or pharmaceutically acceptable derivative thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a platelet aggregation inhibitors for example acadesine, beraprost, beraprost sodium, ciprostene calcium, itezigrel, lifarizine, lotrafiban hydrochloride, orbofiban acetate, oxagrelate, fradafiban, orbofiban, tirofiban and xemilofiban or pharmaceutically acceptable derivative thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable derivative thereof, may be administered in association with a hemorrheologic agents for example pentoxifylline or pharmaceutically acceptable derivative thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable derivative thereof, may be administered in association with lipoprotein associated coagulation inhibitors; or pharmaceutically acceptable derivative thereof.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with a Factor VIIa inhibitor or pharmaceutically acceptable derivative thereof.

Cyclooxygenase inhibitors (i.e. COX-1 and/or COX-2 inhibitors) such as aspirin, indomethacin, ibuprofen, piroxicam, Naproxen®, Celebrex® and NSAIDs; diuretics such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, and spironolactone; anti-hypertensive agents such as alpha adrenergic blockers, beta adrenergic blockers, calcium channel blockers, diuretics, renin inhibitors, ACE inhibitors, (e.g. captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), A II antagonists (e.g. losartan, irbesartan, valsartan), ET antagonists (e.g. sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5, 612, 359 and 6,043, 265), Dual ET/AII antagonist (e.g. compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g. omapatrilat and gemopatrilat), nitrates and combinations of such antihypertensive agents; HMG-CoA reductase inhibitors such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a.itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin); other cholesterol/lipid lowering agents such as LDL lowering agents such as torcetrapid (Pfizer), exetimibe, a combination of atorvastatin and torcetrapid, a combination of simvastatin and ezetimibe, squalene synthetase inhibitors, fibrates, and bile acid sequestrants (e.g. questran).

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an anti-obesity compound, or a pharmaceutically acceptable derivative thereof, for example a pancreatic lipase inhibitor e.g. orlistat (EP 129,748), ATL-962, GT-389255 or an appetite (satiety) controlling substance for example sibutramine (Meridia®, Reductil®, GB 2,184,122 and US 4,929,629), PYY 3-36 (amylin), APD-356, 1426, Axokine, T-71, a cannabinoid 1 (CB1) antagonist or inverse agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example rimonabant (EP 656354), AVE-1625, CP945598, SR-147778, SLV-319, and as described in WO01/70700, or a Fatty Acid Synthesis (FAS) inhibitor, or pharmaceutically acceptable

salts, solvates, solvates of such salts or prodrugs thereof or a melanin concentrating hormone (MCH) antagonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof, for example 856464 and as described in WO 04/004726, anti-diabetic agents such as biguanides (e.g. metformin), glucosidase inhibitors (e.g. acarbose), insulines, meglitinides (e.g. repaglinide), sulfonylureas (e.g. glimepridie, glyburide and glipizide), biguanide/glyburide combinations (i.e. glucovance), thiozolidinediones (e.g. troglitazone, rosiglitazone and pioflitazone), PPAR-gamma agonists, aP2 inhibitors, and DP4 inhibitors; thyroid mimetics (including thyroid receptor antagonists) (e.g. thyrotropin, polythyroid, KB-130015, and dronedarone).

Compounds in the invention can also be administered as the sole active ingredient or in combination with a pacemaker or defribillator device.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, may be administered in association with an anti-coagulants selected from argatroban, bivalirudin, dalteparin sodium, desirudin, dicumarol, lyapolate sodium, nafamostat mesylate, phenprocoumon, tinzaparin sodium and warfarin sodium or pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable derivative thereof; and

(B) an anticoagulant,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier. Component B may also be any of the previously mentioned therapeutic agents.

Such combination products provide for the administration of compounds of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable derivative thereof, an anticoagulant, and a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an anticoagulant with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

When used herein, the term "an anticoagulant" includes references to one a substance selected from the group consisting of aspirin, warfarin, enoxaparin, heparin, low molecular weight heparin, cilostazol, clopidogrel, ticlopidine, tirofiban, abciximab, dipyridamole, plasma protein fraction, human albumin, low molecular weight dextran, hetastarch, reteplase, alteplase, streptokinase, urokinase, dalteparin, filgrastin, immunoglogulin, ginkolide B, hirudins, foropafant, rocepafant, bivalirudin, dermatan sulfate mediolanum, eptilibatide, tirofiban, thrombomodulin, abcxmab, low molecular weight dermatan sulfate-

opocrin, eptacog alfa, argatroban, fondaparinux sodium, tifacogin, lepirudin, desirudin, OP2000, roxifiban, parnaparin sodium, human hemoglobin (Hemosol), bovine hemoglobin (Biopure), human hemoglobin (Northfield), antithrombin III, RSR 13, heparin-oral (Emisphere) transgenic antithrombin III, H37695, enoxaparin sodium, mesoglycan, CTC 111, bivalirudin, and any derivatives and/or combinations thereof.

Particular anticoagulants that may be mentioned include aspirin and warfarin.

The term "an anticoagulant" also includes references to thrombin inhibitors. Thrombin inhibitors that may be mentioned include low molecular weight thrombin inhibitors. The term "low molecular weight thrombin inhibitors" will be understood by those skilled in the art, and includes references to any composition of matter (e.g. chemical compound) that inhibits thrombin to an experimentally determinable degree (as determined by *in vivo* and/or *in vitro* tests), and which possesses a molecular weight of below about 2,000, preferably below about 1,000.

Preferred low molecular weight thrombin inhibitors include low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors, as well as derivatives thereof.

The term "low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors" will be well understood by one skilled in the art to include references to low molecular weight thrombin inhibitors with one to four peptide linkages, and includes those described in the review paper by Claesson in *Blood Coagul. Fibrin.* 5, 411 (1994), as well as those disclosed in
US Patent No 4,346,078, International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371,

WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704 and WO 00/08014; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596, the disclosures in all of which documents are hereby incorporated by reference.

In the present application, derivatives of thrombin inhibitors include chemical modifications, such as esters, prodrugs and metabolites, whether active or inactive, and pharmaceutically acceptable salts and solvates, such as hydrates, of any of these, and solvates of any such salt.

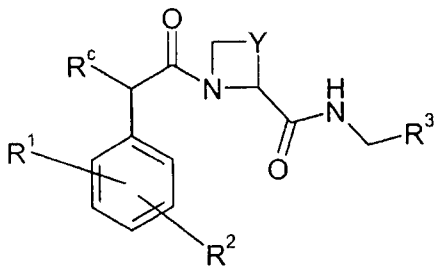
Preferred low molecular weight peptide-based thrombin inhibitors include those known collectively as the "gatrans". Particular gatrans which may be mentioned include HOOC-CH_2-(R)Cha-Pic-Nag-H (known as inogatran) and HOOC-CH_2-(R)Cgl-Aze-Pab-H (known as melagatran) (see International Patent Application WO 93/11152 and WO 94/29336, respectively, and the lists of abbreviations contained therein).

International Patent Application WO 97/23499 discloses a number of compounds which have been found to be useful as prodrugs of thrombin inhibitors. Said prodrugs have the general formula

$$R^aOOC\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}R^b$$

wherein R^a represents H, benzyl or C_{1-10} alkyl, R^b (which replaces one of the hydrogen atoms in the amidino unit of Pab-H) represents OH, $OC(O)R^c$ or $C(O)OR^d$, R^c represents C_{1-17} alkyl, phenyl or 2-naphthyl and R^d represents C_{1-12} alkyl, phenyl, C_{1-3} alkylphenyl, or 2-naphthyl. Preferred compounds include R^aOOC-CH_2-(R)Cgl-Aze-Pab-OH, wherein R^a represents benzyl or C_{1-10} alkyl, e.g. ethyl or isopropyl, especially EtOOC-CH_2-(R)Cgl-Aze-Pab-OH. The active thrombin inhibitors themselves are disclosed in WO 94/29336.

Further low molecular weight thrombin inhibitors that may be mentioned include those disclosed in WO 02/44145, such as compounds of the following general formula,



wherein

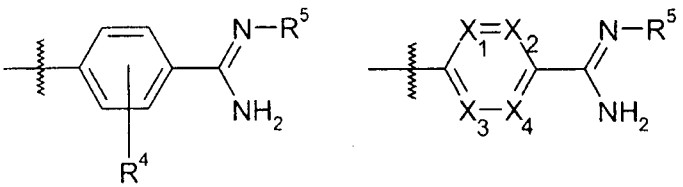
R^c represents -OH or $-CH_2OH$;

R^1 represents at least one optional halo substituent;

R^2 represents one or two C_{1-3} alkoxy substituents, the alkyl parts of which substituents are themselves substituted with one or more fluoro substituents (i.e. R^2 represents one or two fluoroalkoxy(C_{1-3}) groups);

Y represents $-CH_2-$ or $-(CH_2)_2-$; and

R^3 represents a structural fragment of formula I(i) or I(ii):



I(i) I(ii)

wherein

R^4 represents H or one or more fluoro substituents;

R^5 represents H, OR^6 or $C(O)OR^7$;

R^6 represents H, C_{1-10} alkyl, C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo, phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents);

R^7 represents C_{1-10} alkyl (which latter group is optionally interrupted by one or more oxygen atoms), or C_{1-3} alkylaryl or C_{1-3} alkyloxyaryl (the alkyl parts of which latter two groups are optionally interrupted by one or more oxygen atoms, and the aryl parts of which latter two groups are optionally substituted by one or more substituents selected from halo,

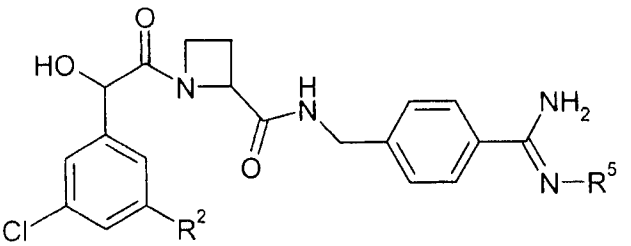
phenyl, methyl or methoxy, which latter three groups are also optionally substituted by one or more halo substituents); and

one or two of X_1, X_2, X_3 and X_4 represent -N- and the others represent -CH-;

or a pharmaceutically-acceptable derivative thereof.

Compounds of the above general formula in which R^5 is other than H have been found to be useful as prodrugs of thrombin inhibitors (which thrombin inhibitors include the corresponding compounds of the above general formula in which R^5 is H).

Particular compounds disclosed in WO 02/44145 that may be mentioned include those of the following general formula:



wherein

R^2 represents $-OCHF_2$, $-OCF_3$, $-OCH_2CH_2F$ or $-OCH_2CHF_2$;

R^5 represents H or OR^6; and

R^6 represents methyl, ethyl, *n*-propyl, *i*-propyl or cyclobutyl.

In this respect, more particular compounds disclosed in WO 02/44145 that may be mentioned include the thrombin inhibitor

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-Aze-Pab

and its methoxyamidino prodrug

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-Aze-Pab(OMe).

The compounds of the invention have the advantage that they are effective against cardiac arrhythmias.

Compounds of the invention have advantageous properties compared to compounds of the prior art, in particular enhanced potency, enhanced selectivity, and/or reduction of total clearance. These advantages may provide for corresponding useful properties in practice. For example, when used as pharmaceutical agents, compounds of the present invention may have a lower daily clinical dose, longer duration of action, and/or an improved side effect profile.

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, be longer acting than, produce fewer side effects (including a lower incidence of proarrhythmias such as *torsades de pointes*) than, be more easily absorbed than, or that they may have other useful pharmacological properties over, compounds known in the prior art.

Biological Tests

Test A

Rb^+ efflux assay

This assay identifies compounds that block the human Kv1.5 channel potassium channel heterologously expressed in Chinese Hamster Ovary (CHO) cells by means of Rb+ ion efflux using Flame Atomic Absorption Spectroscopy. For experimental studies, CHO cells stably transfected with cDNA for human Kv1.5 were grown as confluent layers in Falcon, 384-well tissue culture-treated black-walled clear-bottomed plates and the plates were incubated overnight at 37 °C in a cell culture incubator.

After incubating overnight the cell plates were washed and a buffer containing Rb+ ions were added to the cell plates .The plates were then incubated for another 3-4 hours in a CO2-incubator (37°C). Following this incubation period plates were washed, compounds were added and subsequently a buffer containing elevated K+ concentrations were added in order to activate the Kv1.5 channel. Following a short incubation time, aliquots of the supernatants were transferred to supernatant plates for subsequent determination of the Rb+ content using Atomic Absorption Spectrometry (ICR8000 instrument, Aurora Biomed Inc.). The basal Rb+ efflux (conc. mg/L in wells receiving only wash buffer) was

defined as 100% inhibition and the stimulated Rb+ efflux (conc. mg/L in wells receiving only buffer containing elevated concencentrations of K^+ions) was defined as 0% inhibition.

Test B

Electrophysiological recordings of potassium currents in cells stably expressing the the human Kv1.5 potassium channel confirms activity and provides a functional measure of the potency of compounds that specifically affect Kv1.5 channels. Electrophysiological studies were performed using the high throughput planar patch clamp assay (Schroeder et al, J Biomol. Screen (2003)8(1);50-64,; Willumsen, Am Biotech Lab (2006)24(4);20-21) or the standard whole cell configuration of the patch clamp technique (Hamill et al, Pflugers Archiv (1981) 391:85). CHO cells, stably transfected with cDNA for human Kv1.5, were then exposed to the drugs and Kv1.5 channels were activated

4 1.7 N-benzyl-2-(1-methyl-1-phenylethyl)-3-oxoisoindoline-1-carboxamide

by a test protocol adapted from Pelsson et al (Cardiavasc Pharmacol (2005)46:7-17). Data analysis was performed off-line, paired comparisions between pre-drug and post-drug were used to determine the inhibitory effect of each compound.

The title compounds of the above Examples were tested in Test A and Test B. Most of the compounds of the invention have an activity when tested in Test A, and most of them were found to exhibit an IC_{50} of <30μM, preferably an IC_{50} of <10μM, or an inhibition of >20% at a concentration of 30μM, or

Activity of IC50 <10μMin test A:

The compound of the invention	**IC50 Test A**	**example**
N-benzyl-2-(1-methyl-1-phenylethyl)-3-oxoisoindoline-1-carboxamide	1.7	
N-benzyl-3-oxo-2-(1-phenylpropyl)isoindoline-1-carboxamide	0.4	
N-[3-(difluoromethoxy)benzyl]-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide	2.4	

N,2-dibenzyl-6-bromo-3-oxoisoindoline-1-carboxamide	0.84	
(1R or 1S)-N-benzyl-3-oxo-2-[(1S or 1R)-1-phenylethyl]isoindoline-1-carboxamide (E4)	1.5	25
6-bromo-2-(2-cyclopentylbenzyl)-N-methyl-3-oxoisoindoline-1-carboxamide	2.7	
6-chloro-2-(2-cyclopentylbenzyl)-N-(4,4-difluorobutyl)-3-oxoisoindoline-1-carboxamide	1.3	
N-benzyl-6-chloro-3-oxo-2-[(1S)-1-phenylethyl]isoindoline-1-carboxamide	2.2	
N-benzyl-5-bromo-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide	2.1	
N-benzyl-6-bromo-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide	0.21	
N-[3-(difluoromethoxy)benzyl]-6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide	1.4	
N-(3-chlorobenzyl)-6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide	0.34	
6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide	1.7	
6-chloro-N-[3-(difluoromethoxy)benzyl]-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide	0.41	
6-chloro-N-(3-chlorobenzyl)-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide	2.1	
N-(tert-butyl)-3-oxo-2-[2-(trifluoromethyl)benzyl] isoindoline-1-carboxamide	1.9	
N-(tert-butyl)-6-chloro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide	1.1	
6-chloro-3-oxo-N-(4,4,4-trifluorobutyl)-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide	2.5	
6-chloro-3-oxo-2-[(1R)-1-phenylethyl]-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide	2	

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-6-cyano-3-oxoisoindoline-1-carboxamide	2.4	36
2-[(4-chlorophenyl)(pyridin-4-yl)methyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide	2.1	
2-(biphenyl-2-ylmethyl)-6-chloro-N-ethyl-3-oxoisoindoline-1-carboxamide	1	
2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-propylisoindoline-1-carboxamide	1.1	
2-(biphenyl-2-ylmethyl)-6-fluoro-3-oxo-N-propylisoindoline-1-carboxamide	2.8	
6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide	0.68	
6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide	0.42	
2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide	1.5	
2-[2-(4-chlorophenyl)propyl]-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide	0.78	
2-(biphenyl-2-ylmethyl)-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide	0.94	
N-benzyl-6-chloro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide	0.55	9
N-benzyl-6-fluoro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide	1.3	
N-benzyl-6-fluoro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide	1.4	
2-[2-(4-chlorophenyl)propyl]-6-fluoro-3-oxo-N-	2.3	

propylisoindoline-1-carboxamide		
2-[2-(4-chlorophenyl)propyl]-3-oxo-N-propylisoindoline-1-carboxamide	1.3	
2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide	1.8	
2-(biphenyl-2-ylmethyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide	1.5	
N-(tert-butyl)-2-[(1-methyl-5-phenyl-1H-pyrazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide	2.5	28
2-(biphenyl-2-ylmethyl)-6-bromo-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide	2.4	29
N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide	2	
N-(tert-butyl)-2-[(3',4'-dichlorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide	0.72	
N-[3-(difluoromethoxy)benzyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide	1.8	
N-[3-(difluoromethoxy)benzyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide	1.3	
N-(tert-butyl)-6-chloro-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide	2.8	
2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide	0.61	
N-benzyl-2-(biphenyl-2-ylmethyl)-6-chloro-3-oxoisoindoline-1-carboxamide	0.42	
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-6-chloro-3-oxoisoindoline-1-carboxamide	1.6	
6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide	0.46	
6-chloro-2-[2-(4-chlorophenyl)propyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-	2.8	

carboxamide		
N-(tert-butyl)-6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide	0.91	
N-benzyl-6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide	0.15	
N-(4,4-difluorobutyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide	8	22
2-[2-(4-chlorophenyl)propyl]-N-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]-3-oxoisoindoline-1-carboxamide	0.58	
N-(3,4-dichlorobenzyl)-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide	2.5	
(R or S)2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide(E1)	1.1	3
(S o R) 2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide(E2)	17	3
2-(biphenyl-2-ylmethyl)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide	2.7	19
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-6-fluoro-3-oxoisoindoline-1-carboxamide	6.7	
N-benzyl-2-(biphenyl-2-ylmethyl)-6-fluoro-3-oxoisoindoline-1-carboxamide	1	
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-(fluoromethoxy)-4-methyl-3-oxoisoindoline-1-carboxamide	1.7	14
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-methoxy-4-methyl-3-oxoisoindoline-1-carboxamide	2.2	
N-(3-chlorobenzyl)-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide	2.9	
N-benzyl-2-[2-(4-chlorophenyl)ethyl]-N-ethyl-3-oxoisoindoline-1-carboxamide	0.93	

N-benzyl-2-[2-(4-chlorophenyl)ethyl]-N-methyl-3-oxoisoindoline-1-carboxamide	0.89	
N-(tert-butyl)-5-hydroxy-4-methyl-3-oxo-2-{2-[4-(trifluoromethyl)phenoxy]benzyl}isoindoline-1-carboxamide	2	
N-benzyl-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide	0.56	
2-(diphenylmethyl)-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamid	2.5	
N-benzyl-2-[2-(4-chlorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide	0.71	
N-benzyl-2-[2-(4-chlorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide	0.74	
N-benzyl-N-butyl-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide	0.34	
N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide	2.2	46
N-(tert-butyl)-2-[(4'-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide	7.3	
2-[2-(4-chlorophenyl)propyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide	0.62	
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-7-hydroxy-3-oxoisoindoline-1-carboxamide	3	42
2-(biphenyl-2-ylmethyl)-N-(4-{[(difluoroacetyl)-amino]methyl}benzyl)-3-oxoisoindoline -1-carboxamide	2.4	17
2-(3-chlorobenzyl)-N-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide	2	
2-[2-(4-chlorophenyl)propyl]-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide	1.2	
2-(biphenyl-2-ylmethyl)-N-(4-cyanobenzyl)-3-	2.8	7

oxoisoindoline-1-carboxamide		
N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-(fluoromethoxy)-4-methyl-3-oxoisoindoline-1-carboxamide	3	
2-[3,5-bis(trifluoromethyl)benzyl]-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide	1.8	
2-[2-(4-chlorophenyl)propyl]-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide	1.8	
N-(1,3-benzodioxol-5-ylmethyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide	0.62	
(1S or 1R)-N-butyl-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (E2)	0.73	13
(1R or 1S)-N-butyl-2-[(2S or 2R)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (E4)	1.7	13
(1R or 1S)-N-butyl-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (E3)	0.5	13
(1S or 1R)-N-butyl-2-[(2S or 2R)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (E1)	15	13
N-benzyl-3-oxo-2-[(3-phenylisoxazol-5-yl)methyl]isoindoline-1-carboxamide	1	
N-butyl-2-[2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide	1.3	12
N-(tert-butyl)-5,6-dichloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide	1.8	
2-[2-(4-chlorophenyl)propyl]-3-oxo-N-[2-	0.7	

(trifluoromethyl)benzyl]isoindoline-1-carboxamide		
N-(2-chlorobenzyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide	0.75	
(R or S)2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide	3.4	34
2-[2-(4-chlorophenyl)propyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide	1.9	
N-benzyl-2-[2-(4-chlorophenyl)propyl]-4,5-dimethoxy-3-oxoisoindoline-1-carboxamide	0.61	
N-benzyl-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide	0.51	
N-benzyl-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide	6	24
N-benzyl-2-(2-bromobenzyl)-3-oxoisoindoline-1-carboxamide	2.5	
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide	3.3	33
N-benzyl-2-(2-cyclohex-1-en-1-ylethyl)-3-oxoisoindoline-1-carboxamide	1.8	
N-benzyl-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide	1	
N-butyl-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide	0.73	
N-butyl-2-[2-(4-chlorophenyl)-2-methylpropyl]-3-oxoisoindoline-1-carboxamide	0.53	49
N-(tert-butyl)-2-[(4',5-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide	9.3	
N-(tert-butyl)-2-[(5-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide	13	
N-(tert-butyl)-2-[(4,4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide	5.6	48

N-(tert-butyl)-2-[(4-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide	5.2	
(1R or 1S)-N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide	13	47
(1S or 1R)-N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide	5.5	47

The invention is illustrated by way of the following examples.

EXAMPLES

The naming of compounds in this patent application was made using a program from ACD Labs (version 9.0, Name Batch or labs).

Examples

Abbreviations

AIBN	2,2´-Azobis(2-methylpropionitril)
C	Celsius
BOC-anhydride	di-tert-Butyl dicarbonate
Dess-Martin Reagent	1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one
DCM	dichloromethane
DMF	*N, N*'-dimethylformamide
DME	dimethoxyethane
DMAP	Dimetylaminopyridine
DMSO	dimethylsulfoxide
ES	electrospray
ESI	electrospray ionisation

EtOAc	ethyl acetate
EtOH	ethanol
DME	Dimetoxyethane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
LAH	Lithium aluminiumhydride
MeCN	acetonitrile
MeOH	methanol
MTBE	Methyl tert-butyl ether
K2CO3	Potassium carbonate
MS	mass spectroscopy
NMR	nuclear magnetic resonanc
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
UV	ultra violet
atm	atmosphere
rt	room temperature
h	hour(s)
mins	minutes
br	broad
br s	broad singlet
s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
sep	septett
dd	double doublet
dm	double multiplet
td	triple doublet

General Experimental Procedures

Flash column chromatography was performed using normal phase silica gel 60 (0.040-0.063 mm, Merck) or SP1™ Purification System from Biotage™ using silica FLASH+™ Cartridges unless otherwise stated.

^{1}H NMR and ^{13}C NMR measurements were performed on a BRUKER ACP 300 or on a Varian Unity Plus 400, 500 or 600 spectrometer, operating at ^{1}H frequencies of 300, 400, 500, 600 MHz, respectively, and ^{13}C frequencies of 75, 100, 125 and 150 MHz, Alternatively, ^{13}C NMR measurements were performed on a BRUKER ACE 200 spectrometer at a frequency of 50.3 MHz.

Rotamers may or may not be denoted in spectra depending upon ease of interpretation of spectra.

Chemical shifts are given in δ values (ppm) with the solvents used as internal standard, unless otherwise stated.

*The solutions are taken from a concentrated sample solved in $(CH_3)_2SO$ and are diluted with $(CD_3)_2SO$. Since an substantial amount of $(CH_3)_2SO$ is present in the sample, first a pre-scan is run and analysed to automatically suppress the $(CH_3)_2SO$ (2.54 ppm) and H2O (3.3 ppm) peaks. This means that in this so-called wet1D experiment the intensity of peaks that reside in these areas around 3.3 ppm and 2.54 ppm is reduced. Furthermore impurities are seen in the spectrum which gives rise to a triplet at 1.12 ppm, a singlet at 2.96 and two multiplets between 2.76-2.70 ppm and 2.61-2.55 ppm. Most probably these impurities are dimethylsulfone and diethylsulfoxide.

Microwave heating was performed using single node heating in a Smith Creator or Emrys Optimizer from Personal Chemistry, Uppsala, Sweden.

Mass spectral (MS) data were obtained using ZQ, a quadrupole instrument from Waters and, where appropriate, either positive ion data or negative ion data were collected. Accurate mass (HRMS) spectral data were obtained using TOF-MS on a LCT, Q-TOF micro or LCTP system, all from Waters.

Syringe filter from Advantec MFS Inc. with a pore size of 0.5 μm was used.

Cation exchange columns from Isolute® was used.

Synthesis of intermediates

Preparation A

2-(4-Fluoro-phenyl)-propylamine

(i) 1-Fluoro-4-isopropenyl-benzene

Potassium *tert*-butoxide (52.9 g, 0.47 mol) was added to the suspension of methyl triphenylphosphonium iodide (190 g, 0.47 mol) in THF(400 ml) at ice-cooled condition. After 1 h stirring at ice-cooled condition, a solution of 4-Fluoro acetophenone (30 g, 0.199 mol) in THF (100 ml) was added dropwise. Then the reaction mixture was stirred at room temperature for 2 h and quenched with sat. ammonium chloride solution. THF was removed under reduced pressure and the reaction mixture was extracted with petether, washed with water, brine and dried over anh. sodium sulphate ntrated. The sub-title compound (30 g, 100%) was obtained as pale yellow liquid by concentration of petroleum ether layer

(ii) 2-(4-Fluoro-phenyl)-propylamine

Borane in THF (96 ml, 0.096 mol, 1M solution) was added dropwise to the solution of 1-Fluoro-4-isopropenyl-benzene from step (i) above(30 g, 0.24 mol) in THF (350 ml) at 0°C and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0°C and hydroxylamine-O-sulphonic acid (27.72 g, 0.24 mol) was added portionwise. The reaction mixture was refluxed for overnight. Then the reaction mixture was quenched with water and concentrated, acidified with 1.5 N HCl. The reaction mixture was extracted with ethylacetate, aqueous layer was neutralized with 10% sodium hydroxide solution and extracted with dichloromethane. The dichloromethane layer was washed with, water, brine and evaporated.to give the title compound (8.5 g, 23%)

Preparation B

[2-(4- chlorophenyl)propyl]amine

(i) 1-chloro-4-isopropenylbenzene

Potassium tert-butoxide (72.4 g, 0.646 mol) was added to the suspension of methyl triphenylphosphonium iodide (261 g, 0.646 mol) in THF (500 ml) at ice-cooled condition. After 1 h stirring at ice-cooled condition, a solution of 4-chloroacetophenone (50 g, 0.323 mol) in THF (100 ml) was added dropwise. Then the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with pet ether and filtered, filtrate was concentrated. The sub-title compound was obtained as pale yellow liquid by column chromatographic purification of the crude product using 6% ethyl acetate in pet ether as eluent. Yield (42 g, 86%)

(ii) [2-(4-chlorophenyl)propyl]amine

Borane in THF (124 ml, 1M solution) was added dropwise to the solution of 1-chloro-4-isopropenylbenzene from step (i) above (41.5 g, 0.272 mol) in THF (500 ml) at 0°C and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0°C and hydroxylamine-O-sulphonic acid (30.76 g, 0.272 mol) was added portionwise. The reaction mixture was refluxed overnight. The reaction mixture was quenched with water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine, dried over anh. sodium sulphate and concentrated. The concentrated mass was dissolved in dry diethyl ether (20 ml) and stirred with saturated HCl in diethyl ether for ½ h. The solid salt was isolated by filtration, neutralized with sodium bicarbonate solution and free amine was extracted with diethyl ether. The diethyl ether layer was washed with brine, dried over anh. sodium sulphate and concentrated to give the title compound(18 g, 39%)

Preparation C

1-(4'-fluorobiphenyl-2-yl)methanamine

(i) tert-butyl N-[[2-(4-fluorophenyl)phenyl]methyl]carbamate

N- (Tert-butoxycarbonyl)-2-Bromobensylamine (1.74 mmol, 0.5g) and , Tetrakis(Triphenylphosfin)palladium (0.087mmol, 0.101 g) and 4-fluorobenzeneboronic acid (2.096mmol, 0.293g) were dissolved in (DME ,10 ml) in a vial suitable for use in a microwave oven. Cesiumcarbonate (3.49mmol, 1.14g) was dissolved in 2 ml water and then added to the mixture. Ar (g) was bubbled through the mixture for 5 minutes. The

reaction was performed in a micro oven (10 min, 130 deg). The crude (0.5 g ,1.65 mmol) of the sub-title compound was taken to the next step without further purification

(ii) [2-(4-fluorophenyl)phenyl]methaneamine

Tert-butyl N-[[2-(4-fluorophenyl)phenyl]methyl]carbamate (1.6591mmol, 0.5 g) from step (i) above was dissolved in HCl saturated EtOAc and stirred at rt for 2 h. The solvent was removed by evaporation and the HCl-salt was purified by flashcromatography (started with isocratic heptane/DCM 50/50 and then the DCM concentration was increased to 100% then the product was eluated with 10% MeOH (saturated with NH3), (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation, to give 320 mg (1.59 mmol) of the title compound.

Preparation D

The following amines was made according to Preparation C above:

1-(4'-methylbiphenyl-2-yl)methanamine

1-(4'-methoxybiphenyl-2-yl)methanamine

1-(4'-fluoro-2'-methylbiphenyl-2-yl)methanamine

Preparation E

(2-cyclopentylbenzyl)amine hydrochloric acid salt

(i) 2-cyclopentylphenyl trifluoroacetate

To a solution of 2-cyclopentyl phenol (10 g, 0.09 mol) in dry DCM (150 ml) was added pyridine (8 ml, 0.14 mol) and cooled to 0 °C followed by the addition of trifluoroacteic acid anhydride (15,6 ml, 0.14 mol) drop wise.The reaction mixture was stirred at room temperature overnight.The reaction mixture was quenched with water and extracted with DCM (200 ml).The organic layer was washed with water (2x50 ml) and brine solution (1x50 ml) and concentrated to afford step1 product (18 g, 99.4%) as brown liquid. The crude product was taken as such taken for next step.

(ii) 2-cyclopentylbenzonitrile

To a solution of 2-cyclopentylphenyl trifluoroacetate (18 g, 0.06 mol) in dry DMF (150 ml) was added $Zn(CN)_2$ (7.2 g;0.06 mol) followed by $Pd(PPh_3)_4$(5.6 g;0.005 mol) and refluxed at 130 °C overnight under nitrogen atmosphere. Reaction mixture was then cooled to room temperature, quenched with water (200ml) and diluted with EtOAc (200 ml) and filtered. The filtrate was washed well with water (3x50 ml) and brine solution (1x50 ml).The organic layer was concentrated and the crude purified through silica gel column chromatography using 5% EtOAc in pet. ether to afford step 2 product (10.4 g, 99.3%) as pale yellow solid.

(iii) (2-cyclopentylbenzyl)amine

To suspension of lithium aluminium hydride (5.7 g, 0.15 mol) in dry THF (50 ml) at 0 °C was added 2-cyclopentylbenzonitrile (10.4 g, 0.06 mol) dissolved in dry THF (100 ml) drop wise. Reaction was stirred at room temperature overnight. Reaction mass cooled to 0 °C and quenched with 6 M KOH and diluted with THF. It was then filtered through celite and filtrate concentrated. To a solution of crude product in diethyl ether (100 ml) was added saturtated. HCl in diethyl ether (50 ml) and stirred for 10 minutes. It was then filtered and precipitate was washed with petroleum ether to afford the title compound (10.3 g, 98.1%) as white solid.

Preparation F

(2-cyclohexylbenzyl)amine hydro chloric acid salt

(i) 2-cyclohexylbenzonitrile

To a solution of 2-cyclohexyl bromobenzene (12 g, 0.05 mol) in Dry DMF (100 ml) was added $Zn(CN)_2$ (5.9 g, 0.05 mol) followed by $Pd(PPh_3)_4$ (5.8 g, 0.005 mol) and refluxed at 130 °C for overnight. Reaction mass was then cooled to room temperature, quenched with water (200 ml) and diluted with EtOAc (200 ml) and filtered. The filtrate was washed well with water (3x50 ml) and brine solution (1 x 50 ml). Organic layer was concentrated to afford step1 product (10 g) as yellow gummy liquid. The crude product was used in the next step .

(ii) (2-cyclohexylbenzyl)amine

To a suspension of lithium aluminium hydride (5.1 g, 0.13 mol) in dry THF (60 ml) at 0 °C was added 2-cyclohexylbenzonitrile from step (i) above(10 g, 0.054 mol) dissolved in Dry THF (140 ml) drop wise. After stirring the reaction mixture for overnight at RT, it was cooled to 0 °C and quenched with 6 M KOH. It was further diluted with THF and filtered through celite. The filtrate was concentrated under vacuum. To a solution of crude product in Diethyl ether (100 ml) was added satd. HCl in diethyl ether (20 ml) and stirred for 10 minutes. It was then filtered and precipitate was washed with petroleum ether to afford the title compound (8 g, 78.4%) as white solid.

Preparation G

4-fluorobutyl)amine hydrochloride

(i) (4-{[tert-butyl(dimethyl)silyl]oxy}butyl)amine

To the solution of 4-aminobutanol (20 g, 0.224 mol) in dichloromethane (200 ml) was added triethylamine at 0 °C. tert-butyldimethylchlorosilane (33.8 g, 0.224 mol) was added at the same temperature and stirred at room temperature for 4 h. The reaction mixture was diluted with water. The organic layer was washed with water, brine, dried over anh. sodium sulfate and concentrated.The crude product (42 g, 92%) was used for next step without purification.

(ii) tert-butyl (4-{[tert-butyl(dimethyl)silyl]oxy}butyl)carbamate

To a solution of (4-{[tert-butyl(dimethyl)silyl]oxy}butyl)amine (42 g, 0.20 mol) in dichloromethane (400 ml) and triethylamine (58 ml, 0.413 mol) was added BOC-anhydride (54.12 g, 0.248 mol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ice-cold water. The organic layer was washed with water and brine. The organic layer was then dried over anh. sodium sulfate and concentrated. The residue was purified by silica gel chromatography using (EtOAc/pet ether) to give (60 g, 95%) of the sub-title compound as a colorless oil.

(iii) di-tert-butyl (4-{[tert-butyl(dimethyl)silyl]oxy}butyl)imidodicarbonate

To a solution of tert-butyl (4-{[tert-butyl(dimethyl)silyl]oxy}butyl)carbamate (from step (ii) above (60 g, 95%) in dry acetonitrile (600 ml) was added DMAP (36.23 g, 0. 29 mol).

BOC-anhydride (64.7 g, 0.29 mol) was added and the reaction mixture was stirred at room temperature for 24 h. Then DMAP (36.23 g, 0. 29 mol) and BOC-anhydride(64.7 g, 0.29 mol) were added once more. The reaction mixture was stirred at room temperature for another 4 days. The reaction mixture was concentrated and the residue was purified by silica gel chromatography using (EtOAc/pet ether) to give (62g, 77%) of the sub-title compound as a colorless oil.

(iv) di-tert-butyl (3-hydroxypropyl)imidodicarbonate

To a solution of di-tert-butyl (4-{[tert-butyl(dimethyl)silyl]oxy}butyl)imidodicarbonate (60 g, 0.148) from step (iii) above in THF (600 ml) was added tetrabutylammonium fluoride (150 ml, 1M solution THF) at 0° C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was concentrated and concentrated mass was dissolved in ethyl acetate.The ethyl acetate layer was washed successively with water, 10% citric acid, 10% sodium bicarbonate and brine solution. The reaction mixture was concentrated and the residue was purified by silica gel chromatography using (EtOAc/pet ether) to give (37g, 86%) of the sub-title compound as a pale yellow liquid.

(v) di-tert-butyl (3-fluoropropyl)imidodicarbonate

To a solution of di-tert-butyl (3-hydroxypropyl)imidodicarbonate (35 g, 0.121 mol) from step (iv) above in dry THF (400 ml) was added triethylamine (84.9 mol, 0.60 ml) and (diethylamino) sulfur trifluoride (102 g, 0.60 mol) at –40 °C under nitrogen atmosphere. The reaction mixture was slowly allowed to warm up to room temperature and stirred at room temperature for 3 days. The reaction was quenched by addition of methanol at 0 °C. The reaction mixture was concentrated and residue was purified by silica gel chromatography using (EtOAc/pet ether) to give (11.8 g, 33%) of the sub-title compound as a pale yellow liquid.

(vi) 4-fluorobutyl)amine hydrochloride

To a solution of di-tert-butyl (3-fluoropropyl)imidodicarbonate (11.8 g, 0.040 mol) from step (v) above in dry diethylether (30 ml) was added saturated. HCl in ether (200 ml) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture

was concentrated and the title compound (4.1 g, 80%) was obtained as pale yellow solid by recrystallization of with acetone/diethylether.

Preparation H

(4,4-difluorobutyl)amine hydrochloride

(i) di-tert-butyl (3-oxopropyl)imidodicarbonate

To a solution of Dess-Martin reagent (66 g, 0.155 mol) in dichloromethane (300 ml) was added di-tert-butyl (3-hydroxypropyl)imidodicarbonate (30 g, 0.103 mol) in dichloromethane at –78 °C under nitrogen atmosphere. Then the reaction mixture was allowed to warm up to room temperature and stirred at the same temperature for overnight. The reaction mixture was filtered through celite and the filtrate was concentrated. The concentrated mass was stirred with diethyl ether and ether layer was separated and concentrated. The concentrated crude was purified by column chromatography using (EtOAc/pet.ether) to give (23 g, 77%) of the desired intermediate as pale yellow liquid

(ii) di-tert-butyl (4,4-difluorobutyl)imidodicarbonate

To a solution of step (i) intermediate (23 g, 0.080 mol) in dry dichloromethane (200 ml) was added (diethylamino) sulfur trifluoride (38.7 g, 0.24 mol) at –40 °C under nitrogen atmosphere. The reaction mixture was slowly allowed to warm up to room temperature and stirred at room temperature for 2h. The reaction mixture was slowly poured into cold water. The organic layer separated was washed with water, brine and concentrated. The residue was purified by silica gel chromatography using (EtOAc/pet ether) to give (11.12 g, 45%) of the sub-title compound as a pale yellow liquid .

(iii) (4,4-difluorobutyl)amine hydrochloride

To a solution of step (ii) intermediate (11.2 g, 0.035 mol) in dry diethylether (30 ml) was added satd. HCl in ether (150 ml) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated and the title compound (4.5 g, 86%) was obtained as pale yellow solid by recrystallization of the crude mass with acetone/diethylether.

Preparation I

(4,4-difluorobutyl)formamide

(4,4-difluorobutyl)amine (Prep. H above)(6 g, 0.041 mol) and triethyl amine (14.46 ml, 0.103 mol) was refluxed in ethylformate (150 ml) overnight. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and the crude product was purified by column chromatography using (EtOAc/ pet ether) to give the title compound (4.2 g, 74%) as pale yellow liquid.

Preparation J

(4,4,4-trifluorobutyl)formamide

(i) (4,4,4-trifluorobutyl)amine hydrochloride

A solution of diethyldiazodicarboxylate (31.1 ml, 0.195 mol) in toluene (150 ml) was added slowly to the solution of 4,4.4-trifluorobutanol (25g, 0.195 ml), triphenylphosphine (51 g, 0.195 mol) and di-tert-butyliminodicarboxylate (38 g, 0.175 mol) in toluene (300 ml) at room temperature. The reaction mixture was stirred at the same temperature for 24 h. Trifluoroacetic acid (30 ml) was added to the reaction mixture at ice-cold condition and then stirred at room temperature for another 24 h. The reaction mixture was diluted with water (500 ml). The aqueous layer separated was washed with diethyl ether and then made alkaline with 5N sodium hydroxide solution. The alkaline solution was extracted with diethyl ether. The diethyl ether layer was dried over anhydride magnesium sulphate. Then saturated hydrochloric acid in ether was added the above ether solution and stirred for overnight. The ether was removed under reduced pressure and the resulting mass was azeotroped with toluene to give the title compound (11.8 g, 37%) .

(ii) (4,4,4-trifluorobutyl)formamide

A mixture of (4,4,4-trifluorobutyl)amine (8.7 g) from step (i) above and triethyl amine (14.6 ml, 0.14 mol) was refluxed in ethylformate (250 ml) for 24 h.The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and the crude product was purified by column chromatography using 50% ethyl acetate in pet ether as eluent to give the title compound (5.5 g, 67%, 3.84 g as a colorless liquid.

Preparation K

(4-fluorobutyl)formamide

4-fluorobutyl)amine hydrochloride(Prep.G above) (4.12 g, 0.032 mol) and triethyl amine (14.6 ml, 0.14 mol) was refluxed in ethylformate (13.6 ml, 0.097 mol) for 24 h. Then the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and the crude product was purified by column chromatography using 50% ethyl acetate in pet ether as eluent to give the title (3.12 g, 80%) as pale yellow liquid.

Preparation L

3-Isocyanomethyl-5-methyl-isoxazole

(i) N-(5-methyl-isoxazol-3-ylmethyl)-formamide

A vial suitable for use in a microwave oven was charged with a solution of (5-methyl-isoxazol-3-yl)-methylamine (1 g, 8.9 mmol) and ethyl formate (17 ml, 212 mmol). The mixture was heated under a nitrogen atmosphere at 150°C for 15 min. After irradiation the mixture was cooled to room temperature and evaporated. 1.378g of the crude product, N-(5-methyl-isoxazol-3-ylmethyl)-formamide (99% yield) was obtained and used without further purification.

[M+1] (ES) 141.0

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (br s, 1H); 8.12 (s, 1H); 6.11 (s, 1H); 4.29 (d, 2H); 2.37 (s, 3H)

(ii) 3-Isocyanomethyl-5-methyl-isoxazole

(methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt, (4.2g, 17.7 mmol) was added to a solution of N-(5-methyl-isoxazol-3-ylmethyl)-formamide (1.378 g ; 8.8 mmol from step (i) above) in acetonitrile (15 ml). The mixture was stirred at 50°C for 3h under a nitrogen atmosphere and then cooled to room temperature.

The solution of 3-Isocyanomethyl-5-methyl-isoxazole was used to make compounds in the examples without further purification.

Preparation M

(isocyanomethyl)benzene

(i) *N*-benzylformamide

Benzylamine (2.07 mL, 19 mmol) was dissolved in Ethyl formate (24 mL) and the reaction was left stirring at 45°C for 20 h. The solvent was evaporated and the product was concentrated under reduced pressure to give the title compound (2.44 g, 95.2%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.36-8.25 (s, 1 H), 7.5-7.2 (m, 5 H), 6.02-5.57 (s, 1H), 4.56-4.46 (d, 2 H).

(ii) (isocyanomethyl)benzene

N-benzylformamide From step(i) above(2.44 g, 18.1 mmol) and (Methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (Burgess reagent) (4.31 g, 18.1 mmol) was added to a flask and dry MeCN (25 mL) was added. The reaction mixture was left stirring for 3 h at 50°C and the crude title compound was used without futher purification in the next step

Preparation N

1-chloro-3-(isocyanomethyl)benzene

(i) *N*-(3-chlorobenzyl)formamide

1-(3-chlorophenyl)methanamine (0.283 g, 2.0 mmol) was dissolved in Ethyl formate (8 mL) and the reaction was left stirring at 45°C for 16 h. The solvent was evaporated and the product was concentrated under reduced pressure to give the title compound (0.350 g, 103%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.23-8.09 (m, 1H), 7.38-7.18 (m, 3H), 4.8-4.34 (s, 2H).

(ii)1-chloro-3-(isocyanomethyl)benzene

N-(3-chlorobenzyl)formamide (0.128 g, 0.755 mmol) and (Methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (Burgess reagent) (0.182 g, 0.764 mmol) was added to a flask and MeCN (6 mL) was added. The reaction mixture was left stirring for 3 h at 50°C and the crude was used without futher purification in the next step

Preparation O

4-(isocyanomethyl)-5-methyl-2-phenyl-1,3-oxazole

(i) *N*-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]formamide

1-(5-methyl-2-phenyl-1,3-oxazol-4-yl)methanamine (0.512 g, 2.72 mmol) was dissolved in Ethyl formate (8 mL) and the reaction was left stirring at 45°C for 22 h. The solvent was evaporated and the product was concentrated under reduced pressure to give the sub-title compound (0.559 g, 95%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.3-8.18 (m, 1H), 8.07-7.99 (m, 2H), 7.62-7.34 (m, 3H), 6.51-5.91 (m, 1H),4.46-4.32 (d, 2H), 2.62-2.38 (m, 2H); MS (ESI) m/z 217 ($[M+H]^+$).

(ii) 4-(isocyanomethyl)-5-methyl-2-phenyl-1,3-oxazole

N-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]formamide from step (i) above (0.259 g, 1.20 mmol) and (Methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (Burgess reagent) (0.288 g, 1.21 mmol) was added to a flask and MeCN (6 mL) was added. The reaction mixture was left stirring for 3 h at 50°C and the crude was used without futher purification in the next step

Preparation P

1,1-difluoro-4-isocyanobutane

N-(4,4-difluorobutyl)formamide (from prep. I above)(0.076 g, 0.554 mmol) and (Methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (Burgess reagent) (0.132 g, 0.554 mmol) was added to a flask and MeCN (2 mL) was added. The reaction mixture was left stirring for 3 h at 50°C and the crude was used without futher purificationfor making compounds in exemples below.

Preparation Q

[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]amine hydrochloride

(i) 2,2-difluoro-1,3-benzodioxole-5-carbaldehyde oxime

A solution of 2,2-difluoro-1,3-benzodioxole-5-carbaldehyde (8 g, 0.0429 mol) in methanol (50 ml) was added dropwise to the well-stirred solution of hydroxylamine hydrochloride (4.18 g, 0.060 mol) and sodium acetate (4.9 g, 0.060 mol) in methanol (100 ml) at room temperature. The reaction mixture was stirred at room temperature for 6h. Then the reaction mixture was concentrated under reduced pressure and concentrated mass was diluted with water, extracted with dichloromethane. The dichloromethane layer was washed with water, brine, dried over anh. sodium sulfate and concentrated to give crude intermediate. The title compound (6.2 g, 72%) was obtained on crystallization of crude intermediate from dichloromethane/hexane solvent.

(ii) 1-(2,2-difluoro-1,3-benzodioxol-5-yl)methanamine hydrochloride

A solution of 2,2-difluoro-1,3-benzodioxole-5-carbaldehyde oxime (6.2 g, 0.030 mol) from step (i) above in THF (25 ml) was added slowly to the suspension of LAH (2.9 g, 0.077 mol) in THF (100 ml) at 0°C under nitrogen atmosphere. Then the reaction mixture was allowed to stir at room temperature for 8 h. The reaction mixture was cooled to 0° C and quenched with 6 (M) KOH solution (3 ml). The reaction mixture was filtered through celite and solid residue was washed several times with ethylacetate. The combine filtrate was concentrated to give the crude product. The crude product was dissolved in ether and stirred with satd. HCl in ether (2 0 ml) for 2 h. Then the solution was filtered and residue was dried to give the title compound (4.8 g, 83.3 %) as white powder.

Preparation R

(2,2-difluoro-1,3-benzodioxol-5-yl)methyl isocyanide

(i) 1-(2,2-difluoro-1,3-benzodioxol-5-yl)methanamine

1-(2,2-difluoro-1,3-benzodioxol-5-yl)methanamine hydrochloride (2.0 g, 8.94 mmol) was added to a flask, a 2 M solution of K2CO3 (30 mL) and DCM (30 mL) was added. The reaction mixture was left stirring in r.t. 2 h. The two phases were separated and the water phase was extracted once more with DCM (20 mL). The organic phases were collected and dried with MgSO4 and the salt was filtered off. The organic phase was evaporated and the product was concentrated under reduced pressure to give the title compound (1.53 g, 91.4%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.15-6.95 (m, 3H), 4.07-3.78 (s, 2H); MS (ESI) m/z 188 ($[M+H]^+$).

(ii) *N*-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]formamide

1-(2,2-difluoro-1,3-benzodioxol-5-yl)methanamine (from step (i) above (1.53 g, 8.18 mmol) was dissolved in Ethyl formate (40 mL) and the reaction was left stirring at 45°C for 20 h. The solvent was evaporated and the product was concentrated under reduced pressure to give the title compound (1.72 g, 97.6%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.35-8.25, 7.09-6.95 (m, 3H), 6.01-5.61 (m 1H),4.53-4.45 (d, 2H); MS (ESI) m/z 214 ($[M+H]^+$).

(iii) (2,2-difluoro-1,3-benzodioxol-5-yl)methyl isocyanide

N-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]formamide from step (ii) above (0.320 g, 1.49 mmol) and (Methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (Burgess reagent) (0.359 g, 1.51 mmol) was added to a flask and dry MeCN (8 mL) was added. The reaction mixture was left stirring for 3 h at 50°C and the crude was used without futher purification in the next step (AZ12609901).

Preparation S

1,2-dichloro-4-(isocyanomethyl)benzene

(i) *N*-(3,4-dichlorobenzyl)formamide

To 1-(3,4-dichlorophenyl)methanamine (352mg, 2.00mmol) was added ethyl formate (8.0mL, 99.4mmol). The mixture was stirred at 45°C over night (16h) and then concentrated *in vacuo* to give 433 mg of the crude product. The crude product was used in the next step without further purification.

^{1}H-NMR (500 MHz, CD_3OD) δ 8.18 (s, 1H), 7.51-7.47 (m, 2H), 7.27-7.23 (m, 1H), 4.40 (s, 2H).

(ii) 1,2-dichloro-4-(isocyanomethyl)benzene

To *N*-(3,4-dichlorobenzyl)formamide (from step (i) above)(245mg, 1.20mmol) dissolved in MeCN (6 mL) was added (methoxycarbonylsulfamoyl)triethylammonium hydroxide,

inner salt (Burgess reagent) (286mg, 1.20mmol). The mixture was stirred at 50°C for 3 h. After cooling to rt, the mixture was transferred directly to the next reaction step without any work-up.

Preparation T

Not commercially available isonitriles were made from the corresponding amines via formamides in analogy with preparation L, M,N,O,P,Q,R above, and used to make compounds in exemples below

Preparation U

4-fluoro-3-hydroxy-2-benzofuran-1(3H)-one

(i) 3-fluoro-N-(2-hydroxy-1,1-dimethylethyl)benzamide

To a solution of 3-fluorobenzoic acid (20 g, 0.142 mol) in dichloromethane (200 ml) was added oxalyl chlorode (14.6 ml, 0.171 mol) followed by a drop of DMF at 0°C under nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature. Then the reaction mixture was concentrated and added dropwise to the solution of 2-amino-2-methyl propanol (28 g, 0.314 mol) in dichloromethane (100 ml) at 0°C under nitrogen atmosphere. The resulting solution was stirred at room temperature for another 2 h. The reaction mixture was filtered and the filtrate was concentrated. The concentrated white solid (30 g) was used for the next step without purification .

(ii) 2-(3-fluorophenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole

Thionyl chloride (60 g) was added dropwise to the 3-fluoro-N-(2-hydroxy-1,1-dimethylethyl)benzamide (from step (i) above)(30 g) under stirring at room temperature and stirred for another 15 minutes.The yellow solution was poured into dry diethyl ether (200 ml) and the reaction mixture was neutralized with 20% cold sodium hydroxide solution. The diethyl ether layer was washed with water, brine, dried over anh. sodium sulfate and concentrated. The residue was purified by silica gel chromatography using (EtOAc/ pet ether) to give the sub-title compound (18.5g, 67.3%) as brown liquid

(iii) 4-fluoro-3-hydroxy-2-benzofuran-1(3H)-one

To a solution of 2-(3-fluorophenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (18.5 g, 0.958 mol) (from step (ii) above)in diethyl ether (200 ml) was added dropwise *sec*-BuLi (103 ml, 1.4 M in cyclohexane) at –78°C under nitrogen atmosphere and stirred for another 30 minute at the same temperature. Then dry DMF (20 ml) was added and the reaction mixture was allowed to stir at room temperature for another 2 h. The reaction was quenched with 6(N) HCl and concentrated. The concentrated mass was refluxed with 6(N)HCl (400 ml) for overnight. Then the reaction mixture was cooled to room temperature and stirred with diethyl ether (200 ml).The organic layer was separated and washed with water, brine and dried over anh. sodium sulfate and concentrated to give the crude cyclic product. The crude mass was purified by recrystallization (diethyl ether/pet ether) to give the title compound (8 g, 49.6%) as white solid

Preparation V

5-chloro-3-hydroxy-2-benzofuran-1(3H)-one

(i) 4-chloro-N-(2-hydroxy-1,1-dimethylethyl)benzamide

To a solution of 4-chloroorobenzoic acid (50 g, 0.319 mol) in dichloromethane (400 ml) was added oxalyl chloride (34 ml, 0.383 mol) followed by a drop of DMF at 0° C under nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature. Then the reaction mixture was concentrated and added dropwise to the solution of 2-amino-2-methyl propanol (62.8 g, 0.702 mol) in dichloromethane (200 ml) at 0°C under nitrogen atmosphere. The resulting solution was stirred at room temperature for another 2 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography using ($MeOH/CHCl_3$) to give the desired intermediate (68g, 93.5%) as brown liquid

(ii) 2-(4-chlorophenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole

Thionyl chloride (120.8 g, 1.05 mol) was added dropwise to 4-chloro-N-(2-hydroxy-1,1-dimethylethyl)benzamide (68 g, 0.30 mol) (from step (i) above under stirring at room temperature and stirred for another 15 minutes. Then the yellow solution was poured into dry diethyl ether (500 ml) and the reaction mixture was neutralized with 20% cold sodium hydroxide solution. The diethyl ether layer was washed with water, brine, dried over anh.

sodium sulfate and concentrated. The residue was purified by silica gel chromatography using (EtOAc/ pet ether) to give the sub-title compound (53g, 84.6%) as brown liquid

(iii) 5-chloro-2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)benzaldehyde

To a solution of 2-(4-chlorophenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (19 g, 0.906 mol)(from step (ii) above) in diethyl ether (400 ml) was added dropwise *sec*-BuLi (110 ml, 1.4 M in cyclohexane) at –78°C under nitrogen atmosphere and the reaction mixture was allowed to warm up to 0° C and stirred at 0° C for another 1 h. The reaction mixture was again cooled down to –78°C and dry DMF (10 ml) was added and warmed up to room temperature overnight. The reaction was quenched and diluted with water. The separated organic layer was washed water and brine. Then the organic layer was dried over anhydrous sodium sulfate and concentrated in vacuum to give the crude sub-title compound (20 g) as yellow liquid .

(iv) 5-chloro-3-hydroxy-2-benzofuran-1(3H)-one

5-chloro-2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)benzaldehydefrom step (iii) above (20 g) was heated at 80 °C for overnight with HCl in water (300 ml water, 150 ml Conc. HCl). Then the reaction mixture was cooled to room temperature and stirred with diethyl ether (500 ml). The diethyl ether layer was washed with water and brine. The organic layer was dried over anh. sodium sulfates and concentrated under vacuum. The crude mass was recrystallized from ethylacetate / pet ether solvent system to give the title compound (4.9 g, 31.6%) as a light brown solid

PreparationW

5-bromo-3-hydroxy-2-benzofuran-1(3H)-one

(i) 4-bromo-2-(hydroxymethyl)benzoic acid

5-Bromo phthalide (9 g, 0.042 mol) was refluxed with 2 (N) aqueous sodium hydroxide (100 ml) in methanol (150 ml) for overnight. The reaction mixture was concentrated under reduced pressure. Cocnentrated mass was diluted with water and acidified with dilute HCl. The solid precipitates was filtered and residue was washed with cold water and cold ethyl acetate and dried to give the sub-title compound (9.7 g, 100%) as white solid .

(i) 5-bromo-3-hydroxy-2-benzofuran-1(3H)-one

To a solution of 4-bromo-2-(hydroxymethyl)benzoic acid from step (i) above (9.7 g, 0.042 mol) in acetonitrile (300 ml) was added Dess-Martin periodinane (26.8 g, 0.0633 mol) at 0 °C under nitrogen atmosphere.The reaction mixture was stirred at room temperature for 14 h. The reaction mixture was filtered and the precipitates were washed with dichloromethane. The filtrate was concentrated. The concentrated mass was heated with 200 ml of Conc. HCl for 6 h at 70 °C. The reaction mixture was diluted with large volume of water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anh. sodium sulfate and concentrated. The concentrated mass was purified by recrystallization from ethyl acetate/pet ether to give the title compound (4.9 g, 51%) as white solid .

Preparation X

5-fluoro-3-hydroxy-2-benzofuran-1(3H)-one

(i) 4-fluoro-N-(2-hydroxy-1,1-dimethylethyl)benzamide

To a solution of 4-fluorobenzoic acid (50 g, 0.357mol) in dichloromethane (400 ml) was added oxalyl chlorode (34 ml, 0.393 mol) followed by a drop of DMF at 0°C under nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature. Then the reaction mixture was concentrated and added dropwise to the solution of 2-amino-2-methyl propanol (70 g, 0.785 mol) in dichloromethane (200 ml) at 0°C under nitrogen atmosphere. The resulting solution was stirred at room temperature for another 2 h. The reaction mixture was filtered and the filtrate was concentrated. The concentrated liquid mass (75 g) was used for the next step without purification .

(ii) 2-(4-fluorophenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole

Thionyl chloride (144 g) was added dropwise to 4-fluoro-N-(2-hydroxy-1,1-dimethylethyl)benzamide (75 g) (from step (i) above under stirring at room temperature and stirred for another 15 minutes. Then the yellow solution was poured into dry diethyl ether (500 ml) and the reaction mixture was neutralized with 20% cold sodium hydroxide solution. The diethyl ether layer was washed with water, brine and dried over anh. sodium

sulfate and concentrated. The residue was purified by silica gel chromatography using (EtOAc/ pet ether) to give the sub-title compound (65g, 95%) as brown liquid .

(iii) 2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-5-fluorobenzaldehyde

To 2-(4-fluorophenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (40 g, 0.206 mol)(frpm step (ii) above in diethyl ether (800 ml) was added dropwise *sec*-BuLi (192 ml, 1.4 M in cyclohexane) at –78°C under nitrogen atmosphere and stirred for another 3 h at the same temperature. Then dry DMF (40 ml) was added and warmed up to room temperature overnight. The reaction was quenched and diluted with water. The separated organic layer was washed water and brine. Then the organic layer was dried over anhydrous sodium sulfate and concentrated in vacuum to give crude intermediate (36 g) as yellow liquid .

(iv) 5-fluoro-3-hydroxy-2-benzofuran-1(3H)-one

2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-5-fluorobenzaldehyde (36 g) from step (iii) above was heated at 80 °C for overnight with HCl in water (400 ml water, 200 ml Conc. HCl). The reaction mixture was cooled to room temperature and stirred with diethyl ether (500 ml). The diethyl ether layer was washed with water and brine. The organic layer was dried over anh. sodium sulfates and concentrated under vacuum. The crude mass was recrystallized from ethylacetate / pet ether solvent system to give the title compound (7 g, 26%) an off white solid .

Preparation Y

2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxylic acid

(i) Ethyl 2-(2-ethoxy-2-oxoethyl)benzoate

2-Carboxymethyl benzoic acid (25 g) was dissolved in absolute ethanol (250 ml) and con. Sulfuric acid (1 ml) was added. The resulting solution was refluxed in a Dean & Stark apparatus for 2 days and the solvent was replaced by absolute ethanol for 3 times. Ethanol was removed under reduced pressure and the concentrated mass was dissolved in ethyl acetate. Ethyl acetate layer was washed with saturated sodium bicarbonate solution, water, and brine, dried over anh. Sodium sulfate and concentrated to afford the sub-title compound (30 g) as yellow oil .

(ii) ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)benzoate

ethyl 2-(2-ethoxy-2-oxoethyl)benzoate (30 g, 0.127 mol) from step (i) above was mixed with N-bromosuccinamide (22.5 g, 0.127 mol) in carbon tetrachloride (300 ml). AIBN was added and refluxed for 2 days. Then the reaction mixture was washed with water, dried over anh. sodium sulfate and concentrated. The crude intermediate was purified by column purification by using 2% ethyl acetate in pet ether to give the sub-title compound (26 g, 65%) as brown liquid

(iii) ethyl 2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxylate

[2-(4-chlorophenyl)propyl]amine (20 g, 0.118 mol) was added dropwise to the solution of step 2 intermediate (18.6 g, 0.059 mol) in acetonitrile (150 ml) at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred at room temperature for overnight. The reaction mixture was filtered, residue was washed with dichloromethane and combined filtrate was concentrated. The crude product was purified using 10% ethyl acetate in pet ether as eluent to give the sub-title compound (23 g, 100%) as white solid .

(iv) 2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxylic acid

An aqueous solution of sodium hydroxide (3 g, in 50 ml water, 0.075 mol) was added to the well stirred solution of ethyl 2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxylate (13 g, 0.036 mol) in ethanol (100 ml) at 0° C. The reaction mixture was allowed to stirred at room temperature for 2h. The reaction mixture was concentrated under reduced pressure and diluted with water and extracted with ethyl acetate. The aqueous layer was acidified with 2M HCl and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anh. sodium sulfate and concentrated under reduced pressure to give the title compound (11.5 g, 95.8%)

Preparation Z

ethyl 2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxylate

2-(4-chlorophenyl) ethylamine (25 g, 0.16 mol) was added dropwise to the solution of ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)benzoate (25 g, 0.0793 mol) in acetonitrile (150 ml)

at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred at room temperature for overnight. The reaction mixture was filtered, residue was washed with dichloromethane and combined filtrate was concentrated. The crude product was purified using 15% ethylacetate in petether as eluent to give the title compound (22 g, 80.8%) as white solid.

Preparation AA

2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxylic acid

An aqueous solution of sodium hydroxide (3 g, in 50 ml water, 0.075 mol) was added to the well stirred solution of ethyl 2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxylate (preparation Z above)(15 g, 0.043 mol) in ethanol (100 ml) at 0° C. Then the reaction mixture was allowed to stirred at room temperature for 2h. The reaction mixture was concentrated under reduced pressure and diluted with water and extracted with ethylacetate. The aqueous layer was acidified with 2(N) HCl and extracted with ethylacetate. The ethylacetate layer was washed with brine, dried over anh. sodium sulfate and concentrated under reduced pressure to give the title compound (13 g, 94.8%).

Preparation AB

(2-phenoxybenzyl)amine hydrochloride

(i) 1-bromo-2-phenoxybenzene

A solution of sodium nitrite (9.2 g, 0.135 mol) in water (20 ml) was added dropwise to a solution of 2-phenoxyaniline (25 g, 0.135 mol) in 40% hydrobromic acid (50 ml) at 0 °C and stirred for another 10 minutes. Then the reaction mixture was added to the boiling mixture of cuprous bromide (21.3 g, 0.149 mol) in 40% hydrobromic acid (50 ml) and after addition it was allowed to reflux for another 30 minutes. Reaction mixture was cooled, diluted with water and extracted with diethyl ether. The diethyl ether layer was washed with 5% hydrochloric acid, 10% potassium hydroxide, water, brine, dried over sodium sulfate and concentrated to give the crude intermediate. The sub.-title compound (14.8 g, 45%) was obtained by column purification of the crude intermediate using pet ether as eluent

(ii) 2-phenoxybenzonitrile

A solution of 1-bromo-2-phenoxybenzene from step(i) above (14.8 g, 0.0594 mol), $Zn(CN)_2$ (6.9 g, 0.0594 mol) and Pd $(PPh_3)_4$ (6.8 g, 0.00594 mol) in dimethylformamide (100 ml) was heated at 130 °C for overnight under nitrogen atmosphere. Reaction mixture was cooled to room temperature and diluted with water (200 ml). The reaction mixture was stirred with ethyl acetate (200 ml) for 15 minutes and filtered through celite. The ethyl acetate layer was separated and washed with water, brine, dried over anh. sodium sulfate and concentrated .The crude intermediate was purified by column chromatography using 4% ethyl acetate in pet ether to give the sub-title compound (10.1 g, 87.8%) as colorless liquid .

(iii) (2-phenoxybenzyl)amine hydrochloride

A solution of 2-phenoxybenzonitrile (from step (ii) above (10.1 g, 0.0517 mol) in THF (50 ml) was added dropwise to the well-stirred suspension of LAH (4.9 g, 0.129 mol) in THF (50ml) at 0 °C under nitrogen atmosphere and then allowed to stirr at room temperature for overnight.The reaction mixture was quenched with 6(N) KOH (5 ml) 0 °C and stirred with THF (50 ml) for another 30 minutes.The reaction mixture was filtered and the residue was washed with ethyl acetate. The filtrate was concentrated to give the crude amine. Satd. HCl in diethyl ether (20 ml) was added to the solution of crude amine in diethyl ether (20 ml) and stirred for 2 h. Then the reaction mixture was filtered and residue was dried to give the title compound (10 g, 97.08

Preparation AC

(dipyridin-3-ylmethyl)amine hydrochloride

(i) dipyridin-3-ylmethanone

n-BuLi (71.3 ml, 1.6 M, 0.114 mol) was added dropwise to the solution of 3-bromo pyridine (15 g, 0.095 mol) in dry diethyl ether (200 ml) at –78 °C and stirred for 15 minutes. A solution of ethyl nicotinate (13 g, 0.095 mol) in dry diethyl ether (50 ml) was added dropwise to the reaction mixture at –78 °C and stirred for another 2 h at the same temperature. Then the reaction was quenched with satd. ammonium chloride and extracted with ethyl acetate. The organic layer was washed with satd. brine, dried over anh. sodium

sulfate and concentrated. The crude product was purified on neutral alumina column using (methanol/dichloromethane) to give the sub-title compound (8.5 g, 49% as brown liquid .

(ii) dipyridin-3-ylmethanone oxime

A solution of dipyridin-3-ylmethanone from step (i) above (8.5 g, 0.046 mol) in dry methanol (50 ml) was added to the well stirred solution of sodium acetate (9.6 g, 0.117 mol) and hydroxylamine hydrochloride (8.12 g, 0.117 mol) in dry methanol (50 ml). The reaction mixture was refluxed under nitrogen atmosphere for 2 h. Then the reaction mixture was concentrated, diluted with water and extracted with dichloromethane. The organic layer was washed with water, brine and dried over anh. sodium sulphate and concentrated to give the sub-title compound (9.5 g, 100 %)

(iii) (dipyridin-3-ylmethyl)amine hydrochloride

dipyridin-3-ylmethanone oxime (step (ii) above (9.5 g, 0.0477 mmol) and ammonium acetate (5.5 g, 0.0716 mmol) were dissolved in ethanol (00 ml), water (80 ml) and 40% NH3 (aq) (100 ml). The mixture was heated to 80 °C and zinc dust (15.5 g, 0.23 mmol) was added over a period of 1 h. The reaction was then stirred at 80 °C for overnight and was then cooled to rt, filtered and the filtrate was concentrated in vacuum. The remaining aqueous solution was basified with 10 M NaOH (aq), extracted with dichloromethane. The combined organic phases were washed with brine (40 ml) dried over anh. Sodium sulphate and concentrated. The concentrated yellow gummy mass was dissolved in ethyl acetate and diethyl ether (50 ml) satd. with HCl gas was added drop wise and stirred for 1 h. The reaction mixture was filtered and solid residue was dried to give the title compound (9.2 g, 65%) as off white solid

Preparation AD

3-(2-aminoethyl)benzonitrile trifluoroacetic acid salt

(i) tert-butyl [2-(3-bromophenyl)ethyl]carbamate

BOC anhydride (12 ml, 0.054 mol) was added to the ice-cold solution of 3-Bromo phenethylamine (10 g, 0.049 mol) and triethylamine (10.4 ml, 0.10 mol) in dichloromethane (100 ml). After 1 h stirring at room temperature the reaction mixture was

quenched with water and extracted with dichloromethane. Organic layer was washed with water and brine, dried over anh. sodium sulphate and concentrated to give the sub-title compound (15 g, 100%)

(ii) tert-butyl [2-(3-cyanophenyl)ethyl]carbamate

A mixture tert-butyl tert-butyl [2-(3-bromophenyl)ethyl]carbamate (15 g, 0.05 mol), $Zn(CN)_2$ (5.87 g, 0.05 mol) and tetrakis triphenylphosphine palladium (0)(5.7 g, 0.005 mol) was heated at 140 °C for 5 h in dry DMF (150 ml) under nitrogen atmosphere. Then the reaction mixture was cooled to room temperature, quenched with water and filtered through celite pad. The reaction mixture was extracted with ethyl acetate and the ethyl acetate layer was washed with water, brine successively and dried over anh. sodium sulphate and concentrated. Then the crude material was purified by column chromatography using 20% ethyl acetate in pet ether as eluent to give the sub-title compound desired (7 g, 57%) as white solid

(iii) 3-(2-aminoethyl)benzonitrile trifluoroacetic acid salt

Trifluoroacetic acid (5 ml) was added to a solution of tert-butyl [2-(3-cyanophenyl)ethyl]carbamate (10 g) in dichloromethane (20 ml) and stirred at room temperature for overnight. The solvent and excess trifluoroacetic acid was removed under reduced pressure to give gummy oil. On trituration of gummy oil with diethyl ether, white solid appeared. Diethyl ether was decanted and white solid was dried to get the title compound (6 g)

Preparation AE

[2-fluoro-4-(methylsulfonyl)benzyl]amine

(i) O-(4-cyano-3-fluorophenyl) dimethylthiocarbamate

A mixture of 2-fluoro- 4-hydroxy benzonitrile (10 g, 0.0729 mol), DMAP (900 mg, 0.00729 mol), triethylamine (30 ml, 0.218 mol) and dimethylthiocarbamoyl chloride (11 g, 0.0875 mol) in dry dichloromethane (200 ml) was stirred at reflux under nitrogen atmosphere overnight. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with water, brine and dried over sodium

sulfate. The solvent was evaporated under reduced pressure and the residue was triturated with pet ether. The product was filtered and dried under vacuum to give the sub-title compound (14 g, 85.8%) as yellow solid

(ii) S-(4-cyano-3-fluorophenyl) dimethylthiocarbamate

O-(4-cyano-3-fluorophenyl) dimethylthiocarbamate from step (i) above (14 g) and diphenyl ether (200 ml) were mixed and stirred at 210 °C for 6 h. Then diphenyl ether was removed by distillation under reduced pressure and the crude mass was stirred with pet ether and filtered. The residue was washed with pet ether for several times and air dried to give the sub-title compound (13.4 g, 95.7 %) as light brown solid .

(iii) 2-fluoro-4-mercaptobenzonitrile

S-(4-cyano-3-fluorophenyl) dimethylthiocarbamate from step (ii) above (13.4 g, 0.059 mol) was taken in THF (150 ml) and to which a solution of KOH (6.7 g, 0.11 mol) in methanol (200 L) was added. The reaction mixture was stirred at RT for 3 h and then concentrated. The crude mass was dissolved in ethylacetate. The ethylacetate layer was acidified with 3(N) HCl to pH = 2. The ethylacetate layer was washed with water and brine, dried over anh. sodium sulphate and concentrated. The crude intermediate (9 g) obtained was directly taken for the next step without further

(iv) 2-fluoro-4-(methylthio)benzonitrile

Methyl iodide (12.5 g, 0.058 mol) was added dropwise to a solution of 2-fluoro-4-mercaptobenzonitrile (9 g, 0.058 mol) (from step (iii) above and potassium carbonate (12.1 g, 0.088 mol) in dry acetonitrile (150 ml) and stirred at room temperature for 3 h under nitrogen atmosphere.The reaction mixture was filtered and the filtrate was concentrated to give the sub-title compound (9.6 g, 100 %)

(v) 2-fluoro-4-(methylsulfonyl)benzonitrile

2-fluoro-4-(methylthio)benzonitrile (9.6 g, 0.0524 mol) from step (iv) above) was added to a mixture of glacial acetic acid/water/ethanol (140 ml, 2:2:3) and stirred for 10 min. The reaction mixture was cooled to 0 °C and oxone (40.4 g, 0.065 mol) was added in portions. The reaction mixture was stirred at RT for 2h and diluted with dichloromethane. Filtered

off inorganic and mother liquor was partitioned between water and dichloromethane. Organic layer was washed with water and brine and dried over sodium sulfate. Solvent evaporation under reduced pressure followed by recrystallization of the crude product using ethylacetate/ petether afforded desired sulfone (9 g, 80%) .

(vi) 2-fluoro-4-(methylsulfonyl)benzonitrile

To a solution of 2-fluoro-4-(methylthio)benzonitrile (9 g) in methanol (150 ml), Raney nickel (2 g) was added and then saturated with ammonia (g). The reaction mixture was hydrogenated in parr shaker under 3 kg hydrogen pressure over overnight. The reaction mixture was filtered and the filtrate was concentrated. The concentrated mass was dissolved in ethyl acetate and stirred with saturated HCl in ether for overnight under nitrogen atmosphere. The solid precipitates were filtered, washed with diethyl ether and dried to give the title compound (1.3 g, 14.3 %) as pale yellow solid.

Preparation AF

[2-chloro-4-(methylsulfonyl)benzyl]amine Hydrochloride

(i) O-(3-chloro-4-cyanophenyl) dimethylthiocarbamate:

A mixture of 2-chloro- 4-hydroxy benzonitrile (25 g, 0.162 mol), DMAP (1.9 g, 0.162 mol), triethylamine (68 ml, 0.483 mol) and dimethylthiocarbamoyl chloride (24 g, 0.195 mol) in dry dichloromethane (500 ml) was stirred at reflux under nitrogen atmosphere overnight. The reaction mixture was quenched with water and extracted with dichloromethane. Organic layer was washed with water, brine and dried over sodium sulfate. Solvent evaporated under reduced pressure and the residue was triturated with pet ether. The product was filtered and dried under vacuum to give desired intermediate (38 g, 97%) as yellow solid

(ii) S-(3-chloro-4-cyanophenyl) dimethylthiocarbamate

O-(3-chloro-4-cyanophenyl) dimethylthiocarbamate (38 g) and diphenyl ether (500 ml) were mixed and stirred at 210 °C for 6 h. Then diphenyl ether was removed by distillation under reduced pressure and the crude mass was stirred with pet ether and filtered. The

residue was washed with pet ether for several times and air dried to give desired intermediate (37.8 g, 99.5%) as light brown solid.

(iii) 2-chloro-4-mercaptobenzonitrile

S-(3-chloro-4-cyanophenyl) dimethylthiocarbamate (35 g, 0.145 mol) was taken in THF (400 ml) and to which a solution of KOH (163 g, 0.30 mol) in methanol (200 L) was added. The reaction mixture was stirred at RT for 3 h and then concentrated. The crude mass was dissolved in ethylacetate. The ethylacetate layer was acidified with 3(N) HCl to P_H = 2. The ethylacetate layer was washed with water and brine, dried over anh. sodium sulphate and concentrated. The crude intermediate (25 g) obtained was directly taken for the next step without further purification .

(iv) 2-chloro-4-(methylthio)benzonitrile

Methyl iodide (31.4 g, 0.22 mol) was added dropwise to a solution of 2-chloro-4-mercaptobenzonitrile (25 g, 0.147 mol) and potassium carbonate (20.4 g, 0.22 mol) in dry acetonitrile (300 ml) and stirred at room temperature for 3 h under nitrogen atmosphere. Then the reaction mixture was filtered and the filtrate was concentrated to give the desired intermediate (26 g, 96.2%).

(v) 2-chloro-4-(methylsulfonyl)benzonitrile

2-chloro-4-(methylthio)benzonitrile (26 g, 0.145 mol) was added to a mixture of glacial acetic acid/water/ethanol (900 ml, 2:2:3) and stirred for 10 min. The reaction mixture was cooled to 0 °C and oxone (217 g, 0.353 mol) was added in portions. The reaction mixture was stirred at RT for overnight and diluted with dichloromethane. Filtered off inorganic and mother liquor was partitioned between water and dichloromethane. Organic layer was washed with water and brine and dried over sodium sulfate. Solvent evaporation under reduced pressure followed by recrystallization of the crude product using ethyl acetate/ petether afforded the sub-title compound (18 g, 59%) as white solid .

(vi) [2-chloro-4-(methylsulfonyl)benzyl]amine hydrochloride

To a solution of step 5 intermediate (8 g) in methanol (200 ml), Raney nickel (2.5 g) was added and then saturated with ammonia (g). Then the reaction mixture was hydrogenated

in parr shaker under 3 kg hydrogen pressure over overnight. The reaction mixture was filtered and the filtrate was concentrated. The concentrated mass was dissolved in ethyl acetate and stirred with saturated HCl in ether for overnight under nitrogen atmosphere. The solid precipitates were filtered, washed with diethyl ether and dried to give the title compound (7 g, 86.4%) as a solid.

Preparation AG

2-(4-chlorophenyl)-2-methyl-propan-1-amine hydrochloride

(i) 2-(4-chlorophenyl)-2-methylpropanenitrile

To a stirred solution of 2-(4-chlorophenyl)acetonitrile (10 g, 0.066 mol) in DMF, sodium hydride (3.95 g, 0.1649 mol) was added at 0°C in portions. The reaction mixture was allowed to stir for 1 hour at room temperature. Then it was again cooled to 0°C and methyl iodide (28.0g, 0.198 mol) was added dropwise. The reaction mixture was allowed to stir at 40°C for 4 hr. The reaction mixture was diluted with cold water and product was extracted with EtOAc. The organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfates and concentrated under vacuum. The residue was purified by silica gel chromatography using (EtOAc/ pet ether) to give the sub-title compound (7.7g, 65%) as colourless liquid

(ii) 2-(4-chlorophenyl)-2-methyl-propan-1-amine hydrochloride

To a mixture of $LiAlH_4$ (4.06g, 0.107 mol) in THF was added dropwise step1 intermediate (7.7g, 0.043 mol) in THF at 0°C. The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled to 0°C and quenched with 10 ml of 6M KOH solution. The reaction mixture was diluted with THF and allowed to stir at room temperature for 30min. The reaction mixture was filtered and filtrate was concentrated. The residue was diluted with diethyl ether and HCl in ether was added at 0°C. The white solid was collected by filtration ,washed with dry diethyl ether and dried under vacuum to afford desired product (6g, 77%) of the title compound

Preparation AH

7-fluoro-3-hydroxy-2-benzofuran-1(3H)-one

(i) 1-(dimethoxymethyl)-3-fluorobenzene

To a stirred solution of 3-fluorobenzaldehyde (17.5 g, 0.141mol) in methanol (175ml), trimethyl orthoformate (17.5 ml, 0.159 mol) and PTSA (175 mg) were added. The reaction mixture was stirred at RT overnight. The reaction mixture was quenched with 30 ml of 1% methanol KOH solution. The reaction mass was concentrated, then diluted with water and product was extracted with ethyl acetate. The organic layer was washed with water and brine. The organic layer was dried over anh. Sodium sulfates and concentrated under vacuum. The crude was fractionally distilled to get the desired intermediate (20g, 83.6%) as colorless liquid

(ii) 7-fluoro-3-hydroxy-2-benzofuran-1(3H)-one

To a solution of 1-(dimethoxymethyl)-3-fluorobenzene (20 g, 0.11mol) in THF (200 ml) (from step (i) above was added drop wise *sec*-BuLi (220 ml, 1.4 M in cyclohexane) at –78°C under nitrogen atmosphere and stirred for another 3 h at the same temperature. Then CO2 was purged until the red solution became yellow and slowly warmed up to room temperature. The reaction mixture was stirred for another 1 h and then quenched with 20 ml of HCl. Then the reaction mixture was concentrated. The crude reaction mass so obtained was heated at 80°C for overnight with HCl in water (300ml Conc. HCl, 200 ml water). Then the reaction mixture was cooled to room temperature and stirred with diethyl ether (100 ml). The diethyl ether layer was washed with water and brine. The organic layer was dried over anh. Sodium sulfates and concentrated under vacuum. The crude mass was submitted for prep HPLC to give the title compound (2.3g, 11.7%) as a white solid

Preparation AI

1-(3',4'-difluorobiphenyl-2-yl)methanamine

(i) Tert-butyl [(3',4'-difluorobiphenyl-2-yl)methyl]carbamate

Tert-butyl (2-bromobenzyl)carbamate (1.74 mmol, 0,50 g), Tetrakis(triphenylphosphine)palladium (0.087 mmol, 0,10 g) and (3,4-difluorophenyl)boronic acid (2.10 mmol, 0,33 g) were dissolved in (DME

10 ml) in a micro vial. Cesium carbonate (3.49 mmol, 1,14 g) was dissolved in 2 ml water and then added to the mixture. Ar (g) was bubbled through the mixture for 5 minutes. The crude was purified by flash chromatography (started with isocratic heptane/EtOAc 90/10 and then the EtOAc concentration was increased to 70%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (3,00 g, 89,6 %). 1H-NMR (500MHz, $CDCl_3$): δ 7,46-7,42 (m, 1H); 7,41-7,36 (m, 1H); 7,36-7,30 (m, 1H); 7,25-7,18 (m, 2H); 7,17-7,11 (m, 1H); 7,06-7,01 (m, 1H); 4,75 (bs, 1H); 4,31-4,17 (m, 2H); 1,45 (s, 9H).

(i) 1-(3',4'-difluorobiphenyl-2-yl)methanamine

Tert-butyl [(3',4'-difluorobiphenyl-2-yl)methyl]carbamate (9.39 mmol, 3,00 g) was dissolved in HCl saturated EtOAc and stirred at rt for 2 h. The solvent was removed by evaporation and the HCl-salt was purified by flash chromatography (started with isocratic heptane/DCM 50/50 and then the DCM concentration was increased to 100% then the product was eluated with 10% MeOH (saturated with NH3), (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (2,00 g, 97,1 %)

1H-NMR (500MHz, $CDCl_3$): δ 7,55-7,50 (m, 1H); 7,42-7,35 (m, 1H); 7,32-7,15 (m, 4H); 7,14-7,06 (m, 1H); 4,82-4,79 (m, 2H); 3,78-3,73 (m, 2H).

Preparation AJ

1-(4,4'-difluorobiphenyl-2-yl)methanamine

(i) Tert-butyl [(4,4'-difluorobiphenyl-2-yl)methyl]carbamate

1-bromo-4-fluorobenzene (11.15 mmol, 1,95 g), Tetrakis(triphenylphosphine)palladium (0.41 mmol, 0,47 g) and (2-{[(tert-butoxycarbonyl)amino]methyl}-4-fluorophenyl)boronic acid (9.29 mmol, 2,50 g) were dissolved in (DME 10 ml) in a micro vial. Cesium carbonate (18,58 mmol, 6,05 g) was dissolved in 2 ml water and then added to the mixture. N2 (g) was bubbled through the mixture for 5 minutes. The reaction was performed in a micro oven (20 min, 130 deg). The crude was purified by flash chromatography (started with isocratic heptane/EtOAc 95/5 and then the EtOAc concentration was increased to 60%,

(silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (2,54 g, 85,6 %). 1H-NMR (500MHz, $CDCl_3$): δ 7,30-7,21 (m, 2H), 7,21-7,08 (m, 4H); 7,03-6,97 (m, 1H), 4,79 (bs, 1H), 4,29-4,13 (m, 2H); 1,45 (s, 9H).

(ii) 1-(4,4'-difluorobiphenyl-2-yl)methanamine

Tert-butyl [(4,4'-difluorobiphenyl-2-yl)methyl]carbamate (7.95 mmol, 2,54 g) was dissolved in HCl saturated EtOAc and stirred at rt for 2 h. The solvent was removed by evaporation and the HCl-salt of the product was purified by flash chromatography (started with isocratic heptane/EtOAc 50/50 and then the EtOAc concentration was increased to 100% then the product was eluated with 10% MeOH (saturated with NH3), (silica gel 60 0.004-0.063 mm).The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (1,64 g, 94,1 %). 1H-NMR (500MHz, CD_3OD): δ 7,34-7,27 (m, 3H); 7,22-7,13 (m, 3H), 7,05-7,0 (m, 1H); 4,81 (s, 2H), 3,72 (s, 2H).

Preparation AK

The following amines were made according to preparation AI and AJ above

[(4-fluorobiphenyl-2-yl)methyl]amine

[(5-fluorobiphenyl-2-yl)methyl]amine

[(4',5-difluorobiphenyl-2-yl)methyl]amine

Examples

Example1

2-[2-(4-chlorophenyl)propyl]-N-[(5-methylisoxazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide

A solution of 2-formyl-benzoic acid (1.23 g, 8.2 mmol) in methanol (15 ml) was treated with 2-(4-chloro-phenyl)-propylamine hydrochloride (1.69 g, 8.2 mmol) and triethylamine (1.14 ml). The mixture was stirred at room temperature for 30 min. The 3-

Isocyanomethyl-5-methyl-isoxazole solution from Preparation L above was added and the mixture was stirred at room temperature for 16 hr. The mixture was concentrated, dissolved in 50 ml dichloromethane and washed with 100 ml saturated $NaHCO_3$ solution. The organic phase was separated, dried over $MgSO_4$ and evaporated. The remaining oil was purified using preparative HPLC giving the title compound (0.903g, 26% yield) .

[M+1] (ES) 424.10

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.61 (m, 3H); 7.35–7.44 (m, 1H); 7.07–7.27 (m, 5H); 5.81 (s, 1H); 4.78 (s, 1H); 4.46–4.56 (m, 1H); 4.31–4.39 (m, 1H); 4.12-4.27 (m, 1H); 3.15-3.40 (m, 2H); 2.35 (s, 3H); 1.23 (d, 3H)

Example 2

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

(i) N-(biphenyl-2-ylmethyl)-N-[2-(tert-butylamino)-1-(2-furyl)-2-oxoethyl]but-2-ynamide

(biphenyl-2-ylmethyl)amine (23.78 mmol, 4,36 g) was dissolved in MeOH and 2-furaldehyde(23.78 mmol, 2,29 g) and but-2-ynoic acid (23.78 mmol, 2.00 g) was added. The mixture was stirred at rt for 30 min. Tert-butyl isocyanide (23.78 mmol, 1.98 g) was added and the mixture was stirred at rt over night. The solvent was removed by evaporation. The product was taken on to the next step without further purification.

(ii) 2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

N-(biphenyl-2-ylmethyl)-N-[2-(tert-butylamino)-1-(2-furyl)-2-oxoethyl]but-2-ynamide (23,0 mmol, 9,87g) (from step (i) above was dissolved in Xylene (200 ml), ytterbium (III) trifluoromethansulfonate (2.30 mmol, 1.43 g) was added. The mixture was refluxed for 1.5h and then no starting material was left. The solvent was removed by evaporation. The crude was purified by flashcromatography (started with isocratic heptane/EtOAc 80/20 and then the EtOAc concentration was increased to 100% (silica gel 60 0.004-0.063 mm). The product precipitated on the column and had to be eluated with 50% MeOH. Then the product was re-crystallized from MeOH to give the title compound (4,52 g, 45,9 %).

^{1}H-NMR (500MHz, DMSO-d_6): δ 7,96 (s, 1H), 7,45-7,28 (m, 7H), 7,26-7,20 (m, 1H), 7,20-7,14 (m, 1H), 7,06-7,01 (m, 1H), 6,97-6,92 (m, 1H), 5,07 (d, 1H), 4,63 (s, 1H), 3,90 (d, 1H), 2,45 (s, 3H), 1,11 (s, 9H); HRMS calculated for $(C_{27}H_{28}N_2O_3+H)+$, 429.5436; found (ES [M+H]+), 429.5454.

The synthetic sequence originated in a published procedure:
D. L. Wright, C. V. Robotham and K. Aboud, *Tetrahedron Lett.* 2002, *43*, 943–946.

Example 3

(R or S) 2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

(S or R) 2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

The enantiomers of 2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (example 2)(0.20 g, 0.47 mmol) were separated by preparative HPLC using a Reprosil 20x250 mm chiral column using 40% isopropyl alcohol in heptane as mobile phase which gave (+)-enantiomer (0.10 g) (E1) and (-)-enantiomer (0.10 g) of the title compound.(E2)

(+)-Enantiomer:

HRMS: calculated for $(C_{27}H_{28}N_2O_3+H)^+$ 429.2178; found (ES $[M+H]^+$) 429.2166.

(-)-Enantiomer:

HRMS: calculated for $(C_{27}H_{28}N_2O_3+H)^+$ 429.2178; found (ES $[M+H]^+$) 429.2147.

Example 4

Methyl (2*R*)-2-{1-[(tert-butylamino)carbonyl]-3-oxo-1,3-dihydro-2H-isoindol-2-yl}-3-(4-chlorophenyl)propanoate

2-Formyl-benzoic acid (0.30 g, 2 mmol), methyl 4-chloro-D-phenylalaninate hydrochloride (0.5 g, 2 mmol) and NEt3 (0.28 mL, 2 mmol) were dissolved in MeOH (5

mL) and stirred at ambient temperature for 30 mins. tert-Butyl-isocyanide (0.23 mL, 2 mmol) was added and the resulting mixture was stirred for 3 days at ambient temperature. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC using a Waters HPLC system, equipped with a Kromasil C8 50.8x300 mm column using a MeCN/0.1 M NH4OAc buffer system with a gradient from 100% A (5% MeCN + 95% 0.1 M NH4OAc) to 100% B (100% 0.1 M NH4OAc) as mobile phase. The product fraction was concentrated under reduced pressure and freeze-dried to give the title compound (0.22g, 25%).

1H-NMR (500MHz, CDCl3) δ 7.87-7.83 (m, 1H), 7.60-7.49 (m, 3H), 7.17-7.13 (m, 2H), 7.02-6.98 (m, 2H), 4.17-4.12 (m, 1H), 3.96 (s, 1H), 3.94 (s, 3H), 3.80-3.40 (m, 2H), 1.22 (s, 9H)

13C-NMR (125MHz, CDCl3) δ 170.9, 169.5, 166.7, 142.1, 135.6, 133.4, 133.0, 130.5, 130.0, 129.4, 129.1, 123.8, 123.3, 67.4, 59.5, 53.6, 51.8, 34.0, 28.6

HRMS: calculated for (C23H25ClN2O4+H)+ 429.1581 ; found (ES [M+H]+) 429.1583

Example 5

N-(tert-butyl)-2-{(1*R*)-1-(4-chlorobenzyl)-2-oxo-2-[(4,4,4-trifluorobutyl)amino]ethyl}-3-oxoisoindoline-1-carboxamide

4,4,4-trifluorobutan-1-amine (0.087 g, 0.53 mmol) was mixed with dichloromethane (2 ml) under nitrogen atmosphere and Me_3Al (2M in heptane) was added. The resulting mixture was stirred for 1.5h at ambient temperature and methyl (2*R*)-2-{1-[(tert-butylamino)carbonyl]-3-oxo-1,3-dihydro-2H-isoindol-2-yl}-3-(4-chlorophenyl)propanoate (Example 4 above)(0.11 g, 0.26 mmol) was added. The resulting mixture was stirred at ambient temperature for 20h. The reaction was quenched by addition of methanol and the formed salts were removed by filtration. The filtrate was purified by silica flash chromatography using a Biotage Horizon apparatus with ethyl acetate/heptane as mobile phase. The product fraction was concentrated under reduced pressure to give the title compound (0.075g, 54%).

HRMS: calculated for $(C_{26}H_{29}ClF_3N_3O_3+H)^+$ 524.1927 ; found (ES $[M+H]^+$) 524.1893.

Example 6

N-butyl-2-[2-(4-chlorophenyl)ethyl]-N-methyl-3-oxoisoindoline-1-carboxamide

2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxylic acid (0.4 mmol) (Preparation AA) was dissolved in DCM (2 mL) and (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (0.4 mmol) was added as a solid. After 15 mins N-methylbutan-1-amine (0.4 mmol) was added and the reaction was then allowed to continue at 30 degrees for 2 days. The reaction mixture was purified by silica flash chromatography using a Biotage Horizone apparatus with ethyl acetate/heptane as mobile phase. The product fraction was concentrated under reduced pressure to give the title compound (0.007 g, 5%).

^{1}H-NMR (500MHz, $CDCl_3$) δ 7.91-7.87 (m, 1H), 7.58-7.48 (m, 2H), 7.40-7.32 (m, 1H), 7.30-7.24 (m, 3H), 7.21-7.13 (m, 2H), 5.26-5.15 (m, 1H), 4.40-4.24 (m, 1H), 3.45-3.21 (m, 3H), 3.10-2.89 (m, 4H), 1.57-1.45 (m, 2H), 1.35-1.26 (m, 2H), 0.94 (t, 3H)
HRMS calculated for $(C_{22}H_{25}ClN_2O_2+H)^+$ 385.1683 ; found (ES $[M+H]^+$) 385.1670.

Example 7

2-(biphenyl-2-ylmethyl)-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide

2-formylbenzoic acid (9.09 mmol, 1.36 g) was dissolved in Methanol (20 ml) and 1-biphenyl-2-ylmethanamine (9.09 mmol, 1.66 g) was added and the mixture was stirred at rt for 30 minutes. Then 4-(isocyanomethyl)benzonitrile (9.09 mmol, 1.29 g) dissolved in Acetonitrile (5 ml) was added to the mixture. The reaction was stirred at rt over night. The crude was purified by flashcromatography (started with isocratic Toluene/EtOAc 100/0 and then the EtOAc concentration was increased to 50%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (2.32 g, 55,8 %).

^{1}H-NMR (500MHz, $CDCl_3$): δ 7,63-7,56 (m, 3H), 7,50-7,45 (m, 2H); 7,45-7,39 (m, 3H); 7,37-7,24 (m, 4H); 7,22-7,16 (m, 3H); 7,00 (d, 2H); 6,59-6,54 (m,1H); 5,24 (d, 1H), 4,77 (s, 1H); 4,31 (d, 1H); 4,29-4,18 (m, 2H).

Example 8

N-[4-(aminomethyl)benzyl]-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide

To a solution of 2-(biphenyl-2-ylmethyl)-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (Example 7) (0.43 mmol, 200mg) in 100mL MeOH (2M NH_3) was added Raney-Ni (prewashed with EtOH (abs). The resulting mixture was hydrogenated at 1.3bar for 16 h. The solvent was removed by evaproation. The crude was purified by flashcromatography (started with isocratic toluene/MeOH 90/10 and then the MeOH concentration was increased to 50%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (0.172 g, 85,2 %).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7,69 (d, 1H), 7,55-7,35 (m, 3H); 7,35-7,13 (m, 11H); 7,08 (d, 2H); 4,72 (s, 1H); 4,19 (s, 2H); 3,74 (s, 2H).

Example 9

N-benzyl-6-chloro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide

5-chloro-3-hydroxy-2-benzofuran-1(3H)-one (Preparation V)(3.25 mmol, 0,6 g) was dissolved in Methanol (10 ml) and [(1R)-1-phenylethyl]amine (3.25 mmol, 0.38 g) was added and stirred for 20 min. Then (isocyanomethyl)benzene (3.25 mmol,0.39 g) was added to the mixture. The reaction was stirred at rt over night. The solvent was removed by evaporation. The crude was purified by flashcromatography (started with isocratic heptane/EtOAc 90/10 and then the EtOAc concentration was increased to 50%, (silicagel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation. The substance was not pure enough so it was purified by preparative HPLC (started with isocratic acetonitrile/buffer 20/80 and then the acetonitrile concentration was increased to 95%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions was pooled and the acetonitrile was removed by evaporation. The product was frees dried over night to give the title compound (mixture of diastereomeres)(0.345 g, 26.2 %). ^{1}H-NMR (500MHz, CDCl3): δ 7,59-6,9 (m, 12H), 6,88-6,8 (m, 1H), 5,68-5,44 (m, 1H), 5,16-4,33 (t, 2H), 4,22-3,46 (m, 1H), 1,78-159 (m, 3H); HRMS calculated for $(C_{24}H_{21}ClN_2O_2+H)^+$, 405,1368; found (ES $[M+H]^+$), 405,1370.

Example 10

N-butyl-2-[2-(4-fluorophenoxy)benzyl]-3-oxoisoindoline-1-carboxamide

2-formylbenzoic acid (0.33 mmol, 50 mg) was dissolved in Methanol (1 ml) and [2-(4-fluorophenoxy)benzyl]amine hydrochloride (0.33 mmol, 84 mg) and TEA (0.66 mmol, 64 mg) was added. Then 1-isocyanobutane (0.33 mmol, 28 mg) dissolved in acetonitrile was added to the mixture. The reaction was stirred at rt over night. The solvent was removed by evaporation. The crude was purified by flashcromatography (started with isocratic heptane/EtOAc 90/10 and then the EtOAc concentration was increased to 100%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the EtOAc was removed by evaporation to give the title compound (47mg, 32,6 %).

^{1}H-NMR (500MHz, CDCl3): δ 7,68-7,64 (d, 1H), 7,62-7,56 (d, 1H), 7,56-7,5 (t, 1H), 7,42-7,36 (t, 1H), 7,36-7,31 (d, 1H), 7,27-7,20 (t, 1H), 7,10-6,93 (m, 5h), 6,85-6,80 (d, 1h), 6,77-6,71 (m,1H), 5,33-5,21 (d, 1H), 4,98 (s, 1H), 4,59-4,51 (d, 1H), 3,33-3,22 (m, 1H), 3,16-3,05 (m, 1H), 1,44-1,14 (m, 5H), 0,94-0,75, (m 3H); HRMS calculated for ($C_{26}H_{25}FN_2O_3$+H)+, 433.5069; found (ES [M+H]+), 433.5061

Example 11

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-(difluoromethoxy)-4-methyl-3-oxoisoindoline-1-carboxamide

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (Example 2)(0.252 mmol, 108 mg) was dissolved in DCM (2 ml) in a 2 ml micro vial , tetrabutylammoniumhydrogensulphate (0.262 mmol, 89 mg) and sodiumhydroxide (0.831mmol, 33 mg) was added and the tube was sealed. N2 (g) was bubbled through the mixture for 5 min. chlorodifluoromethane (g) was bubbled through the mixture for 30 sec. The mixture was stirred at rt for 2h. The solvent was removed by evaporation and the reaction mixture was purified by flashcromatography (started with isocratic Heptane/EtOAc 95/5 and then the EtOAc concentration was increased to 50%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (44mg, 36,5 %).

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^{1}H-NMR (500MHz, CDCl3): δ 7,45-7,32 (m, 7H), 7,32-7,25 (m, 4H), 6,53 (t, 1H,), 5,42 (s, 1H), 5,17 (d, 1H), 4,47 (s, 1H), 4,44 (d, 1H), 2,64 (s, 3H), 1,09 (s, 9H); HRMS calculated for ($C_{28}H_{28}F_2N_2O_3$+H)+, 479.5515; found (ES [M+H]+), 479.5485.

Example 12

N-butyl-2-[2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide

4-fluoro-3-hydroxy-2-benzofuran-1(3H)-one (Preparation U)(11.89 mmol, 2,0 g) was dissolved in Methanol (10 ml) and [2-(4-chlorophenyl)propyl]amine hydrochloride (11.89 mmol, 2,452 g) and TEA (13.08 mmol, 1.324 g) was added and stirred for 20 min. Then 1-isocyanobutane (11.89 mmol, 0.98 g) was added to the mixture. The reaction was stirred at rt over night. The solvent was removed by evaporation. The crude was purified by flashcromatography (started with isocratic heptane/EtOAc 90/10 and then the EtOAc concentration was increased to 50%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation. When evaporating the product precipitated and the solid was filtered of and dried to give the title compound (1.05 g, 21,9 %).

^{1}H-NMR (500MHz, CDCl3): δ 7,42-6,90 (m, 7H), 4,95-4,43 (d, 1H, 230,16 Hz), 4,28-4,14 (m, 1H,), 3,38-3,11 (m, 4H), 1,45-1,34 (m, 2H), 1,34-1,18 (m, 5H), 0,92-0,82 (m, 3H) ; MS calculated for ($C_{22}H_{24}ClFN_2O_2$+H)+, 403.90; found (ES [M+H]+), 403,12

Example 13

(1S or 1R)-N-butyl-2-[(2S or 2R)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide, Isomer E1

(1S or 1R)-N-butyl-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide, Isomer E2

(1R or 1S)-N-butyl-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide, Isomer E3

(1R or 1S)-N-butyl-2-[(2S or 2R)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide, Isomer E4

The four stereoisomers of N-butyl-2-[2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (Example 12 above) (2.60 mmol, 1,05 g) were separated by a preparative HPLC system, equipped with a Chiralpak IA, 5µ, 250 mm x 20 mm column, using MTBE/MeOH (95/5) as mobile phase, giving fraction 1 containing isomer E1, fraction 2 containing isomer E2 and fraction 3 containing isomer E3 and isomer E4.

Fraction 1 was concentrated in vacuo to give (0.219 g, 20,9%) of isomer E1: $[\alpha]_D^{20}$= 30 (c 1.0, MeCN), (ee = 98,5 %).

Fraction 2 was concentrated in vacuo to give (0.232 g, 22,1 %) of isomer E2: $[\alpha]_D^{20}$= 156 (c 1.0, MeCN), (ee = 99,3 %).

Fraction 3 was concentrated and isomer E3 and isomer E4 were separated by a preparative HPLC system, equipped with a (R,R) Whelk-O1, 5µ, 250 mm x 20 mm column, using Heptan/IPA (50/50) as mobile phase giving fraction 3 containing isomer E3, and fraction 4 containing isomer E4.

Fraction 3 was concentrated in vacuo to give (0.204 g, 19,4 %) of isomer E3: $[\alpha]_D^{20}$= –36 (c 1.0, MeCN), (ee = 97,7 %).

Fraction 4 was concentrated in vacuo to give (0.160 g, 15,2 %) of isomer E4: $[\alpha]_D^{20}$= –177 (c 1.0, MeCN), (ee = 96,0 %).

Example 14

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-(fluoromethoxy)-4-methyl-3-oxoisoindoline-1-carboxamide

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (Example 2)(0.233 mmol, 100 mg) was dissolved in Acetonitrile (2 ml) in a 2 ml micro vial and K_2CO_3 (0.256mmol, 0.25 mg) was added and the tube were sealed. N2 (g) was bubbled through the mixture for 5 min. bromofluoromethane (g) was bubbled through the mixture for 30 sec. The reaction was performed in a micro oven (20 min, 140°C). The solvent was removed by evaporation and the reaction mixture was purified by flashcromatography (started with isocratic Heptane/EtOAc 95/5 and then the EtOAc concentration was increased to 50%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (68mg, 63.3 %).

^{1}H-NMR (500MHz, CDCl3): δ 7,45-7,25 (m, 11H), 5,82-5,79 (m, 1H), 5,71-5,69 (m, 1H), 5,47 (s, 1H), 5,16 (d, 1H), 4,47 (s, 1H), 4,43 (d, 1H), 2,59 (s, 3H), 1,08 (s, 9H); HRMS calculated for ($C_{28}H_{29}FN_2O_3$+H)+, 461.5611; found (ES [M+H]+), 461.5596.

Example 15

2-(biphenyl-2-ylmethyl)-1-[(tert-butylamino)carbonyl]-4-methyl-3-oxo-2,3-dihydro-1H-isoindol-5-yl methanesulfonate

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (Example 2)(0.24 mmol, 104 mg) was dissolved in DCM and mesylchloride (0.36 mmol, 42 mg) was added, the mixture was cooled to 0°C and TEA was added drop wise. The solution was heated to rt and stirred for 2 h until no starting material remained (LCMS). The solvent was removed by evaporation and the reaction mixture was purified by flashcromatography (started with isocratic Heptane/EtOAc 95/5 and then the EtOAc concentration was increased to 50%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (62 mg, 50,4 %).

^{1}H-NMR (500MHz, CDCl3): δ 7,47-7,42 (m, 8H), 7,30-7,25 (m, 3H), 5,39 (s, 1H), 5,16 (d, 1H), 4,47 (s, 1H), 4,43 (d, 1H), 2,36 (s, 3H), 2,70 (s, 3H), 1,08 (s, 9H); HRMS calculated for ($C_{28}H_{30}N_2O_5S$ +H)+, 507.6335; found (ES [M+H]+), 507.6326.

Example 16

N-{4-[(acetylamino)methyl]benzyl}-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide

Acetic acid (0.19 mmol, 12 mg) and o-(benzotriazol-1-yl)-n,n,n',n'-tetramethyluronium tetrafluoroborate (0.26 mmol, 0,83 mg) was mixed at rt and stirred for 20 min. n-methylmorpholine (0.26 mmol, 0,26 mg) and N-[4-(aminomethyl)benzyl]-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide (example 8)(0.13 mmol, 60 mg) was added and the reaction was stirred at rt over night. The solvent was removed by evaporation and the crude was purified by preparative HPLC (started with isocratic Acetonitrile/buffer 20/80 and then the Acetonitrile concentration was increased to 95%, the buffer was a

mixture of Acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions was pooled and the product was freeze dried over night to give the title compound (10 mg, 15,3 %). ^{1}H-NMR (500MHz, CDCl3): δ 7,75-7,71 (m, 1H), 7,64-7,65 (m, 2H), 7,52-7,47 (m, 1H), 7,46-7,37 (m, 6H), 7,37-7,22 (m, 3H), 7,13 (d, 2H), 6,86 (d, 2H), 6,04-5,99 (m, 1H), 5,67 (brs, 1H), 5,27 (d, 1H), 4,74 (s, 1H), 4,39 (d, 2H), 4,31 (d, 1H), 4,22-4,09 (m, 2H), 2,03 (s, 3H); HRMS calculated for $(C_{32}H_{29}N_3O_3+H)+$, 504.6140; found (ES [M+H]+), 504.6145.

Example 17

2-(biphenyl-2-ylmethyl)-N-(4-{[(difluoroacetyl)amino]methyl}benzyl)-3-oxoisoindoline-1-carboxamide

Difluoroacetic acid (0.19 mmol, 19 mg) and o-(benzotriazol-1-yl)-n,n,n',n'-tetramethyluronium tetrafluoroborate (0.26 mmol, 0,83 mg) was mixed at rt and stirred for 20 min. n-methylmorpholine (0.26 mmol, 0,26 mg) and N-[4-(aminomethyl)benzyl]-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide (Example 8) (0.13 mmol, 60 mg) was added and the reaction was stirred at rt over night. The solvent was removed by evaporation and the crude was purified by preparative HPLC (started with isocratic Acetonitrile/buffer 20/80 and then the Acetonitrile concentration was increased to 95%, the buffer was a mixture of Acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions was pooled and the product was freeze dried over night to give the title compound (12 mg, 17,0 %). ^{1}H-NMR (500MHz, CDCl3): δ 7,61-7,47 (m, 3H), 7,45-7,18 (m, 10H), 7,18-7,12 (m, 1H), 7,07 (d, 2H), 6,85 (d, 2H), 6,49 (brs, 1H), 6,27 (m, 1H), 5,90 (t, 1H), 5,20 (d, 1H), 4,69 (s, 1H), 4,41 (d, 2H), 4,29-4,21 (d, 1H), 4,21-4,05 (m, 2H); HRMS calculated for $(C_{32}H_{27}F_2N_3O_3+H)+$, 540.5948; found (ES [M+H]+), 540.5895.

Example 18:

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-4,7-difluoro-1-methyl-3-oxoisoindoline-1-carboxamide

2-acetyl-3,6-difluorobenzoic acid (0.24 mmol, 50 mg) was dissolved in Methanol (1 ml) and (biphenyl-2-ylmethyl)amine (0.24 mmol, 46 mg) was added. The mixture was stirred at 50°C over night to form the imine. Then tert-butyl isocyanide (0.24 mmol, 21 mg) dissolved in Acetonitrile was added to mixture. The reaction was stirred at 50°C for 170 h. The product precipitated and was filtered of and the solid was washed with EtOAc to give the title compound (23 mg, 20,5 %).

^{1}H-NMR (500MHz, CDCl3): δ 7,64-7,56 (m, 1H), 7,52-7,43 (m, 2H), 7,42-7,08 (m, 8H), 5,08 (s, 1H), 4,65 (dd, 2H), 1,37 (s, 3H), 0,94 (s, 9H); HRMS calculated for ($C_{27}H_{26}F_2N_2O_2$+H)+, 449.5250; found (ES [M+H]+), 449.5248

Example 19

2-(biphenyl-2-ylmethyl)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide

4-fluoro-3-hydroxy-2-benzofuran-1(3H)-one (Preparation X)((0.87 mmol, 147 mg) was dissolved in Methanol (10 ml) and (biphenyl-2-ylmethyl)amine (0.87 mmol, 160 mg) was added and stirred for 20 min. Then 1,1,1-trifluoro-4-isocyanobutane (0.87 mmol, 120 mg) was added to the mixture. The reaction was stirred at rt over night. The solvent was removed by evaporation. The crude was purified by flashcromatography (started with isocratic heptane/Acetone 90/10 and then the Acetone concentration was increased to 50%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (66 mg, 16 %).

^{1}H-NMR (500MHz, CDCl3): δ 7,50-7,02 (m, 12H), 7,02-6,92 (m, 1H), 5,18-5,08 (D, 1H), 4,62 (s, 1H), 4,28 (d, 1H), 3,25-2,93 (m, 2H), 2,00-1,82 (m,2H), 1,62-1,44 (m, 2H);HRMS calculated for ($C_{26}H_{22}F_4N_2O_2$+H)+, 471.4788; found (ES [M+H]+), 471.4789.

Example 20

2-(biphenyl-2-ylmethyl)-1-[(tert-butylamino)carbonyl]-4-methyl-3-oxo-2,3-dihydro-1H-isoindol-5-yl trifluoromethanesulfonate

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (Example 2) (1,40 mmol, 0,6 g) was dissolved in THF (10 ml), K2CO3

(4.20 mmol, 0,58 g) and n-phenyltrifluoromethanesulfonimide (1.54 mmol, 0,55 g) was added. The reaction was performed in a microwave oven (10 min, 120°C).

The solvent was removed by evaporation and the crude was purified by flashcromat ography (started with isocratic heptane/DCM 50/50 and then the DCM concentration was increased to 100%, then EtOAc added as eluent and the EtOAc concentration was increased to 30 % (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation to give the title compound (0,655 g, 83,4 %). ^{1}H-NMR (500MHz, $CDCl_3$): δ 7,521 (d, 1H), 7,42-7,31 (m, 7H), 7,30-7,24 (m, 2H), 6,08 (s, 1H), 5,26 (d, 1H), 4,53 (s, 1H), 4,44 (d, 1H), 2,52 (s, 3H), 1,16 (s, 9H); HRMS calculated for $(C_{28}H_{27}F_3N_2O_5S+H)+$, 561.6048; found (ES [M+H]+), 561.6019.

Example 21

2-(biphenyl-2-ylmethyl)-N-(4-{[(fluoroacetyl)amino]methyl}benzyl)-3-oxoisoindoline-1-carboxamide

Fluoroacetic acid (0.19 mmol, 15 mg) and o-(benzotriazol-1-yl)-n,n,n',n'-tetramethyluronium tetrafluoroborate (0.26 mmol, 83 mg) was mixed at rt and stirred for 20 min. n-methylmorpholine (0.26 mmol, 26 mg) and N-[4-(aminomethyl)benzyl]-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide (Example 8)(0.13 mmol, 60 mg) was added and the reaction was stirred at rt over night. The solvent was removed by evaporation and the crude was purified by preparative HPLC (started with isocratic Acetonitrile/buffer 20/80 and then the Acetonitrile concentration was increased to 95%, the buffer was a mixture of Acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions was pooled and the product was freeze dried over night to give the title compound (35 mg, 51,6 %). ^{1}H-NMR (500MHz, $CDCl_3$): δ 7,63-7,58 (m, 1H), 7,57-7,48 (m, 2H), 7,44-7,35 (m, 4H), 7,35-7,21 (m, 6H), 7,19-7,15 (m, 1H), 7,11 (d, 2H), 6,91 (d, 2H), 6,63-6,58 (m, 1H), 6,55 (bs, 1H), 5,22 (d, 1H), 4,88 (s, 1H), 4,79 (s, 1H), 4,73 (s, 1H), 4,44 (d, 2H), 4,28 (d, 1H), 4,25-4,13 (m, 2H); HRMS calculated for $(C_{32}H_{28}FN_3O_3+H)+$, 522.6044; found (ES [M+H]+), 522.6043.

Example 22

N-(4,4-difluorobutyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide

2-formylbenzoic acid (6,66mmol, 1,00 g) was dissolved in Methanol (10 ml) and (diphenylmethyl)amine (6,66 mmol, 1,22 g) was added and stirred for 20 min. Then 1,1-difluoro-4-isocyanobutane (6,66 mmol, 0,79 g) was added to the mixture. The reaction was stirred at rt over night. The solvent was removed by evaporation. The crude was purified by flashcromatography (started with isocratic heptane/EtOAc 90/10 and then the EtOAc concentration was increased to 50%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation. The substance was not pure enough so it was purified by preparative HPLC (started with isocratic acetonitrile/buffer 20/80 and then the acetonitrile concentration was increased to 95%, the buffer was a mixture of acetonitrile/water 10/90 and ammonium acetate (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions was pooled and the acetonitrile was removed by evaporation. The product was freeze dried over night to give the title compound (140 mg, 32,3 %).

^{1}H-NMR (500MHz, $CDCl_3$): δ 7,68-7,49 (m, 3H), 7,49-7,18 (m, 9H), 7,06-6,93 (m, 2H), 6,78 (s, 1H), 6,25-6,12 (m, 1H), 7,78-5,30 (m, 1H), 5,24 (s, 1H), 2,89-2,70 (m, 1H), 2,63-2,43 (m, 1H), 1,54-1,30 (m, 2H), 1,25-1,05 (m, 2H);; HRMS calculated for $(C_{26}H_{24}F_2N_2O_2+H)^+$, 435,1884; found (ES $[M+H]^+$), 435,1882.

Example 23

(1S or 1R)-N-(4,4-difluorobutyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide; Isomer E1

(1R or 1S)-N-(4,4-difluorobutyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide ; Isomer E2

N-(4,4-difluorobutyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (Example 22) (1.63 mmol, 0,71 g) were separated by a preparative HPLC system, equipped with a ReproSil, 10µ, 250 mm x 20 mm column, using Heptan/IPA (30/70) as mobile phase, giving fraction 1 containing isomer E1, fraction 2 containing isomer E2.

Fraction 1 was concentrated in vacuo to give (0.316 g, 44,5%) of isomer E1, ee = 100%.

Fraction 2 was concentrated in vacuo to give (0.308 g, 43,4%) of isomer E2, ee = 99,6%.

Example 24

N-benzyl-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide

2-Formylbenzoic acid (2.72 g, 18.1 mmol) and 1-Phenylethanamine (2.30 mL, 18.1 mmol) was added to a flask, MeOH (15 ml) was then added and the mixture was left stirring in r.t. for 2 h. (Isocyanomethyl)benzene (2.12 g, 18.1 mmol) dissolved in MeCN (25 ml) was added to the mixture and the reaction was left stirring in r.t. over night. The reaction was finished the next morning and the solvent was evaporated. The crude was dissolved in DCM (20 mL) and extracetd with water (10 mL), the organic phase was collected and most of the solvent was evaporated then EtOAc was added and the solvent was evaporated. The crude was purified by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using heptane and EtOAc as eluent, followed by concentration in vacuo afforded the title compound (4.16 g, 62%).

^{13}C-NMR (500 MHz, $CDCl_3$) δ 170.73, 170.47, 169.09, 168.26, 142.14, 142.02, 140.45, 140.37, 137.34, 137.14, 132.79, 132.75, 131.09, 130.99, 129.38, 129.35, 129.21, 129.10, 128.96, 128.71, 128.50, 128.27, 128.15, 128.02, 127.96, 127.68, 127.58, 127.49, 124.32, 124.26, 122.93, 122.78, 63.75, 63.31, 52.56, 52.12, 43.89, 43.39, 18.19, 17.58; HRMS calculated for (C24 H22 N2 O2+H)$^+$, 371.1760 found (ES $[M+H]^+$), 371.1768 and 371.1771 for respectively diasteromer.

Example 25

(1S or 1R)-N-benzyl-3-oxo-2-[(1R or 1S)-1-phenylethyl]isoindoline-1-carboxamide (E1)

(1S or 1R)-N-benzyl-3-oxo-2-[(1S or 1R)-1-phenylethyl]isoindoline-1-carboxamide (E2)

(1R or 1S)-N-benzyl-3-oxo-2-[(1R or 1S)-1-phenylethyl]isoindoline-1-carboxamide (E3)

(1R or 1S)-N-benzyl-3-oxo-2-[(1S or 1R)-1-phenylethyl]isoindoline-1-carboxamide (E4)

The four stereo isomers of N-benzyl-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide (example 24) were separated by a preparative HPLC system, equipped with a Chiralpak AD-H 5µ 250 mm x 20 mm column, using Heptan/EtOH (85/15) as mobile phase, giving fraction 1 containing isomer 1, fraction 2 containing isomer 2 and isomer 3, and fraction 3 containing isomer 4. Fraction 1 was concentrated in vacuo to give (E1) (0.602 g, 22.8 %) of isomer 1: $[\alpha]_D^{20}$=+121.9 (c 1.0, MeCN); HRMS calculated for (C24 H22 N2 O2+H)$^+$, 371.1759 found (ES $[M+H]^+$), 371.1760

Fraction 3 was concentrated in vacuo to give (E4) (0.516 g, 19.5%) of isomer 4: $[\alpha]_D^{20}$=-121.3 (c 1.0, MeCN); HRMS calculated for (C24 H22 N2 O2+H)$^+$, 371.1759 found (ES $[M+H]^+$), 371.1779

Fraction 2 was concentrated and isomer 2 and isomer 3 were separated by a preparative HPLC system, equipped with a Chiralpak IA 5µ 250 mm x 20 mm column, using Heptan/EtOH (80/20) as mobile phase giving fraction 1 containing isomer 2, and fraction 2 containing isomer 3.

Fraction 1 was concentrated in vacuo to give (E2) (0.571 g, 21.6%) of isomer 2: $[\alpha]_D^{20}$=+161.0 (c 1.0, MeCN); HRMS calculated for (C24 H22 N2 O2+H)$^+$, 371.1759 found (ES $[M+H]^+$), 371.1761

Fraction 2 was concentrated in vacuo to give (E3) (0.718 g, 27.1%) of isomer 3: $[\alpha]_D^{20}$=-153.0 (c 1.0, MeCN); HRMS calculated for (C24 H22 N2 O2+H)$^+$, 371.1759 found (ES $[M+H]^+$), 371.1758

Example 26

N-(3-chlorobenzyl)-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide

The 3-amino-2,2-dimethylpropan-1-ol (0.276 mmol) was dissolved in MeCN (1 mL) and added to 2-Formylbenzoic acid (0.276 mmol) dissolved in MeOH (1 mL), this was stirring for 30 min in r.t. 1-chloro-3-(isocyanomethyl)benzene (0.248 mmol) dissolved in MeCN (2 mL) was added to the mixture and the reaction was left stirring in r.t. over night. The reaction was finished the next morning and the solvent was evaporated. The crude was dissolved in DCM (4 mL) and extracetd with water (3 mL), the organic phase was collected and the solvent was evaporated. The crude was dissolved in DMSO (1 ml),

filtrated and purified by preparative HPLC using a Waters FractionLynx III HPLC system with a mass triggered fraction collector, equipped with an Xbridge Prep C18 150x19 mm column using a MeCN/0.2% NH_3 buffer system with a gradient from 100% A (5% MeCN + 95% 0.2% NH_3) to 100% B (95% MeCN + 5% 0.2% NH_3) as mobile phase, followed by concentration in vacuo afforded the title compound (0.025 g, 23.%).

^{1}H-NMR* (600 MHz, DMSO-d_6, DMSO*) δ 9.29-9.17 (m, 1H), 7.77-7.46 (m, 4H), 7.4-7.15 (m, 4H), 5.48-5.4 (s, 1H), 4.74-4.63 (m, 1H), 4.4-4 26 (m, 2H), 3.79-3.71 (d, 1H), 3.19-3.05 (m), 2.76-2.64 (d), 0.88-0.75 (s, 6H); HRMS calculated for (C21 H23 Cl N2 O3+H)$^+$, 387.1475 found (ES [M+H]$^+$), 387.1475

Example 27

2-[2-(4-chlorophenyl)propyl]-N-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide

2-Formylbenzoic acid (0.060 g, 0.44 mmol), 2-(4-chlorophenyl)propan-1-amine hydrochloride (0.068 g, 0.40 mmol) and TEA (0.062 mL, 0.44 mmol) was addde to a flask and dissolved in MeOH (2 mL), this was stirring for 2 h in r.t. 4-(isocyanomethyl)-5-methyl-2-phenyl-1,3-oxazole (0.079 g, 0.40 mmol) dissolved in MeCN (2 mL) was added to the mixture and the reaction was left stirring in r.t. for two days. The solvent was evaporated, the crude was dissolved in DCM (4 mL) and extracetd with water (3 mL), the organic phase was collected and the solvent was evaporated. The crude was purified by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using heptane and EtOAc as eluent, followed by concentration in vacuo afforded the title compound (0.017 g, 8.5%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.22-7.34 (m, 9H), 7.21-7.01 (m, 4H), 6.56-6.34 (m, 1H), 4.64-3.98 (m, 3H), 3.42-3.12 (m, 2 H), 2.53-2.16 (m, 3H), 1.4-1.08 (m, 3H);

Example 28

N-(tert-butyl)-2-[(1-methyl-5-phenyl-1H-pyrazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide

1-(1-methyl-5-phenyl-1*H*-pyrazol-3-yl)methanamine (0.400 mmol) was dissolved in MeCN (1 mL) and added to 2-Formylbenzoic acid (0.400 mmol) dissolved in MeOH (1 mL), this was stirring for 1 h in r.t. *tert*-butyl isocyanide (0.400 mmol) was added to the mixture and the reaction was left stirring in r.t. for two days. The solvent was evaporated, the crude was dissolved in DCM (4 mL) and extracetd with water (3 mL), the organic phase was collected and the solvent was evaporated. The crude was purified by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using heptane and EtOAc as eluent, followed by concentration in vacuo afforded the title compound (0.078 g, 48.4%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.94-7.36 (m, 9H), 6.39-6.28 (m, 1H), 5.28-5.07 (m, 2H), 4.39-4.23 (d, 1H), 3.92-3.79 (s, 3H), 1.44-1.2 (s, 9H); HRMS calculated for (C24 H26 N4 O2+H)$^+$, 403.2134 found (ES [M+H]$^+$), 403.2156

Example 29

2-(biphenyl-2-ylmethyl)-6-bromo-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide

1-biphenyl-2-ylmethanamine (0.225 g, 1.23 mmol) and 5-bromo-3-hydroxy-2-benzofuran-1(3H)-one (Preparation W) (0.283 g, 1.24 mmol) was added to a flask, MeOH (1 mL) was added an the mixture was left stirring in r.t. for 3 h. . *tert*-butyl isocyanide (0.139 mL, 1.23 mmol) was added to the mixture and the reaction was left stirring in r.t. over night. The solvent was evaporated, the crude was dissolved in DCM (4 mL) and extracetd with water (3 mL), the organic phase was collected and the solvent was evaporated. The crude was purified by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using heptane and EtOAc as eluent, followed by concentration in vacuo afforded the title compound (0.191 g, 32.4%). ^{13}C-NMR (500 MHz, $CDCl_3$) δ 168.58, 166.16, 143.65, 142.49, 140.52, 133.37, 132.34, 130.62, 130.46, 129.15, 128.62, 128.35, 128.15, 127.99, 127.87, 127.28, 126.31, 125.21, 124.92, 62.87, 51.61, 42.93, 31.88, 28.99, 27.52, 27.24, 22.58, 13.28; HRMS calculated for (C26 H25 Br N2 O2+H)$^+$, 477.1178 found (ES [M+H]$^+$), 477.1173

Example 30

2-(biphenyl-2-ylmethyl)-5-bromo-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide

1-biphenyl-2-ylmethanamine (0.106 g, 0.578 mmol) and 5-bromo-2-formylbenzoic acid (commercially available)(0.132 g, 0.578 mmol) was added to a flask, MeOH (1 mL) was added an the mixture was left stirring in r.t. for 30 mins. *.tert*-butyl isocyanide (0.065 mL, 0.578 mmol) was added to the mixture and the reaction was left stirring in r.t. for 16 h. The solvent was evaporated, the crude was dissolved in DCM (4 mL) and extracetd with water (3 mL), the organic phase was collected and the solvent was evaporated. The crude was purified by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using heptane and EtOAc as eluent, followed by concentration in vacuo afforded the title compound (0.143 g, 51.8%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.89-7.82 (m, 1H), 7.78-7.71 (m, 1H), 7.56-7.24 (m, 10H), 5.47-5.33 (d, 1H), 4.72-4.63 (s, 1H), 4.23-4.07 (d, 1H), 1.39-1.13 (s, 9H); HRMS calculated for (C26 H25 Br N2 O2+H)$^+$, 477.1178 found (ES $[M+H]^+$), 477.1184

Example 31

2-(biphenyl-2-ylmethyl)-*N*-(4,4-difluorobutyl)-3-oxoisoindoline-1-carboxamide

The 1-biphenyl-2-ylmethanamine (0.400 mmol) was dissolved in MeCN (1 mL) and added to 2-Formylbenzoic acid (0.400 mmol) dissolved in MeOH (1 mL), this was stirring for 30 min in r.t 1,1-difluoro-4-isocyanobutane (preparation P) (0.400 mmol) dissolved in MeCN (2 mL) was added to the mixture and the reaction was left stirring in r.t. over night. The reaction was finished the next morning and the solvent was evaporated. The crude was dissolved in DCM (4 mL) and extracetd with water (3 mL), the organic phase was collected and the solvent was evaporated. The crude was dissolved in DMSO (1 ml), filtrated and purified by preparative HPLC using a Waters FractionLynx I HPLC system with a mass triggered fraction collector, equipped with an Xbridge Prep C18 150x19 mm column using a MeCN/0.2% NH_3 buffer system with a gradient from 100% A (5% MeCN + 95% 0.2% NH_3) to 100% B (95% MeCN + 5% 0.2% NH_3) as mobile phase, followed by concentration in vacuo afforded the title compound (0.057 g, 33%). ^{1}H-NMR* (600 MHz, DMSO-d_6, DMSO*) δ 8.526-8.3 (m, 1H), 7.75-7.03 (m, 13H), 6.2-5.85 (m, 1H), 5.27-5.07 (d, 1H), 4.83-4.66 (s, 1H), 4.13-3.85 (d, 1H), 3.1-2.83 (m), 1.81-1.55 (m, 2H), 1.5-1.27 (m, 2H); HRMS calculated for (C26 H24 F N2 O2+H)$^+$, 435.1884 found (ES $[M+H]^+$), 435.1865

Example 32

2-(biphenyl-2-ylmethyl)-N-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]-6-fluoro-3-oxoisoindoline-1-carboxamide

The 1-biphenyl-2-ylmethanamine (0.370 mmol) was dissolved in MeCN (1 mL) and added to 5-fluoro-3-hydroxy-2-benzofuran-1(3H)-one (preparation X)(0.370 mmol) dissolved in MeOH (1 mL), this was stirring for 30 min in r.t. (2,2-difluoro-1,3-benzodioxol-5-yl)methyl isocyanide (preparation R) (0.370 mmol) dissolved in MeCN (2 mL) was added to the mixture and the reaction was left stirring in r.t. for 3 days. The solvent was evaporatedand, the crude was dissolved in DCM (4 mL) and extracetd with water (3 mL), the organic phase was collected and the solvent was evaporated. The crude was dissolved in DMSO (1 ml), filtrated and purified by preparative HPLC using a Waters FractionLynx I HPLC system with a mass triggered fraction collector, equipped with an Xbridge Prep C18 150x19 mm column using a MeCN/0.2% NH_3 buffer system with a gradient from 100% A (5% MeCN + 95% 0.2% NH_3) to 100% B (95% MeCN + 5% 0.2% NH_3) as mobile phase, followed by concentration in vacuo afforded the title compound (0.053 g, 26%). ^{1}H-NMR* (600 MHz, DMSO-d_6, DMSO*) δ 8.95-8.83 (m, 1H), 7.76-7.64 (m, 1H), 7.48-6.87 (m, 14H), 5.18-5.08 (d, 1H), 4.84-4.78 (s, 1H), 4.2-3.95 (m) ; HRMS calculated for $(C30\ H21\ F3\ N2\ O4+H)^+$, 531.1532 found (ES $[M+H]^+$), 531.1537

Example 33

2-(biphenyl-2-ylmethyl)-N-tert-butyl-3-oxoisoindoline-1-carboxamide

A mixture of 2-formylbenzoic acid (2.50 g, 16.7 mmol) and 1-biphenyl-2-ylmethanamine (3.05 g, 16.7 mmol) in MeOH (55 ml) was stirred at room temperature for 1 h and then tert-butyl isocyanide (1.38 g, 16.7 mmol) was added. The resulting mixture was stirred at room temperature over night and concentrated under reduced pressure. Crystals were obtained by adding ethanol to the residue. The crystals (2.06 g) were filtered off and dried in vacuo. The filtrate was purified by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using ethyl acetate (gradient from 6 to 50 %) in heptane as eluent. Removal of the solvent gave 2.05 g of a white solid. The products from

crystallisation and chromatography were combined and triturated with methanol giving 2.88 g of a white solid. The remaining material was purified by preparative HPLC giving a second crop of 0.70 g.

^{1}H NMR (500 MHz, CD_3OD) δ 7.71 (dm, 1H), 7.56 (m, 1H), 7.50 (m, 1H), 7.42 (dm, 1H), 7.38-7.24 (m, 9H), 5.37 (d, 1H), 4.71 (s, 1H), 4.15 (d, 1H), 1.22 (s, 9H); HRMS calculated for $(C_{26}H_{26}N_2O_2+H)^+$, 399.2066; found (ESI $[M+H]^+$), 399.2073.

Example 34

(R or S) 2-(biphenyl-2-ylmethyl)-N-tert-butyl-3-oxoisoindoline-1-carboxamide (isomer 1)

(S or R) 2-(biphenyl-2-ylmethyl)-N-tert-butyl-3-oxoisoindoline-1-carboxamide (isomer 2)

The first crop (2.88 g) of example 33 above was separated into its enantiomers on a Chiralpak IA using 25 % 2-propanol in heptane. Concentration under reduced pressure gave 1.39 g of isomer 1 and 1.25 g of isomer 2.

Example 35

N-benzyl-6-cyano-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide

(i) N-benzyl-6-bromo-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide

(R)-(+)-1-Phenylethylamine (0.12 g, 1.0 mmol) was added to a slurry of 5-bromo-3-hydroxy-2-benzofuran-1(3H)-one in MeOH (5 ml). The solution was stirred for 30 mins at room temperature. Benzyl isocyanide (0.12 g, 1.0 mmol) was added and the resulting mixture was stirred at room temperature over night and evaporated. Purification by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using ethyl acetate (gradient from 6 to 50 %) in heptane as eluent, followed by concentration in vacuo afforded the title compound (0.33 g, 72%) as a white powder. ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (m, 2H), 7.52 (m, 1H), 7.44 (m, 1H), 7.36-7.20 (m, 8H), 7.68 (m, 1H), 5.61 and 5.32 (q, 1H, rotamers), 5.22 and 4.79 (s, 1H, rotamers), 4.37 (br s, 1H), 3.97 (m, 1H), 1.74 and 1.61 (d, 3H, rotamers); MS (ESI) m/z 449.0 ($[M+H]^+$);

(ii) N-benzyl-6-cyano-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide

A mixture of *N*-benzyl-6-bromo-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (0.10 g, 0.22 mmol), zinc cyanide (0.040 g, 0.34 mmol), and $Pd(PPh_3)_4$ (0.026 g, 0.022 mmol) in DMF (3 ml) was degassed by argon-bubbling for 15 mins. The mixture was then heated at 200 °C for 30 mins in a microwave reactor and concentrated in vacuo. Purification by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using ethyl acetate (gradient from 9 to 76 %) in heptane as eluent, followed by concentration in vacuo afforded the title compound (0.064 g, 72%) as a white solid. ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 8.24 (br s, 1H), 7.94-7.81 (m, 3H), 7.52 (m, 1H), 7.36-7.19 (m, 8H), 7.13 (m, 1H), 5.63 and 5.21 (q, 1H), 5.41 and 5.04 (s, 1H), 4.43 (m, 1H), 4.15 (m, 1H), 1.84 and 1.67 (d, 3H, rotamers). MS (ESI) m/z 396.0 ($[M+H]^+$); HRMS calculated for $(C_{26}H_{21}N_3O_2+H)^+$, 396.1712; found (ESI $[M+H]^+$), 396.1739.

Example 36

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-6-cyano-3-oxoisoindoline-1-carboxamide was synthesised according the proceduredescribed in example 35 above using 1-biphenyl-2-ylmethanamine instead of (R)-(+)-1-phenylethylamine and tert-butyl isocyanide instead of benzyl isocyanide. HRMS calculated for $(C_{27}H_{25}N_3O_2+H)^+$, 424.2025; found (ESI $[M+H]^+$), 424.2010.

Example 37

2-(2-bromobenzyl)-N-tert-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

(i) N-(2-bromobenzyl)-N-[2-(tert-butylamino)-1-(2-furyl)-2-oxoethyl]but-2-ynamide

A mixture of but-2-ynoic acid (0.42 g, 5.0 mmol), 1-(2-bromophenyl)methanamine (0.93 g, 5.0 mmol), and 2-furaldehyde (0.48 g, 5.0 mmol) in MeOH (20 ml) was stirred at room temperature for 1 h and then tert-butyl isocyanide (0.42 g, 5.0 mmol) was added. The resulting mixture was stirred at room temperature over night and concentrated under reduced pressure. The crude product was used in the next step without purification.

(ii)2-(2-bromobenzyl)-N-tert-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

A mixture of N-(2-bromobenzyl)-N-[2-(tert-butylamino)-1-(2-furyl)-2-oxoethyl]but-2-ynamide (2.10 g, 0.487 mmol) from step (i) above and ytterbium (III)

trifluoromethanesulfonate (0.302 g, 0.487 mmol) in xylene (100 ml) was heated at reflux for 1.5 h. A white precipitate was filtered off giving 0.87 g of pure product. The filtrate was concentrated and purified by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using ethyl acetate (gradient from 30 to 70 %) in heptane as eluent giving a second crop of 0.32 g making the total yield 1.19 g (57 %). ^{1}H NMR (500 MHz, (CD_3OD) δ 7.60 (m, 1H), 7.36-7.27 (m, 2H), 7.21 (m, 1H), 7.08 (m, 1H), 6.95 (m, 1H) 5.23 (d, 1H), 4.66 (s, 1H), 4.37 (d, 1H), 2.55 (s, 3H), 1.30 (s, 9H).

Example 38

2-(biphenyl-2-ylmethyl)-*N*-*tert*-butyl-4-methyl-5-[(methylsulfonyl)amino]-3-oxoisoindoline-1-carboxamide

(i) N-(biphenyl-2-ylmethyl)-N-{2-(tert-butylamino)-1-[1-(methylsulfonyl)-1H-pyrrol-2-yl]-2-oxoethyl}but-2-ynamide

A mixture of but-2-ynoic acid (0.050 g, 0.60 mmol), 1-biphenyl-2-ylmethanamine (0.11 g, 0.60 mmol), and 1-(methylsulfonyl)-1H-pyrrole-2-carbaldehyde (J. Am.Chem. Soc., 1998, 1741.) (0.10 g, 0.60 mmol) in MeOH (6 ml) was stirred at room temperature for 1 h. and then tert-butyl isocyanide (0.050 g, 0.60 mmol) was added. The resulting mixture was stirred at room temperature for three days giving a white precipitate. The precipitate was filtered off and dried in vacou giving 0.23 g (76 %) of a white powder which was used in the next step without further purification. MS (ESI) m/z 506.2 ($[M+H]^+$).

(ii) 2-(biphenyl-2-ylmethyl)-N-tert-butyl-4-methyl-5-[(methylsulfonyl)amino]-3-oxoisoindoline-1-carboxamide

A solution of N-(biphenyl-2-ylmethyl)-N-{2-(tert-butylamino)-1-[1-(methylsulfonyl)-1H-pyrrol-2-yl]-2-oxoethyl}but-2-ynamide from step (i) above(0.050 g, 0.099 mol) in dioxane (4 ml) and 1-butyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate ($BMIMPF_6$, 0.2 ml) was heated at 200°C for 30 mins in a microwave reactor. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous phase was extracted with two portions of ethyl acetate. The combined organic layers were washed with two portions of water, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography

(SP1™ flash system from Biotage™, silica cartridge), using ethyl acetate (gradient from 12 to 100 %) in heptane as eluent, followed by concentration in vacuo afforded the title compound (0.055 g, 56%) as a white solid. ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.00 (br s, 1H), 7.53 (d, 1H), 7.37-7.20 (m, 10H), 5.32 (d, 1H), 4.62 (s, 1H), 4.10 (d, 1H), 2.97 (s, 3H), 2.67 (s, 3H), 1.21 (s, 9H); MS (ESI) m/z 506.2 ($[M+H]^+$).

Example 39

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-[(methylsulfonyl)amino]-3-oxoisoindoline-1-carboxamide

was synthesised according the procedure in example 38 described above using propiolic acid instead of but-2-ynoic acid. MS (ESI) m/z 492.1 ($[M+H]^+$).

Example 40

N-(tert-butyl)-2-(4-chlorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide

(i) N-[2-(tert-butylamino)-1-(2-furyl)-2-oxoethyl]-N-(4-chlorobenzyl)-3-(trimethylsilyl)prop-2-ynamide

A mixture of 3-(trimethylsilyl)prop-2-ynoic acid (0.071 g, 0.50 mmol), 1-(4-chlorophenyl)methanamine (0.071 g, 0.50 mmol), and 2-furaldehyde (0.048 g, 0.50 mmol) in MeOH (2 ml) was stirred at room temperature for 1 h and then tert-butyl isocyanide (0.042 g, 0.50 mmol) was added. The resulting mixture was stirred at room temperature for 2 days and concentrated under reduced pressure. The crude product was used in the next step without purification; MS (ESI) m/z 444.9 ($[M+H]^+$).

(ii)N-(tert-butyl)-2-(4-chlorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide

A mixture of N-[2-(tert-butylamino)-1-(2-furyl)-2-oxoethyl]-N-(4-chlorobenzyl)-3-(trimethylsilyl)prop-2-ynamide (0.223 g, 0.50 mmol) from step (i) above, ytterbium (III) trifluoromethanesulfonate (0.124 g, 0.40 mmol), and 1-butyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate ($BMIMPF_6$, 0.3 ml) in dioxane (15 ml) was heated at 200 °C for 30 mins in a microwave reactor and concentrated under reduced pressure. Purification by flash chromatography (SP1™ flash system from Biotage™, silica cartridge), using ethyl acetate (gradient from 30 to 70 %) in heptane as eluent, followed by concentration in vacuo

afforded 0.032 g (17 %) of the title compound. ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.87 (s, 1H), 8.13 (s, 1H), 7.41 (dm, 2H), 7.26 (dm, 1H), 7.22 (dm, 2H), 7.03 (m, 1H), 6.98 (m, 1H), 5.07 (d, 1H), 4.78 (s, 1H), 3.97 (d, 1H), 1.24 (s, 9H); MS (ESI) m/z 373.0 ($[M+H]^+$); HRMS calculated for $(C_{20}H_{21}ClN_2O_3+H)^+$, 373.1319; found (ESI $[M+H]^+$), 373.1338.

Example 41

N-(tert-butyl)-2-(4-chlorobenzyl)-7-hydroxy-3-oxoisoindoline-1-carboxamide.

The title compoundwas isolated as by-product in the synthesis of N-(tert-butyl)-2-(4-chlorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide

HRMS calculated for $(C_{20}H_{21}ClN_2O_3+H)^+$, 373.1319; found (ESI $[M+H]^+$), 373.1324.

Example 42

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-7-hydroxy-3-oxoisoindoline-1-carboxamide.

The title compound was isolated as by-product in the synthesis of 2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide,

HRMS calculated for $(C_{26}H_{26}N_2O_3+H)^+$, 415.2022; found (ESI $[M+H]^+$), 415.2005.

Example 43

2-(biphenyl-4-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

(i) N-(biphenyl-4-ylmethyl)-N-[2-(tert-butylamino)-1-(2-furyl)-2-oxoethyl]but-2-ynamide

A mixture of but-2-ynoic acid (0.025 g, 0.30 mmol), 1-biphenyl-4-ylmethanamine (0.055 g, 0.30 mmol), and 2-furaldehyde (0.029 g, 0.30 mmol) in MeOH (2 ml) was stirred at room temperature for 30 mins and then tert-butyl isocyanide (0.025 g, 0.30 mmol) was added. The resulting mixture was stirred at room temperature for 3 days and concentrated under reduced pressure giving 0.125 g (97 %) of the title compound. The crude product was used in the next step without purification; MS (ESI) m/z 429.0 ($[M+H]^+$).

(ii) 2-(biphenyl-4-ylmethyl)-*N-tert*-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

A mixture of N-(biphenyl-4-ylmethyl)-N-[2-(tert-butylamino)-1-(2-furyl)-2-oxoethyl]but-2-ynamide (0.125 g, 0.29 mmol) from step (i) above and ytterbium (III) trifluoromethanesulfonate (0.037 g, 0.06 mmol) in dioxane (20 ml) was heated at 200 °C for 30 mins in a microwave reactor and concentrated under reduced pressure. The residue was partitioned between DCM and saturated aqueous $NaHCO_3$ in a Phase Separator. The aqueous phase was extracted with two more portions of DCM and the combined organic layers were concentrated in vacuo. Purification by preparative HPLC using a FractionLynx I HPLC system equipped with a Gemini 5u C18 110A 21.2 X 100 mm column using a gradient of 5 to 95 % CH_3CN in 0.2% NH_3 as mobile phase, followed by concentration in vacuo gave 0.073 g (57 %) of the title compund. ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.61 (s, 1H), 8.10 (s, 1H), 7.61 (m, 4H), 7.59 (m, 2H), 7.32 (m, 1H), 7.26 (dm, 2H), 7.06 (dm, 1H), 6.95 (dm, 1H), 5.12 (d, 1H), 4.73 (s, 1H), 3.91 (d, 1H), 1.23 (s, 9H); MS (ESI) m/z 429.2 ($[M+H]^+$); HRMS calculated for $(C_{27}H_{28}N_2O_3+H)^+$, 429.2178; found (ESI $[M+H]^+$), 429.2144.

Example 44

N-(tert-butyl)-2-[(4'-fluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

A mixture of 2-(2-bromobenzyl)-*N-tert*-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (example 37 above)(0.078 g, 0.18 mmol), (4-fluorophenyl)boronic acid (0.030 g, 0.22 mmol), $Pd(PPh_3)_4$ (0.010 g, 0.009 mmol), and aqueous Cs_2CO_3 (0.117 g in 0.2 ml water) in 1,2-dimethoxyethane (1.0 ml) in a 2 ml microwave reactor vial was degassed by argon-bubbling for 5 mins. The mixture was then heated at 130 °C for 15 mins in a microwave reactor and concentrated in vacuo. Hydrochloric acid (2 ml of a 2 M solution) was added to the residue and the aqueous phase was extracted with three portions of DCM in a Phase Separator. The combined organic layers were concentrated under reduced pressure. Purification by preparative HPLC using a FractionLynx II HPLC system equipped with a Sunfire 5μm C18 OBD 19 X 150 mm column using a gradient of 5 to 95 % CH_3CN in 0.1 M HCO_2H as mobile phase, followed by concentration in vacuo gave 0.078 g (97 %) of the title compund. ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.61 (s, 1H), 7.90 (s, 1H), 7.32 (m, 4H), 7.20 (m, 4H), 7.00 (dm, 1H), 6.91 (dm, 1H), 5.07 (d, 1H), 4.54 (s,

1H), 3.84 (d, 1H), 2.41 (s, 3H), 1.08 (s, 9H); MS (ESI) m/z 447.4 ($[M+H]^+$); HRMS calculated for $(C_{27}H_{27}FN_2O_3+H)^+$, 447.2084; found (ESI $[M+H]^+$), 447.2092.

Example 45

N-benzyl-2-[2-(4-chlorophenyl)ethyl]-1-hydroxy-3-oxoisoindoline-1-carboxamide

(i) 2-[2-(4-chlorophenyl)ethyl]isoquinoline-1,3(2*H*,4*H*)-dione

1*H*-isochromene-1,3(4*H*)-dione (1.50 g, 6.94 mmol) and 2-(4-chlorophenyl)ethanamine (1.08 g, 6.94 mmol) were mixed in toluene (5 ml) under nitrogen atmosphere and the resulting mixture was refluxed for 20 hours. The mixture was cooled by dilution with 20 ml toluene which resulted in formation of a white solid, which was collected by filtration to give the title compound (1.40 g, 67%).

^{1}H-NMR (500MHz, $CDCl_3$) δ 8.23 (d, 1H), 7.61 (t, 1H), 7.48 (t, 1H), 7.31-7.23 (m, 5H), 4.23-4.18 (m, 2H), 4.04 (s, 2H), 2.94-2.89 (m, 2H).

(ii) 2-[2-(4-chlorophenyl)ethyl]isoquinoline-1,3,4(2*H*)-trione

2-[2-(4-chlorophenyl)ethyl]isoquinoline-1,3(2*H*,4*H*)-dione (0.50g, 1.67 mmol) was mixed with SeO_2 (0.19 g, 1.67 mmol) in toluene (10 ml) and heated at reflux for 16 hours. Solid material was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was filtered through a silica gel plug, eluting with DCM. The solvent was removed under reduced pressure to give the title compound (0.52 g, 99%).

[M+H] (ES) 314.0

(iii) *N*-benzyl-2-[2-(4-chlorophenyl)ethyl]-1-hydroxy-3-oxoisoindoline-1-carboxamide

2-[2-(4-chlorophenyl)ethyl]isoquinoline-1,3,4(2*H*)-trione (0.15g, 0.47 mmol) and benzyl amine (0.076g, 0.71 mmol) were mixed in toluene (2 ml) and the resulting mixture was heated at 60 °C for 16 hours. The solvent was removed under reduced pressure. The residue was purified by flash chromatography using a Biotage SP1 with ethyl acetate/heptane as mobile phase and further purified by reverse phase HPLC equipped with

a Kromasil C8 column and MeCN/water (0.1M ammonium acetate) as mobile phase. The product fraction was freeze-dried to give the title compound (0.023g, 12%).
HRMS: calculated for $(C_{24}H_{21}ClN_2O_3+H)^+$ 421.1319 ; found (ES $[M+H]^+$) 421.1336.
^{1}H-NMR (500MHz, DMSO-d_6) δ 7.69-7.61 (m, 3H), 7.58-7.51 (m, 2H), 7.36-7.16 (m, 9H), 4.40-4.28 (m, 2H), 3.64-3.56 (m, 1H), 3.28-3.20 (m, 1H), 2.93-2.75 (m, 2H).

Example 46

N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide

2-formylbenzoic acid (9,12 mmol, 1,37 g) was dissolved in Methanol (10 ml) and 1-(3',4'-difluorobiphenyl-2-yl)methanamine (9.12 mmol, 2,00 g)(prep AI) was added and stirred for 20 min. Then 2-isocyano-2-methylpropane (9.12 mmol, 0,76 g) was added to the mixture. The reaction was stirred at rt over night. The solvent was removed by evaporation. The crude was purified by flash chromatography (started with isocratic heptane/EtOAc 90/10 and then the EtOAc concentration was increased to 50%, (silica gel 60 0.004-0.063 mm). The product containing fractions was pooled and the solvent was removed by evaporation. The substance was not pure enough so it was purified by preparative HPLC (started with isocratic acetonitrile/buffer 20/80 and then the acetonitrile concentration was increased to 95%, the buffer was a mixture of H2O / ACN / FA (94,8 / 5 / 0,2) (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions was pooled and the acetonitrile was removed by evaporation to give the title compound (2,10 g, 53,1 %). 1H-NMR (500MHz, $CDCl_3$): δ 7,60-7,54 (m, 2H); 7,54-7,48 (m,1H); 7,42-7,37 (m, 1H); 7,33-7,27 (m, 3H); 7,22-7,13 (m, 2H); 7,12-7,06 (m, 1H); 7,02-6,96 (m, 1H); 6,08 (s, 1H); 5,18 (d, 1H); 4,56 (s, 1H); 4,37-4,30 (d, 1H), 1,15 (s, 9H).

Example 47

(1R or 1S)-N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide

(1S or 1R)-N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide

N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (Example 46)(4.83 mmol, 2,10 g) were separated by a preparative HPLC system, equipped with a Chiralpak AD, 5µ, 250 mm x 20 mm column, using Heptan/EtOH (75/25) as mobile phase, giving fraction 1 containing isomer E1, fraction 2 containing isomer E2.

Fraction 1 was concentrated in vacuo to give (0.903 g, 43,0 %) of isomer E1, ee = 99,9%. HRMS calculated for (C26H24F2N2O2+H)+, 435.1884; found (ES [M+H]+), 435.1881.

Fraction 2 was concentrated in vacuo to give (0.908 g, 43,2%) of isomer E2, ee = 99,9%. HRMS calculated for (C26H24F2N2O2+H)+, 435.1884; found (ES [M+H]+), 435.1894.

Example 48

N-(tert-butyl)-2-[(4,4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide

2-formylbenzoic acid (0,5 mmol, 75 mg) was dissolved in Methanol (10 ml) and 1-(4,4'-difluorobiphenyl-2-yl)methanamine (0,50 mmol, 110 mg) was added and stirred for 20 min. Then 2-isocyano-2-methylpropane (0,50 mmol, 42 mg) was added to the mixture. The reaction was stirred at rt over night. The solvent was removed by evaporation. The crude was purified by preparative HPLC (started with isocratic acetonitrile/buffer 20/80 and then the acetonitrile concentration was increased to 9
5%, the buffer was a mixture of H2O / ACN / FA (94,8 / 5 / 0,2) (0.1 M, column KR-100-7-C8, 50 mm X 250 mm, flow 40 ml/min). The product containing fractions was pooled and the acetonitrile was removed by evaporation to give the title compound (138 mg, 63,5 %). 1H-NMR (500MHz, $CDCl_3$): δ 7,76-7,72 (m, 1H); 7,60-7,52 (m, 2H); 7,49-7,44 (m, 1H), 7,29-7,18 (m, 3H); 7,14-7,08 (m, 2H); 7,06-6,98 (m, 2H); 5,62 (s, 1H); 5,11 (d, 1H); 4,59 (s, 1H); 4,35 (d, 1H); 1,10 (s, 9H). HRMS calculated for ($C_{26}H_{24}F_2N_2O_2$+H)+, 435.1884; found (ES [M+H]+), 435.1904.

Example 49

N-butyl-2-[2-(4-chlorophenyl)-2-methyl-propyl]-3-oxo-1H-isoindole-1-carboxamide

2-Formylbenzoic acid (0.060g,0.40 mmol), 2-(4-chlorophenyl)-2-methyl-propan-1-amine hydrochloride (0.088g, 0.40 mmol) and NEt_3 (55µL, 0.40 mmol) were mixed in MeOH (2 ml) and the resulting mixture was stirred at ambient temperature for 20

mins. 1-Isocyanobutane (42μL, 0.40 mmol)was added and the resulting mixture was stirred at ambient temperature for 18 hours. The mixture was partitioned between dichloromethane (7 ml) and water (1 ml). The layers were separated in a phase separator and the organic layer was concentrated under reduced pressure. The residue was purified by reverse phase HPLC using a Sunfire prep C18 column and 5-95% MeCN in 0.1 M aqueous HCO_2H as mobile phase, which gave the title compound (0.087g, 54%).

HRMS: calculated for $(C_{23}H_{27}ClN_2O_2+H)^+$ 399.1839; found (ES $[M+H]^+$) 399.1839.

^{1}H-NMR* (500 MHz, DMSO-d_6, DMSO*) δ 8.23-8.19 (m, 1H), 7.65-7.62 (m, 1H), 7.55-7.51 (m, 1H), 7.47-7.42 (m, 2H), 7.37-7.30 (m, 4H), 4.51 (s, 1H), 4.09 (d, 1H), 3.13 (d, 1H), 3.03-2.93 (m, 2H), 1.37-1.31 (m, 2H), 1.28-1.20 (m, 8H), 0.84 (t, 3H).

Example 50

The following compounds were prepared, from appropriate intermediates (such as those described hereinbefore), according to or by analogy with methods described herein, and identified with accurate mass (HRMS) spectral data (Specified as HRMS calculated (M+H) and HRMS found (M+H). In some cases the ammonium adduct is detected, thus showing (M+NH4)):

N-benzyl-2-(1-methyl-1-phenylethyl)-3-oxoisoindoline-1-carboxamide (385.1916; 385.1902);

N-benzyl-3-oxo-2-(1-phenylpropyl)isoindoline-1-carboxamide (385.1916; 385.1899);

N-[3-(difluoromethoxy)benzyl]-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide (437.1676; 437.1670);

N,2-dibenzyl-6-bromo-3-oxoisoindoline-1-carboxamide (435.0708; 435.0693);

6-bromo-2-(2-cyclopentylbenzyl)-N-(4,4-difluorobutyl)-3-oxoisoindoline-1-carboxamide (505.1302; 505.1307);

2-(2-cyclopentylbenzyl)-N-(4,4-difluorobutyl)-6-fluoro-3-oxoisoindoline-1-carboxamide (445.2103; 445.2104);

6-bromo-2-(2-cyclopentylbenzyl)-N-methyl-3-oxoisoindoline-1-carboxamide (427.1021; 427.1015);

2-(2-cyclopentylbenzyl)-6-fluoro-N-methyl-3-oxoisoindoline-1-carboxamide (367.1821; 367.1822);

6-chloro-2-(2-cyclopentylbenzyl)-N-(4,4-difluorobutyl)-3-oxoisoindoline-1-carboxamide (461.1807; 461.1797);

6-chloro-2-(2-cyclopentylbenzyl)-N-methyl-3-oxoisoindoline-1-carboxamide (383.1526; 383.1523);

2-(2-cyclopentylbenzyl)-N-(4,4-difluorobutyl)-3-oxoisoindoline-1-carboxamide (427.2197; 427.2200);

2-(2-cyclopentylbenzyl)-N-methyl-3-oxoisoindoline-1-carboxamide (349.1916; 349.1913);

N-benzyl-6-chloro-3-oxo-2-[(1S)-1-phenylethyl]isoindoline-1-carboxamide (405.1369; 405.1365);

6-chloro-N-(2-methoxyethyl)-3-oxo-2-[2,2,2-trifluoro-1-(3-fluorophenyl)ethyl]isoindoline-1-carboxamide (445.0942; 445.0936);

N-benzyl-6-chloro-2-(dipyridin-3-ylmethyl)-3-oxoisoindoline-1-carboxamide (469.1431; 469.1407);

6-chloro-N-methyl-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (383.0774; 383.0798);

2-[2-(4-chlorophenyl)propyl]-6-fluoro-N-methyl-3-oxoisoindoline-1-carboxamide (361.1119; 361.1130);

6-fluoro-N-methyl-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (313.1352; 313.1359);

6-chloro-2-[2-(4-chlorophenyl)propyl]-N-methyl-3-oxoisoindoline-1-carboxamide (377.0823; 377.0821);

6-chloro-N-methyl-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (329.1056; 329.1062);

2-[2-(4-chlorophenyl)propyl]-N-methyl-3-oxoisoindoline-1-carboxamide (343.1213; 343.1231);

6-chloro-N-ethyl-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (343.1213; 343.1238);

N-benzyl-5-[(methylsulfonyl)amino]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (464.1644; 464.1651);

N-benzyl-4-methyl-5-[(methylsulfonyl)amino]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (478.1800; 478.1820);

N-benzyl-5-cyano-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (396.1712; 396.1734);

N-benzyl-5-bromo-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (449.0864; 449.0868);

N-benzyl-6-bromo-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (449.0864; 449.0872);

N-[3-(difluoromethoxy)benzyl]-6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (437.1688; 437.1702);

N-(3,4-dichlorobenzyl)-6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (439.0991; 439.1017);

N-(3-chlorobenzyl)-6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (405.1381; 405.1379);

6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (439.1644; 439.1643);

6-chloro-N-[3-(difluoromethoxy)benzyl]-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (453.1392; 453.1390);

6-chloro-N-(3,4-dichlorobenzyl)-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (455.0696; 455.0714);

6-chloro-N-(3-chlorobenzyl)-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (421.1085; 421.1044);

6-chloro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (455.1349; 455.1355);

N-(3,4-dichlorobenzyl)-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (421.1085; 421.1091);

N-[3-(difluoromethoxy)benzyl]-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (419.1782; 419.1767);

2-(3-hydroxy-2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (421.1739; 421.1747);

N-(4,4-difluorobutyl)-6-fluoro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (445.1350; 445.1346);

6-chloro-N-(4,4-difluorobutyl)-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (461.1055; 461.1014);

6-chloro-N-(4,4-difluorobutyl)-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (407.1338; 407.1321);

N-(4,4-difluorobutyl)-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (373.1727; 373.1748);

N-(tert-butyl)-6-fluoro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (409.1539; 409.1524);

N-(tert-butyl)-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (391.1633; 391.1629);

N-(tert-butyl)-6-chloro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (425.1243; 425.1239);

6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (463.1256; 463.1240);

3-oxo-N-(4,4,4-trifluorobutyl)-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (445.1350; 445.1341);

6-chloro-3-oxo-N-(4,4,4-trifluorobutyl)-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (479.0961; 479.0967);

N-(tert-butyl)-6-fluoro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (355.1821; 355.1814);

6-fluoro-3-oxo-2-[(1R)-1-phenylethyl]-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (409.1539; 409.1566);

N-(tert-butyl)-6-chloro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (371.1526; 371.1530);

6-chloro-3-oxo-2-[(1R)-1-phenylethyl]-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (425.1243; 425.1255);

3-oxo-2-[(1R)-1-phenylethyl]-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (391.1633; 391.1649);

6-chloro-N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (483.1145; 483.1145);

N-benzyl-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (425.1477; 425.1455);

N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (484.1307; 484.1289);
2-(biphenyl-2-ylmethyl)-N-[(5-methylpyrazin-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (449.1977; 449.1978);
2-(biphenyl-2-ylmethyl)-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide (434.1868; 434.1839);
N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-2-(biphenyl-2-ylmethyl)-6-chloro-3-oxoisoindoline-1-carboxamide (498.1696; 498.1682);
N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide (464.2086; 464.2096);
N-butyl-2-[(4-fluorophenyl)(pyridin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide (418.1930; 418.1921);
N-butyl-3-oxo-2-[phenyl(pyridin-2-yl)methyl]isoindoline-1-carboxamide (400.2025; 400.2018);
N-butyl-2-[(4-chlorophenyl)(pyridin-4-yl)methyl]-3-oxoisoindoline-1-carboxamide (434.1635; 434.1618);
2-[(4-chlorophenyl)(pyridin-4-yl)methyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (486.1384; 486.1342);
6-chloro-2-(diphenylmethyl)-N-ethyl-3-oxoisoindoline-1-carboxamide (405.1369; 405.1332);
2-(biphenyl-2-ylmethyl)-6-chloro-N-ethyl-3-oxoisoindoline-1-carboxamide (405.1369; 405.1336);
2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-propylisoindoline-1-carboxamide (419.1526; 419.1521);
2-(diphenylmethyl)-N-ethyl-3-oxoisoindoline-1-carboxamide (371.1759; 371.1759);
2-(biphenyl-2-ylmethyl)-N-ethyl-3-oxoisoindoline-1-carboxamide (371.1759; 371.1758);
2-(biphenyl-2-ylmethyl)-6-fluoro-3-oxo-N-propylisoindoline-1-carboxamide (403.1821; 403.1805);
N-(4-fluorobenzyl)-2-[(4-fluorophenyl)(pyridin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide (470.1680; 470.1664);
N-benzyl-2-[(4-fluorophenyl)(pyridin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide (452.1774; 452.1761);

2-[2-(4-chlorophenyl)propyl]-N-[(5-methylpyrazin-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (435.1587; 435.1592);

6-chloro-2-[2-(4-chlorophenyl)propyl]-N-[(5-methylpyrazin-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (469.1198; 469.1177);

2-(biphenyl-2-ylmethyl)-6-chloro-N-[(5-methylpyrazin-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (483.1587; 483.1582);

6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide (454.1089; 454.1069);

6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide (522.0963; 522.0932);

N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (450.1696; 450.1699);

2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide (536.1352; 536.1326);

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide (488.1352; 488.1335);

2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide (468.1478; 468.1448);

2-(biphenyl-2-ylmethyl)-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide (502.1742; 502.1722);

N-benzyl-6-fluoro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (389.1665; 389.1656);

N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (449.1535; 449.1510);

6-fluoro-N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide (467.1440; 467.1443);

N-benzyl-6-chloro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (459.1087; 459.1079);

N-benzyl-6-fluoro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (443.1382;443.1373);

6-chloro-N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (537.0862; 537.0843);

6-chloro-N-[2-chloro-4-(methylsulfonyl)benzyl]-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (579.0912; 579.0919);

N-[2-chloro-4-(methylsulfonyl)benzyl]-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (545.1301; 545.1290);

6-chloro-2-(diphenylmethyl)-N-[2-fluoro-4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (563.1207; 563.1201);

2-(diphenylmethyl)-N-[2-fluoro-4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (529.1597; 529.1584);

6-chloro-2-(diphenylmethyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (545.1301; 545.1316);

2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide (468.1478; 468.1479);

6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide (454.1089; 454.1075);

2-(biphenyl-2-ylmethyl)-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide (434.1868; 434.1853);

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-cyano-3-oxoisoindoline-1-carboxamide (424.2025; 424.2027);

6-chloro-2-(diphenylmethyl)-3-oxo-N-propylisoindoline-1-carboxamide (419.1526; 419.1544);

2-[2-(4-chlorophenyl)propyl]-N-ethyl-6-fluoro-3-oxoisoindoline-1-carboxamide (375.1275; 375.1263);

2-(diphenylmethyl)-N-ethyl-6-fluoro-3-oxoisoindoline-1-carboxamide (389.1665; 389.1671);

2-[2-(4-chlorophenyl)propyl]-N-ethyl-3-oxoisoindoline-1-carboxamide (357.1369; 357.1374);

2-[2-(4-chlorophenyl)propyl]-6-fluoro-3-oxo-N-propylisoindoline-1-carboxamide (389.1432; 389.1431);

2-(diphenylmethyl)-6-fluoro-3-oxo-N-propylisoindoline-1-carboxamide (403.1821; 403.1837);

2-(biphenyl-2-ylmethyl)-3-oxo-N-propylisoindoline-1-carboxamide (385.1916; 385.1903);

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-propylisoindoline-1-carboxamide

(371.1526; 371.1546);
2-(diphenylmethyl)-3-oxo-N-propylisoindoline-1-carboxamide (385.1916; 385.1930);
2-(diphenylmethyl)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (471.1695; 471.1715);
2-[2-(4-chlorophenyl)propyl]-6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (457.1306; 457.1325);
2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (439.1400; 439.1401);
2-(biphenyl-2-ylmethyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (453.1790; 453.1784);
2-(diphenylmethyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (453.1790; 453.1807);
N-(tert-butyl)-2-[(4-chlorophenyl)(pyridin-4-yl)methyl]-3-oxoisoindoline-1-carboxamide (434.1635; 434.1620);
N-(4-fluorobenzyl)-3-oxo-2-[phenyl(pyridin-2-yl)methyl]isoindoline-1-carboxamide (452.1774; 452.1789);
N-benzyl-2-[(4-chlorophenyl)(pyridin-4-yl)methyl]-3-oxoisoindoline-1-carboxamide (468.1478; 468.1465);
N-benzyl-3-oxo-2-[phenyl(pyridin-2-yl)methyl]isoindoline-1-carboxamide (434.1868; 434.1871);
2-(2,2-dimethylpropyl)-N-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide (418.2130; 418.2128);
2-(2,2-dimethylpropyl)-N-[(1-methyl-5-phenyl-1H-pyrazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide (417.2290; 417.2298);
N-benzyl-2-[(1-methyl-5-phenyl-1H-pyrazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide (437.1977; 437.1993);
N-benzyl-2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide (438.1817; 438.1825);
N-benzyl-2-(biphenyl-2-ylmethyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (463.2021; 463.2019);
2-(biphenyl-2-ylmethyl)-5-hydroxy-4-methyl-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (483.1895; 483.1881);

2-(biphenyl-2-ylmethyl)-5-hydroxy-4-methyl-3-oxo-N-propylisoindoline-1-carboxamide (415.2021; 415.2033);

2-(biphenyl-2-ylmethyl)-N-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (429.2178; 429.2196);

2-(biphenyl-2-ylmethyl)-N-ethyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (401.1865; 401.1870);

N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (465.1989; 465.2002);

N-(tert-butyl)-2-[(2',4'-dichlorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (497.1398; 497.1393);

N-(tert-butyl)-2-[(3',4'-dichlorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (497.1398; 497.1392);

N-(tert-butyl)-2-[(2'-chlorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (463.1788; 463.1804);

N-(tert-butyl)-2-[(3'-chloro-4'-fluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (481.1694; 481.1681);

N-(tert-butyl)-2-[(4'-chlorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (463.1788; 463.1764);

N-(tert-butyl)-2-[(4'-fluoro-2'-methylbiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (461.2240; 461.2221);

N-(tert-butyl)-2-[(2',4'-difluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (465.1989; 465.1987);

N-(tert-butyl)-2-[(2',5'-difluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (465.1989; 465.1998);

N-(tert-butyl)-2-[(3'-fluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (447.2084; 447.2097);

N-butyl-3-oxo-2-(2-phenoxybenzyl)isoindoline-1-carboxamide (415.2021;415.2060);

N-[3-(difluoromethoxy)benzyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (417.1989; 417.2034);

2-(3,3-dimethylbutyl)-3-oxo-N-[3-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide (435.1895; 435.1855);

2-(2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide (421.1739; 421.1717);

N-[3-(difluoromethoxy)benzyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (403.1833; 403.1873);

6-chloro-2-(diphenylmethyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (487.1400; 487.1445);

6-chloro-2-(diphenylmethyl)-N-(2-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide (483.1475; 483.1472);

N-benzyl-6-chloro-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (467.1526; 467.1544);

N-(tert-butyl)-6-chloro-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (433.1682; 433.1709);

2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (487.1400; 487.1390);

2-(biphenyl-2-ylmethyl)-6-chloro-N-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (492.1478; 492.1513);

N-benzyl-2-(biphenyl-2-ylmethyl)-6-chloro-3-oxoisoindoline-1-carboxamide (467.1526; 467.1513);

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-6-chloro-3-oxoisoindoline-1-carboxamide (433.1682; 433.1723);

6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (473.1010; 473.1010);

6-chloro-2-[2-(4-chlorophenyl)propyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (531.0912; 531.0937);

N-(tert-butyl)-6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (419.1293; 419.1326);

N-benzyl-6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (453.1136; 453.1156);

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-4,5-dimethoxy-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide (488.1934; 488.1938);

2-[1-(1,5-dimethyl-1H-pyrazol-4-yl)ethyl]-5,7-dimethoxy-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (517.2062; 517.2051);

5,7-dimethoxy-2-(2-methoxybenzyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (515.1793; 515.1784);

2-(2-fluorobenzyl)-5,7-dimethoxy-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (503.1594; 503.1598);

N-(tert-butyl)-5,7-dimethoxy-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide (413.2076; 413.2094);

3-oxo-2-(2-phenoxybenzyl)-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (469.1739; 469.1732);

2-[2-(4-chlorophenyl)propyl]-N-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]-3-oxoisoindoline-1-carboxamide (499.1236; 499.1221);

N-(3,4-dichlorobenzyl)-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (405.1136; 405.1137);

2-(2,2-dimethylpropyl)-N-(1H-indol-3-ylmethyl)-3-oxoisoindoline-1-carboxamide (376.2025; 376.2009);

2-(2,2-dimethylpropyl)-3-oxo-N-{2-[3-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide (419.1946; 419.1918);

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-6-fluoro-3-oxoisoindoline-1-carboxamide (417.1978; 417.1967);

N-benzyl-2-(biphenyl-2-ylmethyl)-6-fluoro-3-oxoisoindoline-1-carboxamide (451.1821; 451.1820);

2-[2-(4-chlorophenyl)ethyl]-N-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (503.0985; 503.0987);

2-[2-(4-chlorophenyl)ethyl]-6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (443.1149; 443.1151);

N-(tert-butyl)-2-[2-(4-chlorophenyl)ethyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (389.1432; 389.1446);

N-benzyl-2-[2-(4-chlorophenyl)ethyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (423.1275; 423.1266);

6-fluoro-2-[2-(4-fluorophenyl)ethyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (427.1445; 427.1434);

N-benzyl-6-fluoro-2-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (407.1571; 407.1566);

6-fluoro-2-[2-(4-fluorophenyl)propyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide (441.1601; 441.1592);

N-benzyl-6-fluoro-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (421.1727; 421.1709);

N-(tert-butyl)-6-fluoro-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (387.1884; 387.1868);

2-(biphenyl-2-ylmethyl)-1-methyl-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (525.1848; 525.1854);

2-[2-(4-chlorophenyl)propyl]-4,7-difluoro-1-methyl-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-chlorophenyl)propyl]-1-methyl-3-oxoisoindoline-1-carboxamide (399.1839; 399.1825);

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide (459.2283; 459.2263);

N-benzyl-2-(diphenylmethyl)-5-methoxy-3-oxoisoindoline-1-carboxamide (463.2021; 463.1992);

2-(diphenylmethyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (501.1790; 501.1780);

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-1-methyl-3-oxoisoindoline-1-carboxamide (399.1839; 399.1826);

N-butyl-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (399.2072; 399.2089);

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-methoxy-4-methyl-3-oxoisoindoline-1-carboxamide (443.2334; 443.2317);

2-(biphenyl-2-ylmethyl)-1-[(tert-butylamino)carbonyl]-4-methyl-3-oxo-2,3-dihydro-1H-isoindol-5-yl dimethylcarbamate (500.2549; 500.2561);

2-(biphenyl-2-ylmethyl)-5-hydroxy-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (463.2021; 463.1998);

5-hydroxy-2-[2-(4-methoxyphenyl)ethyl]-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (431.1970; 431.1963);

2-(4-chlorobenzyl)-5-hydroxy-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (421.1319; 421.1311);

N-(4-fluorobenzyl)-5-hydroxy-2-[2-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (435.1720; 435.1714);

2-[2-(3,4-dichlorophenyl)ethyl]-N-(4-fluorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide (473.0835; 473.0795);

2-(4-chlorobenzyl)-N-(4-fluorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide (425.1068; 425.1054);

2-(biphenyl-2-ylmethyl)-N-(4-fluorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide (467.1771; 467.1772);

N-(tert-butyl)-2-[2-(3,4-dichlorophenyl)ethyl]-5-hydroxy-3-oxoisoindoline-1-carboxamide (421.1085; 421.1022);

N-(3,4-dichlorobenzyl)-2-isobutyl-3-oxoisoindoline-1-carboxamide (391.0980; 391.0989);

N-[2-(1H-indol-3-yl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (376.2025; 376.2027);

N-(3-chlorobenzyl)-2-isobutyl-3-oxoisoindoline-1-carboxamide (357.1369; 357.1352);

N-[4-(difluoromethoxy)benzyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (389.1676; 389.1673);

2-isobutyl-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (391.1633; 391.1613);

N-(1H-indol-3-ylmethyl)-2-isobutyl-3-oxoisoindoline-1-carboxamide (362.1868; 362.1859);

N-[2-(1,3-benzodioxol-5-yl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (381.1814; 381.1801);

N-[2-(3-fluorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (355.1821; 355.1813);

2-isobutyl-3-oxo-N-{2-[3-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide (405.1790; 405.1775);

N-[2-(3,4-dichlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (405.1136; 405.1135);

N-[2-(4-chlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (371.1526; 371.1523);

N-[2-(3-chlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (371.1526; 371.1520);

N-[2-(2-chlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (371.1526; 371.1513);

N-[2-(2,4-dichlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (405.1136; 405.1129);

N-[2-(2,6-dichlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide (405.1136; 405.1125);

2-(3,3-dimethylbutyl)-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (404.2338; 404.2336);

N-(3-chlorobenzyl)-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (385.1682; 385.1676);

N-(3,4-dichlorobenzyl)-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (419.1293; 419.1273);

2-(3,3-dimethylbutyl)-N-(1H-indol-3-ylmethyl)-3-oxoisoindoline-1-carboxamide (390.2181; 390.2174);

N-[4-(difluoromethoxy)benzyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (417.1989; 417.1975);

2-(3,3-dimethylbutyl)-N-[2-(3-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (383.2134; 383.2103);

N-[2-(1,3-benzodioxol-5-yl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (409.2127; 409.2125);

N-[2-(3-cyanophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (390.2181; 390.2171);

2-(3,3-dimethylbutyl)-3-oxo-N-{2-[3-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide (433.2103; 433.2092);

N-[2-(3-chlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (399.1839; 399.1830);

N-[2-(3,4-dichlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (433.1449; 433.1431);

N-[2-(4-chlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (399.1839; 399.1831);

N-[2-(2-chlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (399.1839; 399.1841);

N-[2-(2,4-dichlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (433.1449; 433.1428);

2-(2,2-dimethylpropyl)-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (390.2181; 390.2172);

N-(3-chloroenzyl)-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (371.1526; 371.1515);

N-[4-(difluoromethoxy)benzyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (403.1833; 403.1833);

2-(2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (405.1790; 405.1787);

N-[2-(1,3-benzodioxol-5-yl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (395.1970; 395.1967);

2-(2,2-dimethylpropyl)-N-[2-(3-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (369.1978; 369.1977);

N-[2-(3-cyanophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (376.2025; 376.2029);

N-[2-(2-chlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (385.1682; 385.1675);

N-[2-(3-chlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (385.1682; 385.1671);

N-[2-(2,4-dichlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (419.1293; 419.1290);

2-[2-(4-chlorophenyl)ethyl]-N-ethyl-3-oxo-N-(2-pyridin-2-ylethyl)isoindoline-1-carboxamide (448.1791; 448.1776);

2-[2-(4-chlorophenyl)ethyl]-3-(1,3-dihydro-2H-isoindol-2-ylcarbonyl)isoindolin-1-one (417.1369; 417.1382);

2-[2-(4-chlorophenyl)ethyl]-N-methyl-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (487.1400; 487.1352);

N-benzyl-2-[2-(4-chlorophenyl)ethyl]-N-ethyl-3-oxoisoindoline-1-carboxamide (433.1682; 433.1662);

N-benzyl-2-[2-(4-chlorophenyl)ethyl]-N-methyl-3-oxoisoindoline-1-carboxamide (419.1526; 419.1516);

N-(tert-butyl)-3-oxo-2-{2-[4-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide (405.1790; 405.1766);

N-butyl-3-oxo-2-{2-[4-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide (405.1790; 405.1771);

N-benzyl-3-oxo-2-{2-[4-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide (439.1633; 439.1621);

N-(tert-butyl)-5-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-4-methyl-3-oxoisoindoline-1-carboxamide (406.2130; 406.2102);

N-(tert-butyl)-2-[2-(4-fluorophenyl)propyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (399.2084; 399.2061);

2-[3,5-bis(trifluoromethyl)benzyl]-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (489.1613; 489.1611);

N-(tert-butyl)-2-(2,2-diphenylethyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (443.2334; 443.2317);

N-(tert-butyl)-2-(diphenylmethyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (429.2178; 429.2160);

N-(tert-butyl)-2-(9H-fluoren-9-yl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (427.2021; 427.2007);

N-(tert-butyl)-5-hydroxy-4-methyl-3-oxo-2-{2-[4-(trifluoromethyl)phenoxy]benzyl}isoindoline-1-carboxamide (513.2001; 513.1967);

2-(biphenyl-3-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (429.2178; 429.2139);

N-butyl-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (369.1978; 369.1956);

N-butyl-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (371.1526; 371.1507);

N-(tert-butyl)-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (371.1526; 371.1534);

N-(tert-butyl)-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (369.1978; 369.1954);

N-benzyl-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (403.1821; 403.1789);

N-benzyl-2-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (389.1665; 389.1668);

N-benzyl-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (405.1369; 405.1367);

N-[2-(1H-indol-3-yl)ethyl]-3-oxo-2-[4-(piperidin-1-ylcarbonyl)benzyl]isoindoline-1-carboxamide (521.2552; 521.2518);

2-(biphenyl-2-ylmethyl)-N-(2,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide (469.1727; 469.1689);

2-(biphenyl-2-ylmethyl)-N-(4-cyano-2,6-difluorobenzyl)-3-oxoisoindoline-1-carboxamide (494.1680; 494.1667);

N-(2,4-difluorobenzyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (469.1727; 469.1695);

N-(2-chlorobenzyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (467.1526; 467.1486);

2-(diphenylmethyl)-N-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (465.1978; 465.1948);

2-(biphenyl-2-ylmethyl)-N-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (465.1978; 465.1957);

2-(diphenylmethyl)-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (451.1821; 451.1785);

N-(2,4-difluorobenzyl)-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide (470.1680; 470.1645);

N-(2-chlorobenzyl)-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide (468.1478; 468.1437);

N-[2-(4-fluorophenyl)ethyl]-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide (466.1930; 466.1917);

N-benzyl-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide (434.1868; 434.1839);

N-(4-fluorobenzyl)-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide (452.1774; 452.1760);

N-butyl-5-methoxy-2-(2-methyl-2-phenylpropyl)-3-oxoisoindoline-1-carboxamide (395.2334; 395.2298);

2-(biphenyl-2-ylmethyl)-N-butyl-5-methoxy-3-oxoisoindoline-1-carboxamide

(429.2178; 429.2147);
N-butyl-2-[2-(4-fluorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide
(399.2084; 399.2057);
N-butyl-2-[2-(4-chlorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide
(415.1788; 415.1772);
N-(tert-butyl)-5-methoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide
(431.2334; 431.2338);
N-(tert-butyl)-2-[2-(4-fluorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide
(399.2084; 399.2060);
N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide
(415.1788; 415.1774);
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-methoxy-3-oxoisoindoline-1-carboxamide
(429.2178; 429.2162);
N-benzyl-5-methoxy--[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide
(465.2178; 465.2154);
N-benzyl-5-methoxy-2-(2-methyl-2-phenylpropyl)-3-oxoisoindoline-1-carboxamide
(429.2178; 429.2183);
N-benzyl-2-(biphenyl-2-ylmethyl)-5-methoxy-3-oxoisoindoline-1-carboxamide
(463.2021; 463.1988);
N-butyl-5,6-dimethoxy-2-(2-methyl-2-phenylpropyl)-3-oxoisoindoline-1-carboxamide
(425.2440; 425.2408);
N-benzyl-2-[2-(4-chlorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide
(449.1632; 449.1597);
N-butyl-5,6-dimethoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide
(461.2440; 461.2424);
N-butyl-2-[2-(4-fluorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide
(429.2189; 429.2148);
2-(biphenyl-2-ylmethyl)-N-butyl-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide
(459.2283; 459.2237);
N-butyl-2-[2-(4-chlorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide
(445.1894; 445.1857);

N-(tert-butyl)-5,6-dimethoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide (461.2440; 461.2417);

N-benzyl-5,6-dimethoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide (495.2283; 495.2259);

N-benzyl-5,6-dimethoxy-2-(2-methyl-2-phenylpropyl)-3-oxoisoindoline-1-carboxamide (459.2283; 459.2267);

N-benzyl-2-[2-(4-fluorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide (463.2033; 463.2008);

N-benzyl-2-(biphenyl-2-ylmethyl)-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide (493.2127; 493.2099);

N-benzyl-2-(diphenylmethyl)-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide (493.2127; 493.2092);

N-benzyl-2-[2-(4-chlorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide (479.1737; 479.1711);

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-1-methyl-3-oxoisoindoline-1-carboxamide (413.2229; 413.2210);

2-(biphenyl-2-ylmethyl)-N-butyl-1-methyl-3-oxoisoindoline-1-carboxamide (413.2229; 413.2204);

ethyl N-benzyl-N-({2-[2-(4-chlorophenyl)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate (491.1737; 491.1708);

2-[2-(4-chlorophenyl)ethyl]-N-methyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (433.1682; 433.1641);

2-[2-(4-chlorophenyl)ethyl]-N,N-diethyl-3-oxoisoindoline-1-carboxamide (371.1526; 371.1500);

N-benzyl-N-butyl-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide (461.1995; 461.1977);

N-[2-(2,6-dichlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide (433.1449; 433.1440);

N-[2-(4-chlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (385.1682; 385.1677);

N-[2-(2,6-dichlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (419.1293; 419.1270);

N-butyl-5-methoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide (431.2334; 431.2332);

N-benzyl-2-[2-(4-fluorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide (433.1927; 433.1907);

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide (445.1894; 445.1870);

N-(tert-butyl)-2-[(4'-fluoro-2'-methylbiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (431.2134; 431.2122);

N-(tert-butyl)-2-[(4'-methylbiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (413.2229; 413.2214);

N-(tert-butyl)-2-[(4'-methoxybiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (429.2178; 429.2179);

N-(tert-butyl)-2-[(4'-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (417.1978; 417.1974);

methyl N-({2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate (451.1469; 451.1465);

methyl N-({2-[(4'-fluoro-2'-methylbiphenyl-2-yl)methyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate (447.1720; 447.1724);

methyl N-({2-[(4'-fluorobiphenyl-2-yl)methyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate (433.1563; 433.1558);

methyl N-({2-[(4'-methylbiphenyl-2-yl)methyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate (429.1814; 429.1809);

2-[(3',4'-difluorobiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (547.1503; 547.1497);

2-[(4'-fluoro-2'-methylbiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (543.1753; 543.1778);

2-[(4'-methoxybiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (541.1797; 541.1797);

2-[(4'-fluorobiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (529.1597; 529.1594);

2-[(4'-methylbiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (525.1848; 525.1854);

N-(tert-butyl)-2-(4-chlorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (387.1475; 387.1486);

N-(tert-butyl)-5-hydroxy-2-[2-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (383.1970; 383.2007);

2-[2-(4-chlorophenyl)propyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (472.1791; 472.1816);

N-(tert-butyl)-7-hydroxy-2-[2-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (383.1970; 383.1978);

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide (415.2021; 415.2018);

2-[2-(3,4-dichlorophenyl)ethyl]-5-hydroxy-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (469.1085; 469.1005);

N-(3,4-difluorobenzyl)-2-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide (409.1363; 409.1375);

N-(3-chlorobenzyl)-2-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide (407.1162; 407.1162);

2-(4-hydroxybenzyl)-3-oxo-N-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (441.1426; 441.1477);

N-[3,5-bis(trifluoromethyl)benzyl]-2-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide (509.1300; 509.1384);

N-(3-chlorobenzyl)-2-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (416.1165; 416.1188);

N-[3,5-bis(trifluoromethyl)benzyl]-2-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (518.1303; 518.1320);

2-(3-cyanobenzyl)-N-(3,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide (418.1367; 418.1381);

2-(3-cyanobenzyl)-3-oxo-N-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (450.1429; 450.1442);

N-[4-(aminocarbonyl)benzyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (462.1584; 462.1599);

N-[4-(aminocarbonyl)benzyl]-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide (476.1974; 476.1927);

2-(3,4-difluorobenzyl)-N-{4-[(dimethylamino)methyl]benzyl}-3-oxoisoindoline-1-carboxamide;

2-(3-chlorobenzyl)-N-{4-[(dimethylamino)methyl]benzyl}-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-{4-[(dimethylamino)methyl]benzyl}-3-oxoisoindoline-1-carboxamide

2-(3,4-difluorobenzyl)-N-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide (409.1363; 409.1383);

2-(3-chlorobenzyl)-N-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide (407.1162; 407.1158);

2-[3,5-bis(trifluoromethyl)benzyl]-N-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide (509.1300; 509.1281);

2-(3-chlorobenzyl)-N-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (416.1165; 416.1172);

N-(3-cyanobenzyl)-2-(3,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide (418.1367; 418.1353);

2-[2-(4-chlorophenyl)propyl]-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (444.1478; 444.1504);

2-[3,5-bis(trifluoromethyl)benzyl]-N-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (518.1303; 518.1278);

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-hydroxy-3-oxoisoindoline-1-carboxamide (401.1632; 401.1666);

N-{4-[(dimethylamino)methyl]benzyl}-3-oxo-2-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (482.2055; 482.2060);

N-(4-hydroxybenzyl)-3-oxo-2-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (441.1426; 441.1414);

N-(3-cyanobenzyl)-3-oxo-2-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamid (450.1429; 450.1461);

2-(biphenyl-3-ylmethyl)-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (458.1868; 458.1872);

2-(biphenyl-4-ylmethyl)-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (458.1868; 458.1894);

N-butyl-3-oxo-2-[2-(2-phenoxyphenyl)ethyl]isoindoline-1-carboxamide
(429.2178; 429.2170);
N-butyl-2-(2-{4-[(diethylamino)carbonyl]phenyl}ethyl)-3-oxoisoindoline-1-carboxamide
(436.2600; 436.2588);
N-butyl-2-[2-(3-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide
(355.1821; 355.1839);
N-butyl-3-oxo-2-{2-[2-(trifluoromethoxy)phenyl]ethyl}isoindoline-1-carboxamide
(421.1739; 421.1722);
2-(2-biphenyl-4-ylethyl)-N-butyl-3-oxoisoindoline-1-carboxamide (413.2229; 413.2253);
N-butyl-2-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide
(355.1821; 355.1834);
N-butyl-2-[2-(3,5-dimethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide
(397.2127; 397.2129);
N-butyl-3-oxo-2-[2-(4-phenoxyphenyl)ethyl]isoindoline-1-carboxamide
(429.2178; 429.2179);
N-butyl-2-[2-(2-ethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide
(381.2178; 381.2173);
2-[2-(1,3-benzodioxol-5-yl)ethyl]-N-butyl-3-oxoisoindoline-1-carboxamide
(381.1814; 381.1814);
N-(tert-butyl)-3-oxo-2-[2-(2-phenoxyphenyl)ethyl]isoindoline-1-carboxamide
(429.2178; 429.2170);
N-(tert-butyl)-3-oxo-2-{2-[2-(trifluoromethoxy)phenyl]ethyl}isoindoline-1-carboxamide
(421.1739; 421.1741);
2-(2-biphenyl-4-ylethyl)-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide
(413.2229; 413.2261);
N-(tert-butyl)-2-[2-(3,5-dimethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide
(397.2127; 397.2129);
N-(tert-butyl)-3-oxo-2-[2-(4-phenoxyphenyl)ethyl]isoindoline-1-carboxamide
(429.2178; 429.2147);
N-(tert-butyl)-2-[2-(2-ethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide
(381.2178; 381.2169);
2-[2-(1,3-benzodioxol-5-yl)ethyl]-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide

(381.1814; 381.1810);
N-[2-(1H-indol-3-yl)ethyl]-3-oxo-2-[2-(2-phenoxyphenyl)ethyl]isoindoline-1-carboxamide (516.2287; 516.2333);
2-(2-{4-[(diethylamino)carbonyl]phenyl}ethyl)-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (523.2709; 523.2714);
2-[2-(3-fluorophenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (442.1930; 442.1936);
N-[2-(1H-indol-3-yl)ethyl]-3-oxo-2-{2-[2-(trifluoromethoxy)phenyl]ethyl}isoindoline-1-carboxamide (508.1848; 508.1853);
2-[2-(4-fluorophenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (442.1930; 442.1929);
2-[2-(3,5-dimethoxyphenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (484.2236; 484.2237);
2-(2-biphenyl-4-ylethyl)-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (500.2338; 500.2371);
N-[2-(1H-indol-3-yl)ethyl]-3-oxo-2-[2-(4-phenoxyphenyl)ethyl]isoindoline-1-carboxamide (516.2287; 516.2280);
2-[2-(2-ethoxyphenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (468.2287; 468.2276);
2-[2-(1,3-benzodioxol-5-yl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (468.1923; 468.1899);
(1R)-2-[(1S)-1-(4-fluorophenyl)ethyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;
N-[4-(dimethylamino)benzyl]-2-[2-(dimethylamino)-2-phenylethyl]-3-oxoisoindoline-1-carboxamide (457.2603; 457.2610);
N-[4-(dimethylamino)benzyl]-2-(2,2-diphenylethyl)-3-oxoisoindoline-1-carboxamide (490.2494; 490.2497);
2-(1-benzyl-2-fluoroethyl)-N-[(5-methylisoxazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide (408.1723; 408.1700);
N-(tert-butyl)-2-(2-chloro-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (375.1275; 375.1276);

2-(3,4-difluorobenzyl)-N-(4-fluorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (441.1426; 441.1414);

2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide (424.1472; 424.1458);

2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (437.1676; 437.1667);

2-(3,4-difluorobenzyl)-5-hydroxy-3-oxo-4-phenyl-N-(2-phenylethyl)isoindoline-1-carboxamide (499.1833; 499.1788);

N-(2-chlorobenzyl)-2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (457.1130; 457.1088);

2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (491.1394; 491.1378);

N-(tert-butyl)-2-(2-chlorobenzyl)-5-hydroxy-3-oxo-4-(trimethylsilyl)isoindoline-1-carboxamide;

N-(tert-butyl)-2-(2-chlorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (387.1475; 387.1461);

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide (491.2334; 491.2325);

2-[3,5-bis(trifluoromethyl)benzyl]-N-(tert-butyl)-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide (551.1769; 551.1776);

2-[2-(4-chlorophenyl)propyl]-N-{3-[(dimethylamino)carbonyl]-4-fluorobenzyl}-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-(4-cyanophenyl)-3-oxoisoindoline-1-carboxamide;

2-(1-benzyl-2-fluoroethyl)-N-butyl-3-oxoisoindoline-1-carboxamide (369.1978; 369.1972);

2-(1-benzyl-2-fluoroethyl)-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (421.1727; 421.1689);

2-(1-benzyl-2-fluoroethyl)-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide (446.2243; 446.2229);

N-[4-(aminomethyl)phenyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (434.1635; 434.1641);

2-[2-(4-chlorophenyl)propyl]-N-(4-{[(difluoroacetyl)amino]methyl}phenyl)-3-oxoisoindoline-1-carboxamide (512.1552; 512.1567);
N-[4-(aminocarbonyl)phenyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (448.1428; 448.1418);
N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-(fluoromethoxy)-4-methyl-3-oxoisoindoline-1-carboxamide (447.1850; 447.1835);
N-[4-(dimethylamino)benzyl]-3-oxo-2-(4-phenylbutyl)isoindoline-1-carboxamide (442.2494; 442.2494);
N-[4-(dimethylamino)benzyl]-2-(2-hydroxy-2-phenylethyl)-3-oxoisoindoline-1-carboxamide (430.2130; 430.2120);
N-[4-(dimethylamino)benzyl]-3-oxo-2-[2-(1H-pyrazol-1-yl)benzyl]isoindoline-1-carboxamide (466.2243; 466.2235);
N-[4-(dimethylamino)benzyl]-3-oxo-2-(4-phenoxybenzyl)isoindoline-1-carboxamide;
N-[4-(dimethylamino)benzyl]-3-oxo-2-[(1-phenyl-1H-pyrazol-4-yl)methyl]isoindoline-1-carboxamide (466.2243; 466.2254);
N-[4-(dimethylamino)benzyl]-2-[1-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-[4-(dimethylamino)benzyl]-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (476.2338; 476.2325);
2-(2-chloro-4-fluorobenzyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (487.0894; 487.0908);
N-[4-(dimethylamino)benzyl]-3-oxo-2-(1-phenylpropyl)isoindoline-1-carboxamide (428.2338; 428.2318);
N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[2-(1H-pyrazol-1-yl)benzyl]isoindoline-1-carboxamide (501.1596; 501.1581);
2-(2-hydroxy-2-phenylethyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (465.1484; 465.1487);
2-(2,2-diphenylethyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (525.1848; 525.1848);
2-(diphenylmethyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (511.1691; 511.1691);

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide (420.1478; 420.1482);

N-[4-(methylsulfonyl)benzyl]-3-oxo-2-(1,2,3,4-tetrahydronaphthalen-1-yl)isoindoline-1-carboxamide (475.1691; 475.1682);

2-(2-chloro-4-fluorobenzyl)-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide (410.1071; 410.1057);

2-[1-(4-fluorophenyl)ethyl]-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide (390.1617; 390.1623);

(1S)-2-[(2R)-2-(4-chlorophenyl)propyl]-N-(3-methoxypropyl)-1-methyl-3-oxoisoindoline-1-carboxamide (415.1788; 415.1790);

(1R)-2-[(2R)-2-(4-chlorophenyl)propyl]-N-(3-methoxypropyl)-1-methyl-3-oxoisoindoline-1-carboxamide (415.1788; 415.1797);

2-[2-(4-chlorophenyl)propyl]-N-(3-methoxypropyl)-1-methyl-3-oxoisoindoline-1-carboxamide (415.1788; 415.1776);

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-hydroxy-3-oxo-4-(trimethylsilyl)isoindoline-1-carboxamide (473.2027; 473.2016);

N-(tert-butyl)-2-(3,4-difluorobenzyl)-5-hydroxy-3-oxo-4-(trimethylsilyl)isoindoline-1-carboxamide (447.1915; 447.1912);

N-(tert-butyl)-2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (389.1676; 389.1661);

N-(tert-butyl)-2-(3,4-difluorobenzyl)-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide (451.1833; 451.1846);

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (415.1788; 415.1793);

2-(2-chloro-4-fluorobenzyl)-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (452.0977; 452.0974);

2-[3,5-bis(trifluoromethyl)benzyl]-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N,2-bis(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (443.1319; 443.1297);

N-(3-cyano-4-fluorobenzyl)-3-oxo-2-(2-phenylethyl)isoindoline-1-carboxamide (414.1617; 414.1617);

N-(3-cyano-4-fluorobenzyl)-2-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (418.1367; 418.1362);

2-benzyl-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (400.1461; 400.1465);

N-(3-cyano-4-fluorobenzyl)-2-(3,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide (436.1273; 436.1272);

2-(biphenyl-2-ylmethyl)-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (476.1774; 476.1775);

2-[2-(4-chlorophenyl)propyl]-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (462.1384; 462.1371);

2-(2-chloro-4-fluorobenzyl)-N-(3-{[(difluoroacetyl)amino]methyl}-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (534.1207; 534.1210);

2-[2-(4-chlorophenyl)propyl]-N-(3-{[(difluoroacetyl)amino]methyl}-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-[3-(aminomethyl)-4-fluorobenzyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (466.1697; 466.1700);

N-[3-(aminocarbonyl)-4-fluorobenzyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (480.1490; 480.1479);

N-[3-(aminocarbonyl)-4-fluorobenzyl]-2-(2-chloro-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (470.1083; 470.1077);

N-(tert-butyl)-3-oxo-2-(4-phenylbutyl)isoindoline-1-carboxamide (365.2229; 365.2231);

N-(tert-butyl)-3-oxo-2-(1,2,3,4-tetrahydronaphthalen-1-yl)isoindoline-1-carboxamide (363.2072; 363.2064);

N-(tert-butyl)-3-oxo-2-(4-phenoxybenzyl)isoindoline-1-carboxamide (415.2021; 415.2055);

N-(tert-butyl)-3-oxo-2-[2-(1H-pyrazol-1-yl)benzyl]isoindoline-1-carboxamide (389.1977; 389.1992);

N-(tert-butyl)-2-(2,2-diphenylethyl)-3-oxoisoindoline-1-carboxamide (413.2229; 413.2237);

N-(tert-butyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (399.2072; 399.2099);

N-(1,3-benzodioxol-5-ylmethyl)-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (381.1814; 381.1772);

2-(2-chloro-4-fluorobenzyl)-N-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (412.1228; 412.1213);

N-(1,3-benzodioxol-5-ylmethyl)-2-(2-chloro-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (453.1017; 453.0986);

2-(2-chloro-4-fluorobenzyl)-N-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide (475.1036; 475.1006);

2-[3,5-bis(trifluoromethyl)benzyl]-3-oxo-N-(2-pyridin-4-ylethyl)isoindoline-1-carboxamide (508.1459; 508.1463);

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(2-pyridin-4-ylethyl)isoindoline-1-carboxamide (434.1635; 434.1630);

2-[3,5-bis(trifluoromethyl)benzyl]-N-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (496.1459; 496.1419);

2-[2-(4-chlorophenyl)propyl]-N-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (422.1635; 422.1634);

2-[2-(4-chlorophenyl)propyl]-N-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide (485.1443; 485.1420);

2-[3,5-bis(trifluoromethyl)benzyl]-N-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide;

N-(1,3-benzodioxol-5-ylmethyl)-2-[3,5-bis(trifluoromethyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide;

N-(1-benzylpyrrolidin-3-yl)-2-(2-chloro-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (478.1697; 478.1697);

N-(1-benzylpyrrolidin-3-yl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (488.2104; 488.2104);

2-(2-chloro-4-fluorobenzyl)-N-{[5-(2-furyl)isoxazol-3-yl]methyl}-3-oxoisoindoline-1-carboxamide (466.0970; 466.0988);

2-(2,2-dimethylpropyl)-N-{[5-(2-furyl)isoxazol-3-yl]methyl}-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-{[5-(2-furyl)isoxazol-3-yl]methyl}-3-oxoisoindoline-1-carboxamide (550.1201; 550.1180);

2-[2-(4-chlorophenyl)propyl]-N-[3-(1H-imidazol-1-yl)propyl]-3-oxoisoindoline-1-carboxamide (437.1744; 437.1733);

2-[3,5-bis(trifluoromethyl)benzyl]-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide (536.1772; 536.1783);

2-[2-(4-chlorophenyl)propyl]-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide (462.1948; 462.1909);

N-(1-benzylpyrrolidin-3-yl)-2-[3,5-bis(trifluoromethyl)benzyl]-3-oxoisoindoline-1-carboxamide (562.1929; 562.1935);

2-[2-(4-chlorophenyl)propyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide (497.1301; 497.1281);

N-(tert-butyl)-3-oxo-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]isoindoline-1-carboxamide (391.1882; 391.1883);

2-[2-(4-chlorophenyl)propyl]-N-[3-(dimethylamino)propyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[2-(dimethylamino)ethyl]-3-oxoisoindoline-1-carboxamide (400.1791; 400.1766);

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide (420.1478; 420.1465);

N-[2-(4-benzoylpiperazin-1-yl)ethyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(1-pyridin-3-ylethyl)isoindoline-1-carboxamide (434.1635; 434.1627);

2-[2-(4-chlorophenyl)propyl]-N-(3-methoxyphenyl)-3-oxoisoindoline-1-carboxamide (435.1475; 435.1462);

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(1-pyridin-4-ylethyl)isoindoline-1-carboxamide (434.1635; 434.1620);

2-[2-(4-chlorophenyl)propyl]-N-(4-cyanophenyl)-3-oxoisoindoline-1-carboxamide (430.1322; 430.1315);

2-[2-(4-chlorophenyl)propyl]-N-(3-methoxypropyl)-3-oxoisoindoline-1-carboxamide (401.1632; 401.1633);

N-(1,3-benzodioxol-5-ylmethyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (463.1424; 463.1411);

2-[2-(4-chlorophenyl)propyl]-N-(3,4-dimethoxybenzyl)-3-oxoisoindoline-1-carboxamide (479.1737; 479.1748);

2-[2-(4-chlorophenyl)propyl]-N-[(3-methyl-5-phenylisoxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide (500.1741; 500.1745);

N-butyl-2-[2-(4-chlorophenyl)propyl]-7-fluoro-3-oxoisoindoline-1-carboxamide (403.1588; 403.1577);

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-7-fluoro-3-oxoisoindoline-1-carboxamide (403.1588; 403.1569);

N-(tert-butyl)-3-oxo-2-[2-(phenylsulfonyl)ethyl]isoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(4-fluorophenoxy)propyl]-3-oxoisoindoline-1-carboxamide (385.1927; 385.1899);

N-(tert-butyl)-3-oxo-2-(2-phenoxypropyl)isoindoline-1-carboxamide (367.2021; 367.2033);

N-benzyl-2-[(5-methylisoxazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-3-oxo-2-[2-(phenylsulfonyl)ethyl]isoindoline-1-carboxamide (435.1378; 435.1366);

N-benzyl-3-oxo-2-(2-phenoxyethyl)isoindoline-1-carboxamide (387.1708; 387.1705);

N-benzyl-3-oxo-2-(2-phenoxypropyl)isoindoline-1-carboxamide (401.1865; 401.1888);

N-benzyl-2-[2-(4-fluorophenoxy)propyl]-3-oxoisoindoline-1-carboxamide (419.1771; 419.1798);

N-benzyl-2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide (437.1977; 437.1988);

N-benzyl-2-[(5-methyl-3-phenylisoxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide (438.1817; 438.1818);

N-benzyl-3-oxo-2-[(3-phenylisoxazol-5-yl)methyl]isoindoline-1-carboxamide (424.1661; 424.1669);

N-(tert-butyl)-5,6-dichloro-2-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-5,6-dichloro-2-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (409.0886; 409.0912);

N-(tert-butyl)-5,6-dichloro-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide (421.1085; 421.1078);

N-(tert-butyl)-5,6-dichloro-2-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide (457.0897; 457.0864);

N-(tert-butyl)-5-fluoro-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide (371.1771; 371.1768);

N-(4-fluorobenzyl)-3-oxo-2-(2-pyridin-4-ylethyl)isoindoline-1-carboxamide (390.1617; 390.1628);

2-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (428.1586; 428.1586);

N-(2-furylmethyl)-3-oxo-2-(2-phenylpropyl)isoindoline-1-carboxamide (375.1708; 375.1698);

2-[2-(4-chlorophenyl)ethyl]-N-[(5-methyl-2-furyl)methyl]-3-oxoisoindoline-1-carboxamide (409.1319; 409.1317);

N-(4-fluorobenzyl)-2-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (378.1617; 378.1609);

N-(2-chlorobenzyl)-2-[2-(1H-indol-3-yl)-1-methylethyl]-3-oxoisoindoline-1-carboxamide (458.1635; 458.1631);

N-(tert-butyl)-5,6-dichloro-2-[2-(4-chloro-2-methylphenyl)-2,2-difluoroethyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-5,6-dichloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (453.0903; 453.0917);

N-(tert-butyl)-2-[2-(4-chloro-2-methylphenyl)-2,2-difluoroethyl]-3-oxoisoindoline-1-carboxamide (421.1494; 421.1518);

N-benzyl-2-[2-(4-chloro-2-methylphenyl)-2,2-difluoroethyl]-3-oxoisoindoline-1-carboxamide (455.1338; 455.1351);

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (487.1400; 487.1414);

2-[3-(difluoromethoxy)benzyl]-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide (419.1602; 419.1599);

N-(2-chlorobenzyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (453.1136; 453.1123);

2-[4-(difluoromethoxy)benzyl]-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide (419.1602; 419.1601);

N-(2-chlorobenzyl)-2-(2,5-dimethylbenzyl)-3-oxoisoindoline-1-carboxamide (419.1526; 419.1513);

2-(biphenyl-2-ylmethyl)-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (451.1821; 451.1804);

N-(2-chlorobenzyl)-2-[(1R)-1-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (435.1475; 435.1466);

N-(2-chlorobenzyl)-2-[(1R)-1-(3-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (435.1475; 435.1469);

N-(2-chlorobenzyl)-2-[(1S)-1-(1-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide (455.1526; 455.1518);

N-benzyl-3-oxo-2-(4-phenoxybenzyl)isoindoline-1-carboxamide (449.1865; 449.1849);

N-(2-chlorobenzyl)-3-oxo-2-(3-phenylpropyl)isoindoline-1-carboxamide (419.1526; 419.1524);

N-(2-chlorobenzyl)-3-oxo-2-(2-phenylethyl)isoindoline-1-carboxamide (405.1369; 405.1336);

N-(2-chlorobenzyl)-3-oxo-2-(1-phenylpropyl)isoindoline-1-carboxamide (419.1526; 419.1520);

N-(2-chlorobenzyl)-2-(1-methyl-3-phenylpropyl)-3-oxoisoindoline-1-carboxamide (433.1682; 433.1693);

N-(2-chlorobenzyl)-3-oxo-2-(2-phenylpropyl)isoindoline-1-carboxamide (419.1526; 419.1516);

2-(biphenyl-2-ylmethyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (501.1790; 501.1790);

2-(biphenyl-2-ylmethyl)-N-(2-chlorobenzyl)-3-oxoisoindoline-1-carboxamide (467.1526; 467.1514);

3-oxo-2-(1-phenylpropyl)-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (453.1790; 453.1809);

3-oxo-2-(2-phenylpropyl)-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (453.1790; 453.1777);

2-(1-methyl-3-phenylpropyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (467.1946; 467.1926);

3-oxo-2-(2-phenylethyl)-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (439.1633; 439.1626);

N-benzyl-2-[2-(5-bromo-2-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (479.0970; 479.0968);

3-oxo-2-(3-phenylpropyl)-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (453.1790; 453.1769);

N-benzyl-2-[2-(3-bromo-4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (479.0970; 479.0972);

2-(2-methylbutyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (405.1790; 405.1786);

N-benzyl-2-(2,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide (393.1414; 393.1432);

2-(cyclohexylmethyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (431.1946; 431.1945);

2-(3-fluorobenzyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (443.1382; 443.1384);

2-(2-ethoxybenzyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide (469.1739; 469.1753);

3-oxo-2-[4-(trifluoromethoxy)benzyl]-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (493.1894; 493.1895);

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-[2-(2-thienyl)ethyl]isoindoline-1-carboxamide (439.1247; 439.1242);

2-[2-(4-chlorophenyl)propyl]-N-[2-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (463.1788; 463.1794);

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (433.1682; 433.1679);

2-[2-(4-chlorophenyl)propyl]-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide (387.1475; 387.1483);

2-[2-(4-chlorophenyl)propyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (437.1432; 437.1448);

N-benzyl-2-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide

(423.1520; 423.1511);
N-benzyl-2-[3-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide
(423.1520; 423.1518);
N-butyl-2-(1-naphthylmethyl)-3-oxoisoindoline-1-carboxamide (373.1916; 373.1883);
N-benzyl-2-cycloheptyl-3-oxoisoindoline-1-carboxamide (363.2072; 363.2062);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-[2-(4-bromophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(1-ethylpropyl)-3-oxoisoindoline-1-carboxamide;
N-benzyl-3-oxo-2-[3-(1H-pyrrol-1-yl)benzyl]isoindoline-1-carboxamide
(422.1868; 422.1874);
N-benzyl-2-(3-fluorobenzyl)-3-oxoisoindoline-1-carboxamide (375.1508; 375.1501);
N-benzyl-2-[2-(2-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide
(401.1865; 401.1854);
N-benzyl-2-(2-ethoxybenzyl)-3-oxoisoindoline-1-carboxamide (401.1865; 401.1869);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-3-oxo-2-(2-phenylpropyl)isoindoline-1-carboxamide;
N-benzyl-2-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide (382.1555; 382.1558);
N-benzyl-2-(3,5-dimethoxybenzyl)-3-oxoisoindoline-1-carboxamide (417.181; 417.1806);
N-benzyl-2-[1-(1-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide (421.1916; 421.1899);
N-benzyl-3-oxo-2-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide
(425.1477; 425.1482);
ethyl N-({2-[3,5-bis(trifluoromethyl)benzyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)-beta-alaninate (503.1405; 503.1403);
2-(1-naphthylmethyl)-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide
(403.1841; 403.1844);
ethyl N-({2-[2-(3,4-dichlorophenyl)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)-beta-alaninate (449.1035; 449.1038);
methyl 4-({1-[(benzylamino)carbonyl]-3-oxo-1,3-dihydro-2H-isoindol-2-yl}methyl)benzoate (415.1657; 415.1665);
3-oxo-2-[3-(trifluoromethyl)benzyl]-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide
(421.1559; 421.1552);

2-[1-(1-naphthyl)ethyl]-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide (417.1998; 417.1983);
3-oxo-2-[4-(trifluoromethyl)benzyl]-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide (421.1559; 421.1546);
2-[2-(4-bromophenyl)ethyl]-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide (445.0947; 445.0931);
2-(2-chloro-6-phenoxybenzyl)-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide (479.1557; 479.1568);
2-(3,4-dichlorobenzyl)-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide (421.0906; 421.0896);
N-benzyl-2-(1-benzylpyrrolidin-3-yl)-3-oxoisoindoline-1-carboxamide (426.2181; 426.2169);
N-benzyl-2-(1-benzylpyrrolidin-3-yl)-4,5-dimethoxy-3-oxoisoindoline-1-carboxamide (486.2392; 486.2405);
N-benzyl-2-(3,4-difluorobenzyl)-4,5-dimethoxy-3-oxoisoindoline-1-carboxamide (453.1626; 453.1620);
N-benzyl-2-[2-(4-chlorophenyl)propyl]-4,5-dimethoxy-3-oxoisoindoline-1-carboxamide (479.1737; 479.1729);
N-benzyl-4,5-dimethoxy-2-(1-methyl-3-phenylpropyl)-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide (360.1712; 360.1697);
N-benzyl-3-oxo-2-(1-phenyl-2-pyrrolidin-1-ylethyl)isoindoline-1-carboxamide (440.2338; 440.2336);
N-benzyl-2-[2-(4-methoxyphenyl)-2-oxoethyl]-3-oxoisoindoline-1-carboxamide (415.1657; 415.1674);
N-benzyl-2-[(1R)-1-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (401.1865; 401.1883);
N-benzyl-2-(3,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide (393.1414; 393.1403);
N-benzyl-2-[(1R)-1-(3-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide (401.1865; 401.1859);
N-benzyl-2-(2,5-dimethylbenzyl)-3-oxoisoindoline-1-carboxamide (385.1916; 385.1924);
N-benzyl-2-(1-methyl-3-phenylpropyl)-3-oxoisoindoline-1-carboxamide

(399.2072; 399.2062);
N-benzyl-3-oxo-2-{2-[3-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide (439.1633; 439.1634);
N-benzyl-2-[3,5-bis(trifluoromethyl)benzyl]-3-oxoisoindoline-1-carboxamide (493.1350; 493.1341);
N-benzyl-2-[2-(6-chloro-1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide (444.1478; 444.1484);
N,2-dibenzyl-3-oxoisoindoline-1-carboxamide (357.1603; 357.1613);
N-benzyl-2-(cyclohexylmethyl)-3-oxoisoindoline-1-carboxamide (363.2072; 363.2079);
N-benzyl-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide (363.1167; 363.1162);
2-(1,3-benzodioxol-5-ylmethyl)-N-cyclohexyl-3-oxoisoindoline-1-carboxamide (393.1814; 393.1807);
2-(2-methoxybenzyl)-N-(4-methylcyclohexyl)-3-oxoisoindoline-1-carboxamide (393.2178; 393.2169);
tert-butyl N-{[3-oxo-2-(3-pyrrolidin-1-ylpropyl)-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate (402.2392; 402.2388);
N-(tert-butyl)-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide (353.1865; 353.1861);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(2-bromobenzyl)-3-oxoisoindoline-1-carboxamide;
2-[2-(4-chlorophenyl)ethyl]-N-cyclohexyl-3-oxoisoindoline-1-carboxamide (397.1682; 397.1648);
N-(2,3-dimethylcyclohexyl)-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide (383.1793; 383.1778);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide (474.1930; 474.1937);
2-(2-chlorobenzyl)-N-(4-methylcyclohexyl)-3-oxoisoindoline-1-carboxamide (397.1682; 397.1671);
N-butyl-2-(2-cyclohex-1-en-1-ylethyl)-3-oxoisoindoline-1-carboxamide (341.2229; 341.2213);
N-benzyl-2-[(2R)-2-hydroxy-1,2-diphenylethyl]-3-oxoisoindoline-1-carboxamide (463.2021; 463.2000);

2-(biphenyl-2-ylmethyl)-N-butyl-3-oxoisoindoline-1-carboxamide
(399.2072; 399.2090);
2-(biphenyl-2-ylmethyl)-N-isopropyl-3-oxoisoindoline-1-carboxamide
(385.1916; 385.1915);
tert-butyl N-{[2-(2-bromobenzyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate
(459.0919; 459.0904);
2-[2-(4-chlorophenyl)propyl]-N-isopropyl-3-oxoisoindoline-1-carboxamide
(371.1526; 371.1545);
methyl N-{[3-oxo-2-(2-phenylethyl)-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate
(353.1501; 353.1496);
N-(tert-butyl)-2-[1-(2-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide
(387.2072; 387.2083);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-[1-(2-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide (462.1930; 462.1919);
2-[2-(3,4-diethoxyphenyl)ethyl]-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide
(473.2440; 473.2461);
2-benzyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (371.1759; 371.1755);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide (441.2039; 441.2030);
N-benzyl-2-(3-methoxybenzyl)-3-oxoisoindoline-1-carboxamide
(387.1708; 387.1705);
2-(2-chloro-4-fluorobenzyl)-N-cyclopentyl-3-oxoisoindoline-1-carboxamide
(387.1275; 387.1291);
2-(2-chloro-4-fluorobenzyl)-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide
(410.1071; 410.1057);
2-(2,5-dimethoxybenzyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide
(431.1970; 431.1964);
N-(sec-butyl)-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide
(371.1526; 371.1496);
N-benzyl-2-(2,3-difluorobenzyl)-3-oxoisoindoline-1-carboxamide
(393.1414; 393.1390);
2-(2-chloro-4-fluorobenzyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide

(423.1275; 423.1260);
2-[2-(4-chlorophenyl)ethyl]-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (419.1526; 419.1539);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(2-methylbenzyl)-3-oxoisoindoline-1-carboxamide (412.1773; 412.1747);
N-(tert-butyl)-2-(cyclohexylmethyl)-3-oxoisoindoline-1-carboxamide (329.2229; 329.2238);
2-(1-methyl-3-phenylpropyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide (413.2229; 413.2227);
N-benzyl-2-cyclohexyl-3-oxoisoindoline-1-carboxamide (349.1916; 349.1906);
N-(tert-butyl)-2-(2-cyclohex-1-en-1-ylethyl)-3-oxoisoindoline-1-carboxamide (341.2229; 341.2216);
N-(tert-butyl)-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;
tert-butyl N-{[2-(cyclohexylmethyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate (387.2283; 387.2270);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(2-cyclohex-1-en-1-ylethyl)-3-oxoisoindoline-1-carboxamide (416.2086; 416.2081);
tert-butyl N-{[2-(biphenyl-2-ylmethyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate (457.2127; 457.2120);
N-benzyl-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide (337.1916; 337.1917);
N-benzyl-2-(3-methylbutyl)-3-oxoisoindoline-1-carboxamide (337.1916; 337.1907);
N-benzyl-3-oxo-2-[2-(2-thienyl)ethyl]isoindoline-1-carboxamide (377.1323; 377.1326);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-3-oxo-2-(2-phenylethyl)isoindoline-1-carboxamide (412.1773; 412.1770);
N-benzyl-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (419.1526; 419.1497);
N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (385.1682; 385.1663);
N-benzyl-2-(2-methylbenzyl)-3-oxoisoindoline-1-carboxamide (371.1759; 371.1779);
N-benzyl-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide (387.1708; 387.1711);

N-benzyl-3-oxo-2-(2-phenylethyl)isoindoline-1-carboxamide (371.1759; 371.1746);
N-benzyl-2-[1-(2-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide
(421.1916; 421.1919);
methyl N-({2-[2-(4-chlorophenyl)propyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate (401.1268; 401.1258);
tert-butyl N-({2-[1-(2-naphthyl)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate (445.2127; 445.2119);
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide (460.1540; 460.1520);
N-butyl-2-[1-(2-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide
(387.2072; 387.2103);
N-benzyl-2-(2-bromobenzyl)-3-oxoisoindoline-1-carboxamide (435.0708; 435.0700);
N-benzyl-2-(2-cyclohex-1-en-1-ylethyl)-3-oxoisoindoline-1-carboxamide
(375.2072; 375.2065);
N-benzyl-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide
(433.1916; 433.1916);
N-butyl-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide
(385.1682; 385.1676);
2-[2-(4-chlorophenyl)-2-methylpropyl]-N-[(1-isopropyl-5-oxopyrrolidin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide (482.221; 482.218);
2-[2-(4-chlorophenyl)propyl]-N-[(1-isopropyl-5-oxopyrrolidin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;
1H-isoindole-1-carboxamide, 2-[2-(4-chlorophenyl)propyl]-2,3-dihydro-N-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-oxo- (428.1741; 428.174);
N-(tert-butyl)-2-[(4',5-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide
(435.1884; 435.1892);
N-(tert-butyl)-2-[(5-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide
(417.1978; 417.1976);
N-(tert-butyl)-2-[(4-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide
(417.1978; 417.1978);
2-[2-(4-chlorophenyl)-2-methylpropyl]-N-[(1-isopropyl-5-oxopyrrolidin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[(1-isopropyl-5-oxopyrrolidin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

1H-isoindole-1-carboxamide, 2-[2-(4-chlorophenyl)propyl]-2,3-dihydro-N-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-oxo-;

2-(2,2-dimethylpropyl)-6-fluoro-3-oxo-N-(1-phenylethyl)isoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-6-fluoro-N-(3-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-6-fluoro-N-(2-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-N-(3-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-N-(2-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(1-methyl-1-phenylethyl)-3-oxo-N-(1-phenylethyl)isoindoline-1-carboxamide;

6-fluoro-3-oxo-N,2-bis(1-phenylethyl)isoindoline-1-carboxamide;

N-(1-methyl-1-phenylethyl)-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;

3-oxo-N,2-bis(1-phenylethyl)isoindoline-1-carboxamide;

N-(3-fluorobenzyl)-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;

N-(2-fluorobenzyl)-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;

(1R or 1S)-2-[(2S or 2R)-2-(4-chlorophenyl)propyl]-3-oxo-N-propylisoindoline-1-carboxamide;

(1S or 1R)-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-3-oxo-N-propylisoindoline-1-carboxamide;

(1R or 1S)-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-3-oxo-N-propylisoindoline-1-carboxamide;

(R or S)2-(biphenyl-2-ylmethyl)-6-chloro-N-ethyl-3-oxoisoindoline-1-carboxamide;

(S or R)2-(biphenyl-2-ylmethyl)-6-chloro-N-ethyl-3-oxoisoindoline-1-carboxamide;

N-(4-fluorobenzyl)-2-[1-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[1-(4-chlorophenyl)ethyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[1-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[1-(4-chlorophenyl)-1-methylethyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-6-fluoro-2-[1-(4-fluorophenyl)-1-methylethyl]-3-oxoisoindoline-1-carboxamide;

2-[1-(4-chlorophenyl)-1-methylethyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

N-(4-fluorobenzyl)-2-[1-(4-fluorophenyl)-1-methylethyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-6-fluoro-2-(1-methyl-1-phenylethyl)-3-oxoisoindoline-1-carboxamide;

2-[1-(4-fluorophenyl)-1-methylethyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

N-(4-fluorobenzyl)-2-(1-methyl-1-phenylethyl)-3-oxoisoindoline-1-carboxamide;

2-(1-methyl-1-phenylethyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(5-cyanopentyl)-6-fluoro-3-oxoisoindoline-1-carboxamide;

N-benzyl-6-bromo-3-oxo-2-(1-phenylpropyl)isoindoline-1-carboxamide;

N-benzyl-2-[2-(4-chlorophenyl)propyl]-4-fluoro-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(4,4-difluorobutyl)-4-fluoro-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-4-fluoro-3-oxo-N-propylisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-ethyl-4-fluoro-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(biphenyl-2-ylmethyl)-4-fluoro-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(4,4-difluorobutyl)-4-fluoro-3-oxoisoindoline-1-carboxamide;

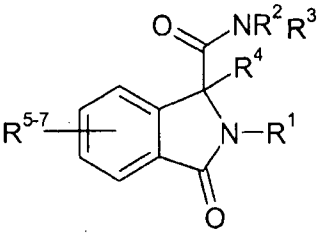
2-(biphenyl-2-ylmethyl)-4-fluoro-3-oxo-N-propylisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-ethyl-4-fluoro-3-oxoisoindoline-1-carboxamide;

N-benzyl-4-fluoro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide.

Claims

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 represents C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, $-OR^8$, $-COR^9$, $-SR^{10}$, $-COXR^{11}$, $-N(R^{12a})(R^{12b})$, $-N(R^{13a})C(O)OR^{13b}$, $-OC(O)N(R^{14a})(R^{14b})$, $-SO_2R^{15}$, aryl or Het^1); further R^1 represents aryl or Het^2;

R^8 to R^{11}, R^{13a}, R^{13b}, R^{15} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^9 (which C_1-C_6 alkyl, aryl and Het^9 groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{10});

R^{12a} and R^{12b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{11} (which C_1-C_6 alkyl, aryl and Het^{11} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{12}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{14a} and R^{14b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{13} (which C_1-C_6 alkyl, aryl and Het^{13} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{14}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^2 represents C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, -OR^{16}, -COR^{17}, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, trialkylsilyl, –$COXR^{18}$, aryl or Het^3);
further R^2 represents -$(CH_2)_kN(R^{19a})(R^{19b})$, -$(CH_2)_kNR^{20a}C(O)N(R^{20b})(R^{20c})$, -$(CH_2)_nNR^{21a}SO_2R^{21b}$, -$(CH_2)_nSO_2R^{22}$, -$(CH_2)_kN(R^{23a})C(O)OR^{23b}$, -$OC(O)N(R^{24a})(R^{24b})$, C_3-C_8 cycloalkyl, aryl or Het^4;

R^{16} to R^{18}, R^{21}, R^{22}, R^{23a}, R^{23b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{15} (which C_1-C_6 alkyl, aryl and Het^{15} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{16});

R^{19a} and R^{19b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{19} (which C_1-C_6 alkyl, aryl and Het^{19} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{20}) or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{20a}, R^{20b} and R^{20c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{21} (which C_1-C_6 alkyl, aryl and Het^{21} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{22}); R^{20b} and R^{20c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^3 represents hydrogen, C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, -OR^{25}, -COR^{26}, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, trialkylsilyl, –$COXR^{27}$, aryl or Het^5);
further R^3 represents -$(CH_2)_kN(R^{28a})(R^{28b})$, -$(CH_2)_kN(R^{29a})C(O)N(R^{29b})(R^{29c})$, -$(CH_2)_nNR^{30a}SO_2R^{30b}$, -$(CH_2)_nSO_2R^{31}$, -$(CH_2)_kN(R^{32a})C(O)OR^{32b}$, -$OC(O)N(R^{33a})(R^{33b})$,

C_3-C_8 cycloalkyl, aryl or Het^6;

R^{25} to R^{27}, R^{30}, R^{31}, R^{32a}, R^{32b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{23} (which C_1-C_6 alkyl, aryl and Het^{23} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{24});

R^{28a} and R^{28b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{25} (which C_1-C_6 alkyl, aryl and Het^{25} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{26}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{33a} and R^{33b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{27} (which C_1-C_6 alkyl, aryl and Het^{27} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{28}) or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{29a}, R^{29b}, and R^{29c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{29} (which C_1-C_6 alkyl, aryl and Het^{29} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{30}); R^{29b} and R^{29c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^4 represents hydrogen, –OH, aryl, C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, hydroxy, C_2-C_4 alkenyl, trialkylsilyl), $-OR^{34}$, $-(CH_2)_mR^{35}$;

R^{34} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{31} (which C_1-C_6 alkyl, aryl and Het^{31} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{32});

R^{35} independently represent aryl or Het^{33} (which aryl and Het^{33} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{34});

R^5 to R^7 independently represent, at each occurence, hydrogen, -OH, halogen, cyano, nitro, C_{1-6} alkyl, $-OR^{36}$, $-N(R^{37a})(R^{37b})$, $-C(O)R^{38}$, $-C(O)OR^{39}$, $-C(O)N(R^{40a})(R^{40b})$, $-NC(O)OR^{41}$, $-OC(O)N(R^{42a})(R^{42b})$, $-N(R^{43a})C(O)R^{43b}$, $-N(R^{44a})S(O)_2R^{44b}$, $-S(O)_2R^{45}$, $-OS(O)_2R^{46}$, $-(CH_2)_nN(R^{47a})(R^{47b})$, $-(CH_2)_nNR^{48a}C(O)N(R^{48b})(R^{48c})$, $-(CH_2)_nNR^{49a}SO_2R^{49b}$, trialkylsilyl, aryl or Het^7;

R^{36}, R^{38}, R^{39}, R^{41}, R^{43}, R^{44a}, R^{44b}, R^{45}, R^{46}, R^{49a} and R^{49b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{35} (which C_1-C_6 alkyl, aryl and Het^{35} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{36});

R^{37a} and R^{37b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{37} (which C_1-C_6 alkyl, aryl and Het^{37} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{38}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{40a} and R^{40b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{39} (which C_1-C_6 alkyl, aryl and Het^{39} groups are optionally substituted with one or

more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{40}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{42a} and R^{42b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{41} (which C_1-C_6 alkyl, aryl and Het^{41} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{42}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{47a} and R^{47b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{43} (which C_1-C_6 alkyl, aryl and Het^{43} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{44}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{48a}, R^{48b} and R^{48c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{45} (which C_1-C_6 alkyl, aryl and Het^{45} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{46}); R^{48b} and R^{48c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

aryl is independently, at each occurrence, optionally substituted by –OH, halogen, cyano, nitro, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, phenyl, Het^8, $-OR^{50}$, $-(CH_2)_mR^{51}$, $-SR^{52}$, $-C(O)R^{53}$, $-COXR^{54}$, $-N(R^{55a})(R^{55b})$, $-SO_2R^{56}$, $-OS(O)_2R^{57}$, $-(CH_2)_mN(R^{58a})(R^{58b})$, $-CH_2)_mNR^{59a}C(O)N(R^{59b})(R^{59c})$, $-C(O)OR^{60}$, $-C(O)N(R^{61a})(R^{61b})$, $-N(R^{62a}C(O)R^{62b}$, $-N(R^{63a})C(O)OR^{63b}$, $-OC(O)N(R^{64a})(R^{64b})$, $-N(R^{65a})S(O)_2R^{65b}$ and $OC(O)R^{66}$;

R^{50} to R^{54}, R^{56}, R^{57}, R^{60}, R^{62a}, R^{62b}, R^{63a}, R^{63b}, R^{65a}, R^{65b} and R^{66} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{47} (which C_1-C_6 alkyl, aryl and Het^{47} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{48});

R^{51} independently represent aryl or Het^{49} (which aryl and Het^{49} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{50});

R^{55a} and R^{55b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{51} (which C_1-C_6 alkyl, aryl and Het^{51} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{52}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{58a} and R^{58b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{53} (which C_1-C_6 alkyl, aryl and Het^{53} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{54}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{59a}, independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{55} (which C_1-C_6 alkyl, aryl and Het^{55} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{56}); R^{59b} and R^{59c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{61a} and R^{61b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{57} (which C_1-C_6 alkyl, aryl and Het^{57} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{58}); or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{64a} and R^{64b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{59} (which C_1-C_6 alkyl, aryl and Het^{59} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{60});

Het^{1} to Het^{60} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, a further Het, $-OR^{67}$, $-(CH_2)_mR^{68}$, $-SR^{69}$, $-COXR^{70}$, $-N(R^{71a})(R^{71b})$, $-SO_2R^{72}$, $-(CH_2)_mN(R^{73a})(R^{73b})$, $-(CH_2)_mNR^{74a}C(O)N(R^{74b})(R^{74c})$, $-C(O)R^{75}$, $-C(O)OR^{76}$, $-C(O)N(R^{77a})(R^{77b})$, $-N(R^{78a})C(O)R^{78b}$, $-N(R^{79a})S(O)_2R^{79b}$, $OC(O)R^{80}$, $-NC(O)OR^{81}$, $-OC(O)N(R^{82a})(R^{82b})$;

R^{67}, R^{69}, R^{70}, R^{72}, R^{75}, R^{76}, R^{78a}, R^{78b}, R^{79a}, R^{79b}, R^{80} or R^{81} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{61} (which C_1-C_6 alkyl, aryl and Het^{61} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{62});

R^{68} represents aryl or Het^{63} (which aryl and Het^{63} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{64});

R^{71a} and R^{71b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{65} (which C_1-C_6 alkyl, aryl and Het^{65} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{66}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{73a} and R^{73b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{67} (which C_1-C_6 alkyl, aryl and Het^{67} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{68}); or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{74a}, R^{74b} and R^{74c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{69} (which C_1-C_6 alkyl, aryl and Het^{69} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{70}); R^{74b} and R^{74c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

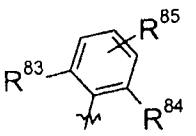
R^{77a}, and R^{77b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{71} (which C_1-C_6 alkyl, aryl and Het^{71} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{72}); or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{82a}, and R^{82b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{73} (which C_1-C_6 alkyl, aryl and Het^{73} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{74}) or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

Het^{61} to Het^{74} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl;

X represents a nitrogen or oxygen atom;
m is an integer of 0 to 10;
n is an integer of 0 to 4;
k is an integer of 1 to 5;
provided that

a) R^2 or R^3 do not represent a fragment of formula



wherein

R^{83} and R^{84} represent independently, at each occurrence, halogen, C_1-C_{12} alkyl, C_1-C_{12} alkoxy, C_1-C_{12} haloalkyl, C_1-C_{12} haloalkoxy, cyano, $-SR^{86}$, $-N(R^{87a})R^{87b}$, C_2-C_6 alkynyl, aryl or Het^{75};

R^{85} represents hydrogen, C_1-C_{12} alkyl group or C_1-C_{12} alkoxy group (which C_1-C_{12} alkyl and C_1-C_{12} alkoxy groups are optionally substituted by one or more groups selected from halogen, C2-C6 alkenyl, C_2-C_6 alkynyl, cyano, oxo, aryl, Het^{76}, $-OR^{88}$, $-SR^{89}$, $-COXR^{90}$, $-N(R^{91a})R^{91b}$, $-SO_2R^{92}$);

Het^{75} to Het^{76} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryloxy, $-N(R^{93a})R^{93b}$, $-C(O)R^{93c}$, $-C(O)OR^{93d}$, $-C(O)N(R^{93e})R^{93f}$, $-N(R^{93g})C(O)R^{93h}$ and $-N(R^{93i})S(O)_2R^{93j}$, $OC(O)R^{93k}$ and a further Het;

R^{86} to R^{93} represent independently, at each occurrence, hydrogen or C_{1-6} alkyl;

b) the compound is not:

2-(4-nitrophenyl)-3-(pyrrolidin-1-ylcarbonyl)isoindolin-1-one;

N,2-dibenzyl-3-oxoisoindoline-1-carboxamide;

N,2-diethyl-3-oxoisoindoline-1-carboxamide;

N,2-dibutyl-3-oxoisoindoline-1-carboxamide;

N,2-didodecyl-3-oxoisoindoline-1-carboxamide;

N,2-bis(4-metoxybenzyl)-3-oxoisoindoline-1-carboxamide;

3-oxo-N,2-dipropylisoindoline-1-carboxamid;

N,2-diheptyl-3-oxoisoindoline-1-carboxamide;

3-oxo-N,2-diphenylisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-propylisoindoline-1-carboxamide;

N-(tert-butyl)-1-methyl-3-oxo-2-propyl-isoindoline-1-carboxamide;

N,1-dimethyl-3-oxo-2-propylisoindoline-1-carboxamide ;

N-cyclohexyl-3-oxo-2-propylisoindoline-1-carboxamide;

N-(phenyl)-3-oxo-2-propylisoindoline-1-carboxamide;

2-benzyl-N-tert-butyl-3-oxoisoindoline-1-carboxamide:

2-benzyl-N,1-dimethyl-3-oxoisoindoline-1-carboxamide;

2-benzyl-N-tert-butyl-1-methyl-3-oxoisoindoline-1-carboxamide;

2-benzyl-N,1-dimethyl-3-oxoisoindoline-1-carboxamide;

tert-butyl (4-{1-[(tert-butylamino)carbonyl]-3-oxo-1,3-dihydro-2H-isoindol-2-yl}butyl)carbamate;

2-benzyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

2-benzyl-N-butyl-3-oxoisoindoline-1-carboxamide;

2-benzyl-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide;

2-(2-hydroxyethyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-butyl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide;

2-(2-hydroxyethyl)-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide;

2-(3-(1H-imidazol-1-yl)propyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-butyl-2-[3-(1H-imidazol-1-yl)propyl]-3-oxoisoindoline-1-carboxamide;

2-[3-(1H-imidazol-1-yl)propyl]-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide

2-(cyclohexyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-butyl-2-cyclohexyl-3-oxoisoindoline-1-carboxamide;

2-cyclohexyl-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide;

N,2-dibenzyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-tert-butyl-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide;

N-benzyl-2-tert-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N,2-dibenzyl-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide;

N-benzyl-2-tert-butyl-5-hydroxy-3-oxoisoindoline-1-carboxamide;

2-cyclohexyl-N-hexyl-3-oxoisoindoline-1-carboxamide;

N,2-dihexyl-3-oxoisoindoline-1-carboxamide;

N-hexyl-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide;

N-hexyl-2-(4-hydroxybutyl)-3-oxoisoindoline-1-carboxamide;

N,2-dicyclohexyl-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-2-hexyl-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-2-(4-hydroxybutyl)-3-oxoisoindoline-1-carboxamide;

tert-butyl (4-{1-[(cyclohexylamino)carbonyl]-3-oxo-1,3-dihydro-2H-isoindol-2-yl}butyl)carbamate;

N-adamantan-1-yl-2-cyclohexyl-3-oxoisoindoline-1-carboxamide;

N-adamantan-1-yl-2-hexyl-3-oxoisoindoline-1-carboxamide;

N-adamantan-1-yl-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide ;

N-adamantan-1-yl-2-(2-morpholin-4-ylethyl)-3-oxoisoindoline-1-carboxamide;

N,2-dibenzyl-5-{[(2-nitrophenyl)sulfonyl]amino}-3-oxoisoindoline-1-carboxamide;

ethyl [1-(tert-butylcarbamoyl)-3-oxo-1,3-dihydro-2H-isoindol-2-yl]acetate;

N-[2-(3,4-dimethoxyphenyl)ethyl]-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide

N-cyclopentyl-2-(3-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;

2-(1,3-benzodioxol-5-ylmethyl)-N-{[(4-methylphenyl)sulfonyl]methyl}-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide;

2-benzyl-N-cyclohexyl-3-oxoisoindoline-1-carboxamide;

N-{[(4-methylphenyl)sulfonyl]methyl}-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide;

2-(4-chlorobenzyl)-N-{[(4-methylphenyl)sulfonyl]methyl}-3-oxoisoindoline-1-carboxamide;

N-cyclohexyl-2-(2-furylmethyl)-3-oxoisoindoline-1-carboxamide;

2-(4-chlorobenzyl)-N-cyclohexyl-3-oxoisoindoline-1-carboxamide;

tert-butyl {1-benzyl-2-hydroxy-3-[(2-hydroxy-3-{[(3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbonyl]amino}-4-phenylbutyl)amino]propyl}carbamate;

1-hydroxy-2-methyl-3-oxo-N-(pyridin-2-ylmethyl)isoindoline-1-carboxamide;

N-[3-(dimethylamino)propyl]-1-hydroxy-2-(2-hydroxyethyl)-3-oxoisoindoline-1-carboxamide;

N-(3-azepan-1-ylpropyl)-1-hydroxy-3-oxo-2-phenylisoindoline-1-carboxamide;

2-benzoyl-1-hydroxy-3-oxo-N-phenylisoindoline-1-carboxamide;

3-oxo-N,2-diphenylisoindoline-1-carboxamide;

6-{[(1-methyl-2-octyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbonyl]amino}hexanoic acid;

N-(methyl)-2-benzoyl-1-hydroxy-3-oxoindoline-1-carboxamide;
N-(phenyl)-2-benzoyl-1-hydroxy-3-oxoisoindoline-1-carboxamide;
6-[(2-allyl-1-methyl-3-oxoisoindoline-1-carbonyl)-amino]-hexanoic acid;
N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-ethyl-3-oxoisoindoline-1-carboxamide;
N1-cyclopentyl-N4-(2,6-difluorophenyl)-2-(2,4-dimethylphenyl)-5-methyl-3-oxoisoindoline-1,4-dicarboxamide;
methyl [1-(tert-butylcarbamoyl)-3-oxo-1,3-dihydro-2H-isoindol-2-yl]acetate;
1-hydroxy-2-methyl-3-oxoisoinoline-1-carbohydrazide;
1-hydroxy-3-oxo-phenylisoindoline-1-carbohydrazide;
or a pharmaceutically acceptable derivative thereof;

c) the compound is not:
2-(2-ethoxyethyl)-N-isopropyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-3-oxo-2-(3-pyrrolidin-1-ylpropyl)isoindoline-1-carboxamide;
N-(tert-butyl)-3-oxo-2-(tetrahydrofuran-2-ylmethyl)isoindoline-1-carboxamide;
2-[1-(hydroxymethyl)butyl]-N-isopropyl-3-oxoisoindoline-1-carboxamide;
N-isopropyl-2-(3-methylbutyl)-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-cyclohexyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-(3-methylbutyl)-3-oxoisoindoline-1-carboxamide;
methyl N-{[2-(3-methylbutyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;
tert-butyl N-({2-[1-(hydroxymethyl)butyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;
tert-butyl N-{[2-(3-methylbutyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;
N-(tert-butyl)-2-[1-(methoxymethyl)propyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(diethylamino)ethyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[1-(hydroxymethyl)butyl]-3-oxoisoindoline-1-carboxamide;
tert-butyl N-{[3-oxo-2-(2-thienylmethyl)-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;
tert-butyl N-({2-[2-(methylthio)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;

methyl N-{[2-(cyclopropylmethyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate; or
2-(2,2-dimethylpropyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide.

2. A compound according to claim 1 wherein R^1 represents C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, -OR^8, -$COXR^{10}$, aryl or Het^1); further R^1 represents Het^2.

3. A compound according to claim 1 wherein R^1 represents C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, -OR^8, -$COXR^{10}$, phenyl, naphtalen or Het^1).

4. A compound according to claim 1 wherein R^1 represents (1-benzylpyrrolidin-3-yl); (1-fluoro-3-phenyl-propan-2-yl); (1-methyl-5-phenyl-pyrazol-3-yl)methyl; (1-methylpyrrol-2-yl)methyl; (2,3-difluorophenyl)methyl; (2,4-difluorophenyl)methyl; (2,5-dimethoxyphenyl)methyl (2,5-dimethylphenyl)methyl; (2-bromophenyl)methyl; (2-chloro-4-fluoro-phenyl)methyl (2-chloro-6-phenoxy-phenyl)methyl; (2-chlorophenyl)methyl; (2-dimethylamino-2-phenyl-ethyl); (2-ethoxyphenyl)methyl; (2-fluorophenyl)methyl; (2-methoxyphenyl)methyl; (2-methyl-2-phenyl-propyl); (2-methylphenyl)methyl; (2-phenoxyphenyl)methyl; (2-phenylphenyl)methyl; (2-pyridin-3-ylphenyl)methyl; (3,4-dichlorophenyl)methyl; (3,4-difluorophenyl)methyl; (3,5-dimethoxyphenyl)methyl; (3-chlorophenyl)methyl; (3-cyano-4-fluoro-phenyl)methyl; (3-cyanophenyl)methyl; (3-fluorophenyl)methyl; (3-hydroxy-2,2-dimethyl-propyl); (3-methoxyphenyl)methyl; (3-phenyl1,2-oxazol-5-yl)methyl; (3-phenylphenyl)methyl; (3-pyrrol-1-ylphenyl)methyl; (4-chlorophenyl)methyl; (4-dimethylaminophenyl)methyl; (4-fluorophenyl)methyl; (4-hydroxyphenyl)methyl; (4-methoxycarbonylphenyl)methyl; (4-phenoxyphenyl)methyl; (4-phenylphenyl)methyl; (5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl; (5-methyl-3-phenyl-1,2-oxazol-4-yl)methyl; (phenyl-pyridin-2-yl-methyl); [(1R)-1-(4-methoxyphenyl)ethyl]; [(1S)-1-phenylethyl]; [(1R)-1-phenylethyl]; [(1R)-2-(4-chlorophenyl)-1-(4,4,4- trifluorobutylcarbamoyl)ethyl]; [(1R)-2-(4-chlorophenyl)-1-methoxycarbonyl-ethyl]; [(1S)-1-naphthalen-1-ylethyl]; [(2R)-

2-(4-chlorophenyl)propyl]; [(2S)-2-(4- chlorophenyl)propyl]; [(4-chlorophenyl)-pyridin-4-yl-methyl]; [(4-fluorophenyl)-pyridin-3-yl-methyl]; [(4-fluorophenyl)-pyridin-3-yl-methyl]; [(4-fluorophenyl)-pyridin-3-yl- methyl]; [2-(2,4-dichlorophenyl)phenyl]methyl; [2-(2,4-difluorophenyl)phenyl]methyl; [2-(2,5-difluorophenyl)phenyl]methyl; [2-(2-chlorophenyl)phenyl]methyl; [2-(3,4-dichlorophenyl)phenyl]methyl; [2-(3,4-difluorophenyl)phenyl]methyl; [2-(3-chloro-4-fluoro-phenyl)phenyl]methyl; [2-(3-fluorophenyl)phenyl]methyl; [2-(4-chloro-2-methyl-phenyl)-2,2-difluoro-ethyl]; [2-(4-chloro-2-methyl-phenyl)-2,2-difluoro-ethyl]; [2-(4-chlorophenyl)phenyl]methyl; [2-(4-fluoro-2-methyl-phenyl)phenyl]methyl; [2-(4-fluorophenoxy)phenyl]methyl; [2-(4-fluorophenyl)phenyl]methyl; [2-(4-methoxyphenyl)-2-oxo-ethyl]; [2-(4-methoxyphenyl)phenyl]methyl; [2-(4-methylphenyl)phenyl]methyl; [2-(trifluoromethyl)phenyl]methyl; [2-[4-(trifluoromethyl)phenoxy]phenyl]methyl; [3-(difluoromethoxy)phenyl]methyl; [3,5-bis(trifluoromethyl)phenyl]methyl; [4-(difluoromethoxy)phenyl]methyl; [4-(trifluoromethyl)phenyl]methyl; 1-(1H-indol-3-yl)propan-2-yl; 1-(4-fluorophenyl)ethyl; 1-naphthalen-1-ylethyl; 1-naphthalen-2-ylethyl 1-phenylethyl; 1-phenylpropyl; 2-(1-cyclohexenyl)ethyl; 2-(2-ethoxyphenyl)ethyl; 2-(2-methoxyphenyl)ethyl; 2-(2-phenoxyphenyl)ethyl; 2-(3,4-dichlorophenyl)ethyl; 2-(3,5-dimethoxyphenyl)ethyl; 2-(3-bromo-4-methoxy-phenyl)ethyl; 2-(3-fluorophenyl)ethyl; 2-(4-bromophenyl)ethyl; 2-(4-chlorophenyl)ethyl; 2-(4-chlorophenyl)propyl; 2-(4-fluorophenoxy)propyl; 2-(4-fluorophenyl)ethyl; 2-(4-fluorophenyl)propyl; 2-(4-phenoxyphenyl)ethyl; 2-(4-methoxyphenyl)ethyl; 2-(4-methoxyphenyl)ethyl; 2-(4-phenylphenyl)ethyl; 2-(5-bromo-2-methoxy-phenyl)ethyl; 2-(6-chloro-1H-indol-3-yl)ethyl; 2,2-dimethylpropyl; 2,2-diphenylethyl; 2-[2-(trifluoromethoxy)phenyl]ethyl; 2-[3-(trifluoromethyl)phenyl]ethyl; 2-[4-(diethylcarbamoyl)phenyl]ethyl; 2-[4-(trifluoromethyl)phenyl]ethyl; 2-benzo[1,3]dioxol-5-ylethyl; 2-methylbutyl; 2-methylpropyl; 2-naphthalen-1-ylpropyl; 2-phenoxypropyl; 2-phenylpropyl; 2-thiophen-2-ylethyl; 3,3-dimethylbutyl; 3-phenylpropyl; 3-pyrrolidin-1-ylpropyl; 4-phenylbutan-2-yl; 4-phenylbutyl; 9H-fluoren-9-yl; benzhydryl; benzyl; cycloheptyl; cyclohexyl; cyclohexylmethyl; naphthalen-1-ylmethyl; pentan-3-yl; phenethyl; thiophen-2-ylmethyl; 2-phenylpropan-2-yl; 1-phenylpropyl; [2-(4-chlorophenyl)-2-methyl-propyl]; [4-fluoro-2-(4-fluorophenyl)phenyl]methyl; (4-fluoro-2-phenyl-phenyl)methyl; [5-fluoro-2-(4-fluorophenyl)phenyl]methyl; (5-fluoro-2-phenyl-phenyl)methyl; 1-(4-fluorophenyl)ethyl

2-(4-chlorophenyl)propan-2-yl; 2-(4-fluorophenyl)propan-2-yl; or 1-(4-chlorophenyl)ethyl.

5. A compound according to any of claims 1 to 4 wherein R^2 represents C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from fluoro, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, $-COR^{17}$, trimethylsilyl, $-COXR^{18}$, aryl or Het^3); further R^2 aryl or Het^4.

6. A compound according to any of claims 1 to 5 wherein R^2 represents (1-benzylpyrrolidin-3-yl); (1-methylpyrrol-2-yl)methyl; (2,2-difluorobenzo[1,3]dioxol-5-yl)methyl; (2,3-dimethylcyclohexyl); (2,4-difluorophenyl)methyl; (2-chloro-4-methylsulfonyl-phenyl)methyl; (2-chlorophenyl)methyl; (2-fluoro-4-methylsulfonyl-phenyl)methyl; (2-hydroxyphenyl)methyl; (2-methylpropan-2-yl)oxycarbonylmethyl; (3,4-dichlorophenyl)methyl; (3,4-difluorophenyl)methyl; (3,4-dimethoxyphenyl)methyl; (3-carbamoyl-4-fluoro-phenyl)methyl; (3-chlorophenyl)methyl; (3-cyano-4-fluoro-phenyl)methyl; (3-cyanophenyl)methyl; (3-methoxyphenyl); (3-methyl-5-phenyl-1,2-oxazol-4-yl)methyl; (4-amino-2-methyl-pyrimidin-5-yl)methyl; (4-carbamoylphenyl); (4-carbamoylphenyl)methyl; (4-cyano-2,6-difluoro-phenyl)methyl; (4-cyanophenyl); (4-cyanophenyl)methyl; (4-dimethylaminophenyl)methyl; (4-fluorophenyl)methyl; (4-hydroxyphenyl)methyl; (4-methylcyclohexyl); (4-methylsulfonylphenyl)methyl; (5-methyl-1,2-oxazol-3-yl)methyl; (5-methyl-2-furyl)methyl; (5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl; (5-methylpyrazin-2-yl)methyl; [2-(trifluoromethyl)phenyl]methyl; [3-(aminomethyl)-4-fluoro-phenyl]methyl; [3-(difluoromethoxy)phenyl]methyl; [3-(dimethylcarbamoyl)-4-fluoro-phenyl]methyl; [3-(trifluoromethyl)phenyl]methyl; [3,5-bis(trifluoromethyl)phenyl]methyl; [3-[[(2,2-difluoroacetyl)amino]methyl]-4-fluoro-phenyl]methyl; [4-(acetamidomethyl)phenyl]methyl; [4-(aminomethyl)phenyl]; [4-(difluoromethoxy)phenyl]methyl; [4-(trifluoromethyl)phenyl]methyl; [4-[[(2,2-difluoroacetyl)amino]methyl]phenyl]; [4-[[(2-fluoroacetyl)amino]methyl]phenyl]methyl; [5-(2-furyl)1,2-oxazol-3-yl]methyl; [6-(trifluoromethyl)pyridin-3-yl]methyl; 1H-indol-3-ylmethyl; 1-pyridin-4-ylethyl; 2-(1H-indol-3-yl)ethyl; 2-(2,4-dichlorophenyl)ethyl; 2-(2,6-dichlorophenyl)ethyl; 2-(2-chlorophenyl)ethyl; 2-(3,4-dichlorophenyl)ethyl; 2-(3,4-dimethoxyphenyl)ethyl; 2-(3-chlorophenyl)ethyl; 2-(3-fluorophenyl)ethyl;

2-(4-benzoylpiperazin-1-yl)ethyl; 2-(4-chlorophenyl)ethyl; 2-(4-fluorophenyl)ethyl; 2-(4-methoxyphenyl)ethyl; 2-[3-(trifluoromethyl)phenyl]ethyl; 2-benzo[1,3]dioxol-5-ylethyl; 2-ethoxycarbonylethyl; 2-furylmethyl; 2-methoxyethyl; 2-pyridin-2-ylethyl; 2-pyridin-4-ylethyl; 2-thiophen-2-ylethyl; 3-imidazol-1-ylpropyl; 3-methoxypropyl; 4,4,4-trifluorobutyl; 4,4-difluorobutyl; benzo[1,3]dioxol-5-ylmethyl; benzotriazol-1-ylmethyl; benzyl; butyl; cyclohexyl; ethyl; methoxycarbonylmethyl; phenethyl; propan-2-yl; propyl; pyridin-3-ylmethyl; pyridin-4-ylmethyl; tert-butyl; trimethylsilylmethyl; (5-oxo-1-propan-2-yl-pyrrolidin-3-yl)methyl; propan-2-ylcarbamoylmethyl; (2-fluorophenyl)methyl; (3-fluorophenyl)methyl; 1-phenylethyl; 2-phenylpropan-2-yl or 5-cyanopentyl.

7. A compound according to claim 1 wherein R^1 represents C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from fluoro, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, $-OR^8$, $-COXR^{11}$, aryl or Het^1); further R^1 represents Het^2; and

R^2 represents C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from fluoro, C_2-C_6 alkenyl, C_3-C_7 cycloalkyl, $-COR^{17}$, trimethylsilyl, $-COXR^{18}$, aryl or Het^3); further R^2 represents aryl or Het^4.

8. A compound according to any of claims 1 to 7 wherein R^3 represents hydrogen, C_1-C_4 alkyl (which alkyl group is optionally substituted by one or more groups selected from fluoro, C_2-C_6 alkenyl, trialkylsilyl, $-COXR^{27}$, aryl or Het^5).

9. A compound according to any of claims 1 to 8 wherein R^3 represents hydrogen.

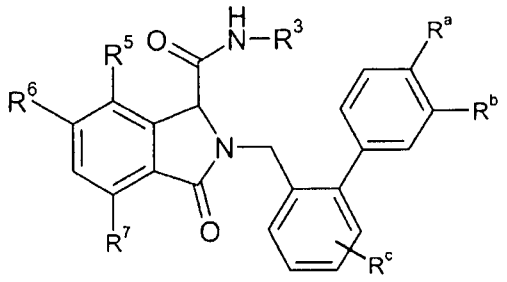
10. A compound according to any of claims 1 to 9 wherein R^4 represents hydrogen.

11. A compound according to any of claims 1 to 10 wherein R^5 to R^7 independently represent, at each occurence, hydrogen, -OH, halogen, cyano, C_{1-6} alkyl, $-OR^{36}$, $-C(O)N(R^{40a})(R^{40b})$, $-N(R^{44a})S(O)_2R^{44b}$.

12. A compound according to any of claims 1 to 11 wherein aryl is independently, at each occurrence, optionally substituted by –OH, halogen, cyano, nitro, C_1-C_6 alkyl, -OR^{50}, C_2-C_6 alkenyl, aryl, Het^8; wherein R^{50} represents C_1-C_6 alkyl or phenyl.

13. A compound according to any of claims 1 to 12 wherein aryl is, at each occurrence, phenyl.

14. A compound according to any of claims 1 to 13 wherein the compound of formula I is



in which R^a is hydrogen or fluoro;

R^b is hydrogen or fluoro;

R^c is hydrogen or fluoro;

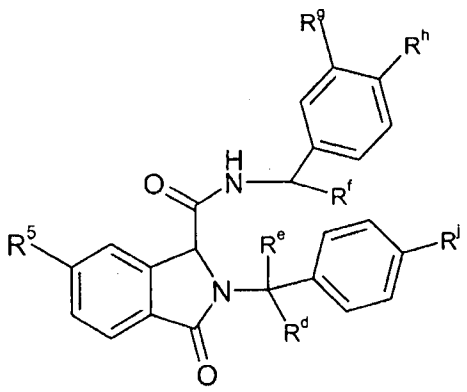
R^3 is C_{1-4} alkyl optionally terminally substituted by 1, 2 or 3 fluoro;

R^5 is hydrogen or C_{1-4} alkyl,

R^6 is hydrogen, OH, halo or C_{1-4}alkoxy;

R^7 is hydrogen or halo.

15. A compound according to any of claims 1 to 13 wherein the compound of formula I is



in which

R^d is hydrogen or C_{1-4} alkyl;

R^e is hydrogen or C_{1-4} alkyl;

R^f is hydrogen or C_{1-4} alkyl;

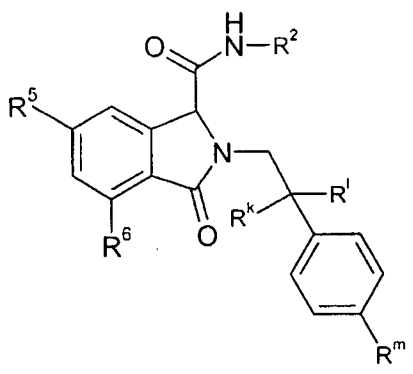
R^g is hydrogen or halo;

R^h is hydrogen or halo;

R^j is hydrogen or halo;

R^5 is hydrogen or halo.

16. A compound according to any of claims 1 to 13 wherein the compound of formula I is



in which

R^k is hydrogen or C_{1-4} alkyl;

R^l is hydrogen or C_{1-4} alkyl;

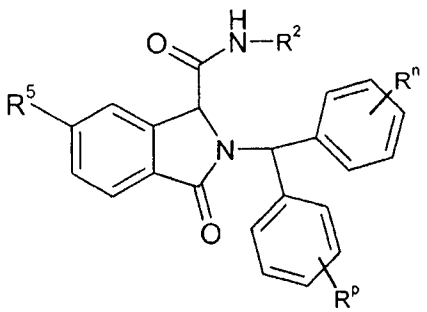
R^m is hydrogen or halo;

R^2 is C_{3-6} alkyl;

R^5 is hydrogen or halo;

R^6 is hydrogen or halo.

17. A compound according to any of claims 1 to 13 wherein the compound of formula I is



in which

R^n is hydrogen or halo;

R^p is hydrogen or halo;

R^2 is C_{3-6} alkyl or benzyl, optionally substituted by halo in the phenyl ring;

R^5 is hydrogen or halo.

18. A compound according to any of claims 1 to 13 wherein

R^1 is (2-phenylphenyl)methyl, optionally substituted by one to three fluoro;

R^2 is selected from ethyl, propyl, n-butyl, tert-butyl, 4,4,4-trifluorobutyl, 4,4-difluorobutyl, 4-fluorobutyl, benzo[1,3]dioxol-5-yl-methyl, (2,2-difluorobenzo[1,3]dioxol-5-yl)methyl, benzyl, (2-chlorophenyl)methyl, (4-fluorophenyl)methyl, (2-trifluoromethylphenyl)methyl, (3-cyanophenyl)methyl, (4-cyanophenyl)methyl, (3-cyano-4-fluorophenyl)methyl, (4-carbamoylphenyl)methyl, (5-methylpyrazin-2-yl)methyl, pyridin-3-ylmethyl, (4-amino-2-methyl-pyrimidin-5-yl)methyl, [6-(trifluoromethyl)pyridin-3-yl]methyl, pyridin-3-ylmethyl, [6-(trifluoromethyl)pyridin-3-yl]methyl, pyridin-4-ylmethyl, [4-[[(2,2-difluoroacetyl)amino]methyl]phenyl]methyl, [4-(acetamidomethyl)phenyl]methyl,

[4-[[(2-fluoroacetyl)amino]methyl]phenyl]methyl, 2-phenylethyl or 2-(4-fluorophenyl)ethyl;

R^5 to R^7 are independently selected from –OH, methyl, methoxy, chloro, fluoro, cyano, methylsulfonylamino, fluoromethoxy, difluoromethoxy, trifluoromethanesulfonate;
or an enantiomer thereof.

19. A compound according to any of claims 1 to 13 wherein
R^1 is benzhydryl, optionally substituted by one or more substitutents selected from fluoro or chloro;
R^2 is selected from ethyl, propyl, butyl, tert-butyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, benzyl, (2-chloro-4-methylsulfonyl-phenyl)methyl, (4-methylsulfonylphenyl)methyl, (2-fluoro-4-methylsulfonyl-phenyl)methyl, (4-methylsulfonylphenyl)methyl, (2-hydroxyphenyl)methyl, [2-(trifluoromethyl)phenyl]methyl, (2,4-difluorophenyl)methyl, (2-chlorophenyl)methyl or 2-(4-fluorophenyl)ethyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, –OH, methyl, methoxy, fluoro or chloro;
or an enantiomer thereof.

20. A compound according to any of claims 1 to 13 wherein
R^1 is 4-phenylbutan-2-yl, optionally substituted by one or more substitutents selected from fluoro or chloro;
R^2 is selected from (2-chlorophenyl)methyl, [2-(trifluoromethyl)phenyl]methyl, benzyl, 2-phenylethyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, –OH, methyl, methoxy, fluoro or chloro;
or an enantiomer thereof.

21. A compound according to any of claims 1 to 13 wherein

R^1 is 3,3-dimethylbutyl;

R^2 is selected from [3-(difluoromethoxy)phenyl]methyl, [3-(trifluoromethoxy)phenyl]methyl, 2-(1H-indol-3-yl)ethyl, 1H-indol-3-ylmethyl, (3-chlorophenyl)methyl, (3,4-dichlorophenyl)methyl, [4-(difluoromethoxy)phenyl]methyl, 2-(3-fluorophenyl)ethyl, 2-benzo[1,3]dioxol-5-ylethyl, 2-[3-(trifluoromethyl)phenyl]ethyl, 2-(3,4-dichlorophenyl)ethyl, 2-(2,4-dichlorophenyl)ethyl, 2-(2,6-dichlorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(3-chlorophenyl)ethyl or 2-(2-chlorophenyl)ethyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, –OH, methyl, methoxy, fluoro or chloro;

or an enantiomer thereof.

22. A compound according to any of claims 1 to 13 wherein

R^1 is benzyl, optionally substituted by one or more substiutents selected from fluoro, chloro, cyano;

R^2 is selected from ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, benzo[1,3]dioxol-5-yl-methyl, benzyl, 1-phenylethyl, 2-phenylethyl, cyclopentyl, which groups are optionally substituted by one or more substiutents selected from fluoro, chloro, cyano, trifluoromethyl;

further R^2 represents pyridin-3-ylmethyl, pyridin-4-ylmethyl, [3-[[(2,2-difluoroacetyl)amino]methyl]-4-fluoro-phenyl]methyl, [4-(difluoromethoxy)phenyl]methyl, (4-dimethylaminophenyl)methyl, [5-(2-furyl)1,2-oxazol-3-yl]methyl, [5-(2-furyl)1,2-oxazol-3-yl]methyl, 2-(3,4-dimethoxyphenyl)ethyl, butan-2-yl, cyclopentyl, (2,3-dimethylcyclohexyl), (4-hydroxyphenyl)methyl, [2-(trifluoromethyl)phenyl]methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, –OH, methyl, methoxy, bromo, chloro, fluoro, trimethylsilyl;

or an enantiomer thereof.

23. A compound according to any of claims 1 to 13 wherein

R^1 is (2-cyclopentylphenyl)methyl;

R^2 is selected from 4,4-difluorobutyl, methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from bromo, fluoro, chloro or cyano;

or an enantiomer thereof.

24. A compound according to any of claims 1 to 13 wherein

R^1 is 1-phenylethyl, optionally substituted by one or more substiutents selected from fluoro, chloro, cyano, methoxy;

R^2 is selected from ethyl, propyl, tert-butyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, 4-methylsulfonyl, benzyl, which benzyl group is optionally substituted by one or more substituents selected from fluoro, chloro, cyano;

further R^2 represents pyridinmethyl, ((2,2-difluoroacetyl)amino)methyl, difluoromethoxy, dimethylamino, 5-(2-furyl)1,2-oxazol-3-yl-methyl, cyclopentyl

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from bromo, fluoro, chloro or cyano;

or an enantiomer thereof.

25. A compound according to any of claims 1 to 13 wherein

R^1 is 3-hydroxy-2,2-dimethylpropyl;

R^2 is selected from [3-(difluoromethoxy)phenyl]methyl, (3,4-dichlorophenyl)methyl, (3-chlorophenyl)methyl, [3-(trifluoromethyl)phenyl]methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, fluoro, chloro;

or an enantiomer thereof.

26. A compound according to any of claims 1 to 13 wherein

R^1 is 2-(4-chlorophenyl)propyl;

R^2 is selected from methyl, ethyl, n-propyl, propan-2-yl, butyl, (4-amino-2-methyl-pyrimidin-5-yl)methyl, (5-methylpyrazin-2-yl)methyl, pyridin-3-ylmethyl, [6-(trifluoromethyl)pyridin-3-yl]methyl, (4-amino-2-methyl-pyrimidin-5-yl)methyl, [6-(trifluoromethyl)pyridin-3-yl]methyl, (5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl, 4,4,4-trifluorobutyl, (4-methylsulfonylphenyl)methyl, benzyl, (2,2-difluorobenzo[1,3]dioxol-5-yl)methyl, (4-methylsulfonylphenyl)methyl, butyl, 2-(1H-indol-3-yl)ethyl; (4-carbamoylphenyl)methyl, (4-cyanophenyl)methyl, [3-(dimethylcarbamoyl)-4-fluoro-phenyl]methyl, [3-(dimethylcarbamoyl)-4-fluoro-phenyl]methyl, [4-(aminomethyl)phenyl], [4-[[(2,2-difluoroacetyl)amino]methyl]phenyl], (4-carbamoylphenyl), pyridin-4-ylmethyl, 3-methoxypropyl, (3-cyano-4-fluoro-phenyl)methyl, [3-[[(2,2-difluoroacetyl)amino]methyl]-4-fluoro-phenyl]methyl, [3-(aminomethyl)-4-fluoro-phenyl]methyl, (3-carbamoyl-4-fluoro-phenyl)methyl, 2-pyridin-4-ylethyl, (1-methylpyrrol-2-yl)methyl, [4-(difluoromethoxy)phenyl]methyl, (1-benzylpyrrolidin-3-yl), 3-imidazol-1-ylpropyl, (4-dimethylaminophenyl)methyl, (4-methylsulfonylphenyl)methyl, 3-dimethylaminopropyl, 1-pyridin-3-ylethyl, (3-methoxyphenyl), 1-pyridin-4-ylethyl, (4-cyanophenyl), 3-methoxypropyl, benzo[1,3]dioxol-5-ylmethyl, (3,4-dimethoxyphenyl)methyl, (3-methyl-5-phenyl-1,2-oxazol-4-yl)methyl, (5-methyl 1,2-oxazol-3-yl)methyl, [2-(trifluoromethyl)phenyl]methyl, (2-chlorophenyl)methyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-thiophen-2-ylethyl, 2-(4-methoxyphenyl)ethyl, phenethyl, 2-methoxyethyl, (4-fluorophenyl)methyl, methoxycarbonylmethyl, benzotriazol-1-ylmethyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro;

or an enantiomer thereof.

27. A compound according to any of claims 1 to 13 wherein

R1 is 2-(4-chlorophenyl)propyl;

R^2 is tert-butyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5- R^7 are independently selected from hydrogen, -OH, bromo, fluoro, chloro, methyl, $-OCH_3$, $-OCH_2F$, trimethylsilyl;
or an enantiomer thereof.

28. A compound according to any of claims 1 to 13 wherein
R^1 is 2-(4-fluorophenyl)propyl;
R^2 is 4,4,4-trifluorobutyl, benzyl, tert-butyl, butyl,
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, -OH, bromo, fluoro, chloro, methoxy;
or an enantiomer thereof.

29. A compound according to any of claims 1 to 13 wherein
R^1 is 2,2-dimethylpropyl;
R^2 is [3-(trifluoromethoxy)phenyl]methyl, [3-(difluoromethoxy)phenyl]methyl, (3,4-dichlorophenyl)methyl, 2-[3-(trifluoromethyl)phenyl]ethyl, 2-(1H-indol-3-yl)ethyl, (3-chlorophenyl)methyl, [4-(difluoromethoxy)phenyl]methyl, [3-(trifluoromethyl)phenyl]methyl, 2-(3-fluorophenyl)ethyl, 2-(2-chlorophenyl)ethyl, 2-(3-chlorophenyl)ethyl, 2-(2,4-dichlorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(2,6-dichlorophenyl)ethyl, benzo[1,3]dioxol-5-ylmethyl,
or phenylmethyl;
R^3 is hydrogen;
R^4 is hydrogen;
R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro,
or an enantiomer thereof.

30. A compound according to any of claims 1 to 13 wherein
R^1 is 2-phenylpropan-2-yl;
R^2 is benzyl, 1-phenylethyl, (4-fluorophenyl)methyl,4,4,4-trifluorobutyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro,

or an enantiomer thereof.

31. A compound according to any of claims 1 to 13 wherein

R^1 is 1-phenylpropyl;

R^2 is benzyl, (2-chlorophenyl)methyl, [2-(trifluoromethyl)phenyl]methyl or(4-dimethylaminophenyl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro;

or an enantiomer thereof.

32. A compound according to any of claims 1 to 13 wherein

R^1 is [2-(4-chlorophenyl)-2-methyl-propyl];

R^2 is n-butyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro or chloro;

or an enantiomer thereof.

33. A compound according to any of claims 1 to 13 wherein

R^2 is (2-chlorophenyl)methyl;

R^1 is benzhydryl, (2-pyridin-3-ylphenyl)methyl, (3,4-difluorophenyl)methyl 1-(1H-indol-3-yl)propan-2-yl, 2-(4-chlorophenyl)propyl, (2,5-dimethylphenyl)methyl, [(1R)-1-(4-methoxyphenyl)ethyl], 2-(1H-indol-3-yl)propyl, [(1R)-1-(3-methoxyphenyl)ethyl], [(1S)-1-naphthalen-1-ylethyl], 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenethyl,

4-phenylbutan-2-yl, (2-phenylphenyl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

34. A compound according to any of claims 1 to 13 wherein

R^2 is (3,4-dichlorophenyl)methyl;

R^1 is (3-hydroxy-2,2-dimethyl-propyl), 2,2-dimethylpropyl, 2-methylpropyl or 3,3-dimethylbutyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

35. A compound according to any of claims 1 to 13 wherein

R^2 is (3-chlorophenyl)methyl;

R^1 is (3-hydroxy-2,2-dimethyl-propyl), 2-methylpropyl, 2,2-dimethylpropyl, 3,3-dimethylbutyl, (4-hydroxyphenyl)methyl or (3-cyanophenyl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

36. A compound according to any of claims 1 to 13 wherein

R^2 is (3-cyano-4-fluoro-phenyl)methyl;

R^1 is (2-chloro-4-fluoro-phenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl, (3-cyano-4-fluoro-phenyl)methyl, 2-phenylethyl, benzyl, (3,4-difluorophenyl)methyl, (2-phenylphenyl)methyl or 2-(4-chlorophenyl)propyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

37. A compound according to any of claims 1 to 13 wherein

R^2 is (3-cyanophenyl)methyl;

R^1 is (2-phenylphenyl)methyl, (3-chlorophenyl)methyl, (3,4-difluorophenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl or [4-(trifluoromethyl)phenyl]methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

38. A compound according to any of claims 1 to 13 wherein

R^2 is (4-fluorophenyl)methyl;

R^1 is [(4-chlorophenyl)-pyridin-4-yl-methyl], [(4-fluorophenyl)-pyridin-3-yl-methyl], (phenyl-pyridin-2-yl-methyl), 2-(4-methoxyphenyl)ethyl, (4-chlorophenyl)methyl (2-phenylphenyl)methyl, benzhydryl, (2-pyridin-3-ylphenyl)methyl, (3,4-difluorophenyl)methyl, (1-fluoro-3-phenyl-propan-2-yl), (1-methylpyrrol-2-yl)methyl, (2-phenylphenyl)methyl, 2-(4-chlorophenyl)propyl, 1-(4-chlorophenyl)ethyl, 2-(4-chlorophenyl)propan-2-yl, 2-(4-fluorophenyl)propan-2-yl, 2-phenylpropan-2-yl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

39. A compound according to any of claims 1 to 13 wherein

R^2 is (4-hydroxyphenyl)methyl;

R^1 represents (3,4-difluorophenyl)methyl, (3-chlorophenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl or [4-(trifluoromethyl)phenyl]methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

40. A compound according to any of claims 1 to 13 wherein

R^2 is [(2-trifluoromethyl)phenyl]methyl;

R^1 is (2-methoxyphenyl)methyl, (2-fluorophenyl)methyl, benzhydryl, 2-(4-chlorophenyl)ethyl, [4-(piperidine-1-carbonyl)phenyl]methyl, 2-(4-chlorophenyl)propyl, (2-phenylphenyl)methyl, 1-phenylpropyl, 2-phenylpropyl, 4-phenylbutan-2-yl, 2-phenylethyl, 3-phenylpropyl, 2-methylbutyl, cyclohexylmethyl, (3-fluorophenyl)methyl, (2-ethoxyphenyl)methyl, [4-(trifluoromethoxy)phenyl]methyl or (3,4-difluorophenyl)methyl

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, methoxy or methyl;

or an enantiomer thereof.

41. A compound according to any of claims 1 to 13 wherein

R^2 is [3-difluoromethoxy)phenyl]methyl;

R^1 is 1-phenylethyl, (3-hydroxy-2,2-dimethyl-propyl), 3,3-dimethylbutyl or 2,2-dimethylpropyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 - R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

42. A compound according to any of claims 1 to 13 wherein

R^2 is [3-trifluoromethoxy)phenyl]methyl;

R^1 represents 3,3-dimethylbutyl or 2,2-dimethylpropyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

43. A compound according to any of claims 1 to 13 wherein

R^2 is [3-trifluoromethyl)phenyl]methyl;

R^1 is (3-hydroxy-2,2-dimethyl-propyl), 2-methylpropyl, 3,3-dimethylbutyl, 2,2-dimethylpropyl or (1-methylpyrrol-2-yl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

44. A compound according to any of claims 1 to 13 wherein

R^2 is [4-difluoromethoxy)phenyl]methyl;

R^1 is 2-methylpropyl, 3,3-dimethylbutyl, 2,2-dimethylpropyl, (2-chloro-4-fluoro-phenyl)methyl, 2-(4-chlorophenyl)propyl or [3,5-bis(trifluoromethyl)phenyl]methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

45. A compound according to any of claims 1 to 13 wherein

R^2 is [6-(trifluoromethyl)pyridin-3-yl]methyl;

R^1 is 2-(4-chlorophenyl)propyl or (2-phenylphenyl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

46. A compound according to any of claims 1 to 13 wherein

R^2 is 2-(1H-indol-3-yl)ethyl;

R^1 is 2-(4-chlorophenyl)propyl, 2-(2-phenoxyphenyl)ethyl, 2-[4-(diethylcarbamoyl)phenyl]ethyl, 2-(3-fluorophenyl)ethyl, 2-[2-(trifluoromethoxy)phenyl]ethyl, 2-(4-fluorophenyl)ethyl, 2-(3,5-dimethoxyphenyl)ethyl, 2-(4-phenylphenyl)ethyl, 2-(4-phenoxyphenyl)ethyl, 2-(2-ethoxyphenyl)ethyl or 2-benzo[1,3]dioxol-5-ylethyl, 2,2-dimethylpropyl; 3,3-dimethylbutyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

47. A compound according to any of claims 1 to 13 wherein

R^2 is 2-(2,4-dichlorophenyl)ethyl;

R^1 is 2-methylpropyl, 3,3-dimethylbutyl or 2,2-dimethylpropyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

48. A compound according to any of claims 1 to 13 wherein

R^2 is 2-(2,6-dichlorophenyl)ethyl;

R^1 is 2-methylpropyl, 3,3-dimethylbutyl or 2,2-dimethylpropyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

49. A compound according to any of claims 1 to 13 wherein

R^2 is 4,4,4-trifluorobutyl;

R^1 is [2-(trifluoromethyl)phenyl]methyl, [(1R)-1-phenylethyl], benzhydryl, 2-(4-chlorophenyl)propyl, (2-phenylphenyl)methyl, (2-phenoxyphenyl)methyl, (2-phenylphenyl)methyl, 2-(4-chlorophenyl)ethyl, 2-(4-fluorophenyl)ethyl, 2-(4-fluorophenyl)propyl, 2-(4-chlorophenyl)propan-2-yl, 2-(4-fluorophenyl)propan-2-yl or 2-phenylpropan-2-yl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, –OH, methyl, bromo, fluoro and chloro;

or an enantiomer thereof.

50. A compound according to any of claims 1 to 13 wherein

R^2 is 4,4-difluorobutyl;

R^1 is (2-cyclopentylphenyl)methyl, [2-(trifluoromethyl)phenyl]methyl, [(1R)-1-phenylethyl], (2-phenylphenyl)methyl, benzhydryl, 2-(4-chlorophenyl)propyl or (2-phenylphenyl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro;

or an enantiomer thereof.

51. A compound according to any of claims 1 to 13 wherein

R^2 is benzyl;

R^1 is benzyl, benzhydryl, [2-(trifluoromethyl)phenyl]methyl, (2-pyridin-3-ylphenyl)methyl, (4-phenoxyphenyl)methyl, (2,4-difluorophenyl)methyl, [4-(difluoromethoxy)phenyl]methyl, [3-(difluoromethoxy)phenyl]methyl, (3-pyrrol-1-ylphenyl)methyl, (3-fluorophenyl)methyl, (4-cyanophenyl)methyl, (3,5-dimethoxyphenyl)methyl, (2-methoxyphenyl)methyl, (2-ethoxyphenyl)methyl, [4-(trifluoromethyl)phenyl]methyl, (3,4-difluorophenyl)methyl, (2,5-dimethylphenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl, (2-methylphenyl)methyl, (2,3-difluorophenyl)methyl, (2-bromophenyl)methyl, [(4-fluorophenyl)-pyridin-3-yl-methyl], [(4-chlorophenyl)-pyridin-4-yl-methyl], (phenyl-pyridin-2-yl-methyl), (1-methyl-5-phenyl-pyrazol-3-yl)methyl, (5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl, (5-methyl-3-phenyl-1,2-oxazol-4-yl)methyl, (3-phenyl1,2-oxazol-5-yl)methyl, 2-(4-chlorophenyl)ethyl, 2-(4-fluorophenyl)ethyl, 2-[4-(trifluoromethyl)phenyl]ethyl, 2-(5-bromo-2-methoxy-phenyl)ethyl, 2-(3-bromo-4-methoxy-phenyl)ethyl, 2-(4-fluorophenyl)propyl, 2-(4-chlorophenyl)propyl, 4-phenylbutan-2-yl, [2-(4-chloro-2-methyl-phenyl)-2,2-difluoro-ethyl], 2-naphthalen-1-ylpropyl, (2-methyl-2-phenyl-propyl), 2-phenoxypropyl, 2-(4-fluorophenoxy)propyl, 2-phenylpropan-2-yl, cycloheptyl, 2-(2-methoxyphenyl)ethyl, 1-naphthalen-1-ylethyl, 2-[3-(trifluoromethyl)phenyl]ethyl, 2-(6-chloro-1H-indol-3-yl)ethyl, 2-(4-chlorophenyl)propyl, [(1R)-1-(4-methoxyphenyl)ethyl], [(1R)-1-(3-methoxyphenyl)ethyl], 4-phenylbutan-2-yl, 1-phenylethyl, 2-phenylethyl, 1-naphthalen-2-ylethyl, 2-(1-cyclohexenyl)ethyl, 1-(4-fluorophenyl)ethyl, 2-(4-fluorophenyl)propan-2-yl, 2-phenylpropan-2-yl, 1-phenylpropyl or (2-phenylphenyl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro and chloro, -OH, methyl, or methoxy;

or an enantiomer thereof.

52. A compound according to any of claims 1 to 13 wherein

R^2 is n-butyl;

R^1 is (2-phenylphenyl)methyl, (2-phenoxyphenyl)methyl, [2-(4-fluorophenoxy)phenyl]methyl, 2-(3-fluorophenyl)ethyl, 2-(4-fluorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-[4-(trifluoromethyl)phenyl]ethyl, 2-(4-chlorophenyl)propyl, 2-(4-fluorophenyl)propyl, (2-phenylphenyl)methyl, 2-(4-phenylphenyl)ethyl, 2-naphthalen-1-ylpropyl,

2-(2-ethoxyphenyl)ethyl, 2-(2-phenoxyphenyl)ethyl, 2-(4-phenoxyphenyl)ethyl, 2-[2-(trifluoromethoxy)phenyl]ethyl, 2-(3,5-dimethoxyphenyl)ethyl, 2-benzo[1,3]dioxol-5-ylethyl, (1-fluoro-3-phenyl-propan-2-yl), 2-(4-chlorophenyl)propyl, naphthalen-1-ylmethyl, 1-naphthalen-2-ylethyl, (2-phenylphenyl)methyl, [2-(4-chlorophenyl)-2-methyl-propyl];

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH, methyl, methoxy;

or an enantiomer thereof.

53. A compound according to any of claims 1 to 13 wherein

R^2 is ethyl;

R^1 is benzhydryl, (2-phenylphenyl)methyl or 2-(4-chlorophenyl)propyl

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH, methyl, methoxy;

or an enantiomer thereof.

54. A compound according to any of claims 1 to 13 wherein

R^2 is 2-phenylethyl;

R^1 is (2-phenylphenyl)methyl, 2-(4-methoxyphenyl)ethyl, (4-chlorophenyl)methyl, 2-(4-chlorophenyl)ethyl, 2-(3,4-dichlorophenyl)ethyl, (3,4-difluorophenyl)methyl, 2-(4-chlorophenyl)propyl, (2-chloro-4-fluoro-phenyl)methyl or 4-phenylbutan-2-yl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH, methyl, methoxy;

or an enantiomer thereof.

55. A compound according to any of claims 1 to 13 wherein

R^2 is propyl;

R^1 is (2-phenylphenyl)methyl, benzhydryl or 2-(4-chlorophenyl)propyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH, methyl, methoxy;

or an enantiomer thereof.

56. A compound according to any of claims 1 to 13 wherein

R^2 is pyridin-3-ylmethyl or pyridin-4-ylmethyl;

R^1 is (2-phenylphenyl)methyl, 2-(4-chlorophenyl)propyl, (3,4-difluorophenyl)methyl, (2-chloro-4-fluoro-phenyl)methyl or 1-(4-fluorophenyl)ethyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro, -OH;

or an enantiomer thereof.

57. A compound according to any of claims 1 to 13 wherein

R^2 is tert-butyl;

R^1 is (2-phenylphenyl)methyl, [2-(trifluoromethyl)phenyl]methyl, [4-(difluoromethoxy)phenyl]methyl, (2-chlorophenyl)methyl, (2-methoxyphenyl)methyl, (3,4-difluorophenyl)methyl, (3,4-difluorophenyl)methyl, (4-phenoxyphenyl)methyl, [3,5-bis(trifluoromethyl)phenyl]methyl, (4-fluoro-2-phenyl-phenyl)methyl, (5-fluoro-2-phenyl-phenyl)methyl, 1-phenylethyl, 2-(4-chlorophenyl)ethyl, 2-(2-phenoxyphenyl)ethyl, 2-[2-(trifluoromethoxy)phenyl]ethyl, 2,2-diphenylethyl, 2-(4-fluorophenyl)propyl, 2-(4-chlorophenyl)propyl, (2-phenylphenyl)methyl, 2-(4-phenylphenyl)ethyl, [2-(3-fluorophenyl)phenyl]methyl, [2-(4-fluorophenyl)phenyl]methyl, [2-(3,4-difluorophenyl)phenyl]methyl, [2-(2,4-difluorophenyl)phenyl]methyl, [2-(2,5-difluorophenyl)phenyl]methyl, [2-(2,4-dichlorophenyl)phenyl]methyl, [2-(3,4-dichlorophenyl)phenyl]methyl, [2-(2-chlorophenyl)phenyl]methyl, [2-(4-chlorophenyl)phenyl]methyl,

[2-(4-methylphenyl)phenyl]methyl, [2-(4-fluoro-2-methyl-phenyl)phenyl]methyl,

[2-(4-methoxyphenyl)phenyl]methyl, [4-fluoro-2-(4-fluorophenyl)phenyl]methyl, [2-(3-chloro-4-fluoro-phenyl)phenyl]methyl, [2-(4-fluoro-2-methyl-phenyl)phenyl]methyl, [5-fluoro-2-(4-fluorophenyl)phenyl]methyl, benzhydryl, [(1R)-2-(4-chlorophenyl)-1-(4,4,4-trifluorobutylcarbamoyl)ethyl], [3,5-bis(trifluoromethyl)phenyl]methyl, 9H-fluoren-9-yl, [2-[4-(trifluoromethyl)phenoxy]phenyl]methyl, 2-naphthalen-1-ylpropyl, [(1R)-2-(4-chlorophenyl)-1-methoxycarbonyl-ethyl], (1-methyl-5-phenyl-pyrazol-3-yl)methyl or [2-(4-chloro-2-methyl-phenyl)-2,2-difluoro-ethyl], (3-phenylphenyl)methyl, (4-fluorophenyl)methyl, (4-phenylphenyl)methyl, [(4-chlorophenyl)-pyridin-4-yl-methyl], 2-(4-fluorophenyl)propyl or 2-(4-phenoxyphenyl)ethyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently –OH, bromo, chloro, fluoro, methyl, methoxy methylsulfonylamino, trimethylsilyl, cyano, $-OCHF_2$, $-OCH_2F$, $-OSO_2CF_3$,

or an enantiomer thereof.

58. A compound according to any of claims 1 to 13 wherein

R^2 is trimethylsilylmethyl;

R^1 is [3-(difluoromethoxy)phenyl]methyl, [4-(difluoromethoxy)phenyl]methyl, naphthalen-1-ylmethyl, 1-naphthalen-1-ylethyl, 2-(4-bromophenyl)ethyl, (2-chloro-6-phenoxy-phenyl)methyl or (3,4-dichlorophenyl)methyl;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 to R^7 are independently selected from hydrogen, bromo, fluoro, chloro;

or an enantiomer thereof.

59. A compound selected from one or more of the following group consisting of:

(1R or 1S)-N-(4,4-difluorobutyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (E2);

(1S or 1R)-N-(4,4-difluorobutyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide (E1);

(1R or 1S)-N-benzyl-3-oxo-2-[(1S or 1R)-1-phenylethyl]isoindoline-1-carboxamide (E4);

(1S or 1R)-N-benzyl-3-oxo-2-[(1S or 1R)-1-phenylethyl]isoindoline-1-carboxamide (E3);

(1R or 1S)-N-benzyl-3-oxo-2-[(1R or 1S)-1-phenylethyl]isoindoline-1-carboxamide (E2);
(1S or 1R)-N-benzyl-3-oxo-2-[(1R or 1S)-1-phenylethyl]isoindoline-1-carboxamide (E1);
N-benzyl-6-cyano-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-[(methylsulfonyl)amino]-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-4-methyl-5-[(methylsulfonyl)amino]-3-oxoisoindoline-1-carboxamide;
N-(3-chlorobenzyl)-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-6-cyano-3-oxoisoindoline-1-carboxamide;
N-benzyl-6-chloro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;
N-benzyl-2-[2-(4-chlorophenyl)ethyl]-1-hydroxy-3-oxoisoindoline-1-carboxamide;
2-[2-(4-chlorophenyl)propyl]-N-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[(1-methyl-5-phenyl-1H-pyrazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-6-bromo-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[(4'-fluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-5-bromo-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide;
N-butyl-2-[2-(4-fluorophenoxy)benzyl]-3-oxoisoindoline-1-carboxamide;
N-(4,4-difluorobutyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(4,4-difluorobutyl)-3-oxoisoindoline-1-carboxamide;
(R or S)2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide(E1);
(S o R) 2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (E2);
2-(biphenyl-2-ylmethyl)-N-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]-6-fluoro-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-1-[(tert-butylamino)carbonyl]-4-methyl-3-oxo-2,3-dihydro-1H-isoindol-5-yl methanesulfonate;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-(difluoromethoxy)-4-methyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-(fluoromethoxy)-4-methyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-1-[(tert-butylamino)carbonyl]-4-methyl-3-oxo-2,3-dihydro-1H-isoindol-5-yl trifluoromethanesulfonate;

N-(tert-butyl)-2-{(1R)-1-(4-chlorobenzyl)-2-oxo-2-[(4,4,4-trifluorobutyl)amino]ethyl}-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-chlorophenyl)ethyl]-N-methyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-4,7-difluoro-1-methyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-4-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-7-hydroxy-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-(4-chlorobenzyl)-7-hydroxy-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-(4-chlorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(4-{[(difluoroacetyl)amino]methyl}benzyl)-3-oxoisoindoline-1-carboxamide;

N-{4-[(acetylamino)methyl]benzyl}-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(4-{[(fluoroacetyl)amino]methyl}benzyl)-3-oxoisoindoline-1-carboxamide;

N-[4-(aminomethyl)benzyl]-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide;

methyl (2R)-2-{1-[(tert-butylamino)carbonyl]-3-oxo-1,3-dihydro-2H-isoindol-2-yl}-3-(4-chlorophenyl)propanoate;

2-(biphenyl-2-ylmethyl)-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[(5-methylisoxazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

(1S or 1R)-N-butyl-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (E2);

(1R or 1S)-N-butyl-2-[(2S or 2R)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (E4);

(1R or 1S)-N-butyl-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (E3);

(1S or 1R)-N-butyl-2-[(2S or 2R)-2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide (E1);

N-butyl-2-[2-(4-chlorophenyl)propyl]-6-fluoro-3-oxoisoindoline-1-carboxamide;

(S or R)2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide;

(R or S)2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide;

2-(2-bromobenzyl)-N-tert-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(1-methyl-1-phenylethyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-3-oxo-2-(1-phenylpropyl)isoindoline-1-carboxamide;

N-[3-(difluoromethoxy)benzyl]-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;

N,2-dibenzyl-6-bromo-3-oxoisoindoline-1-carboxamide;

6-bromo-2-(2-cyclopentylbenzyl)-N-(4,4-difluorobutyl)-3-oxoisoindoline-1-carboxamide;

2-(2-cyclopentylbenzyl)-N-(4,4-difluorobutyl)-6-fluoro-3-oxoisoindoline-1-carboxamide;

6-bromo-2-(2-cyclopentylbenzyl)-N-methyl-3-oxoisoindoline-1-carboxamide;

2-(2-cyclopentylbenzyl)-6-fluoro-N-methyl-3-oxoisoindoline-1-carboxamide;

6-chloro-2-(2-cyclopentylbenzyl)-N-(4,4-difluorobutyl)-3-oxoisoindoline-1-carboxamide;

6-chloro-2-(2-cyclopentylbenzyl)-N-methyl-3-oxoisoindoline-1-carboxamide;

2-(2-cyclopentylbenzyl)-N-(4,4-difluorobutyl)-3-oxoisoindoline-1-carboxamide;

2-(2-cyclopentylbenzyl)-N-methyl-3-oxoisoindoline-1-carboxamide;

N-benzyl-6-chloro-3-oxo-2-[(1S)-1-phenylethyl]isoindoline-1-carboxamide;

6-chloro-N-(2-methoxyethyl)-3-oxo-2-[2,2,2-trifluoro-1-(3-fluorophenyl)ethyl]isoindoline-1-carboxamide;

N-benzyl-6-chloro-2-(dipyridin-3-ylmethyl)-3-oxoisoindoline-1-carboxamide;

6-chloro-N-methyl-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-6-fluoro-N-methyl-3-oxoisoindoline-1-carboxamide;

6-fluoro-N-methyl-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

6-chloro-2-[2-(4-chlorophenyl)propyl]-N-methyl-3-oxoisoindoline-1-carboxamide;

6-chloro-N-methyl-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-methyl-3-oxoisoindoline-1-carboxamide;

6-chloro-N-ethyl-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;
N-benzyl-5-[(methylsulfonyl)amino]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;
N-benzyl-4-methyl-5-[(methylsulfonyl)amino]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;
N-benzyl-5-cyano-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;
N-benzyl-5-bromo-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;
N-benzyl-6-bromo-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;
N-[3-(difluoromethoxy)benzyl]-6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
N-(3,4-dichlorobenzyl)-6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
N-(3-chlorobenzyl)-6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
6-fluoro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;
6-chloro-N-[3-(difluoromethoxy)benzyl]-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
6-chloro-N-(3,4-dichlorobenzyl)-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
6-chloro-N-(3-chlorobenzyl)-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
6-chloro-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;
N-(3,4-dichlorobenzyl)-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
N-[3-(difluoromethoxy)benzyl]-2-(3-hydroxy-2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
2-(3-hydroxy-2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;
N-(4,4-difluorobutyl)-6-fluoro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

6-chloro-N-(4,4-difluorobutyl)-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

6-chloro-N-(4,4-difluorobutyl)-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

N-(4,4-difluorobutyl)-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

N-(tert-butyl)-6-fluoro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-(tert-butyl)-6-chloro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

3-oxo-N-(4,4,4-trifluorobutyl)-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

6-chloro-3-oxo-N-(4,4,4-trifluorobutyl)-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-(tert-butyl)-6-fluoro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

6-fluoro-3-oxo-2-[(1R)-1-phenylethyl]-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

N-(tert-butyl)-6-chloro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

6-chloro-3-oxo-2-[(1R)-1-phenylethyl]-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

3-oxo-2-[(1R)-1-phenylethyl]-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

6-chloro-N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

N-benzyl-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-[(5-methylpyrazin-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide;

N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-2-(biphenyl-2-ylmethyl)-6-chloro-3-oxoisoindoline-1-carboxamide;

N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[(4-fluorophenyl)(pyridin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-3-oxo-2-[phenyl(pyridin-2-yl)methyl]isoindoline-1-carboxamide;

N-butyl-2-[(4-chlorophenyl)(pyridin-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-[(4-chlorophenyl)(pyridin-4-yl)methyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

6-chloro-2-(diphenylmethyl)-N-ethyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-6-chloro-N-ethyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-propylisoindoline-1-carboxamide;

2-(diphenylmethyl)-N-ethyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-ethyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-6-fluoro-3-oxo-N-propylisoindoline-1-carboxamide;

N-(4-fluorobenzyl)-2-[(4-fluorophenyl)(pyridin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[(4-fluorophenyl)(pyridin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[(5-methylpyrazin-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

6-chloro-2-[2-(4-chlorophenyl)propyl]-N-[(5-methylpyrazin-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-6-chloro-N-[(5-methylpyrazin-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide;

6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide;

N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-3-oxo-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}isoindoline-1-carboxamide;

N-benzyl-6-fluoro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

6-fluoro-N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;

N-benzyl-6-chloro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-benzyl-6-fluoro-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

6-chloro-N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

6-chloro-N-[2-chloro-4-(methylsulfonyl)benzyl]-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;

N-[2-chloro-4-(methylsulfonyl)benzyl]-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;

6-chloro-2-(diphenylmethyl)-N-[2-fluoro-4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-(diphenylmethyl)-N-[2-fluoro-4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

6-chloro-2-(diphenylmethyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide;

6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-cyano-3-oxoisoindoline-1-carboxamide;

6-chloro-2-(diphenylmethyl)-3-oxo-N-propylisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-ethyl-6-fluoro-3-oxoisoindoline-1-carboxamide;

2-(diphenylmethyl)-N-ethyl-6-fluoro-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-ethyl-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-6-fluoro-3-oxo-N-propylisoindoline-1-carboxamide;

2-(diphenylmethyl)-6-fluoro-3-oxo-N-propylisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-3-oxo-N-propylisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-propylisoindoline-1-carboxamide;

2-(diphenylmethyl)-3-oxo-N-propylisoindoline-1-carboxamide;

2-(diphenylmethyl)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

2-(diphenylmethyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;
N-(tert-butyl)-2-[(4-chlorophenyl)(pyridin-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-(4-fluorobenzyl)-3-oxo-2-[phenyl(pyridin-2-yl)methyl]isoindoline-1-carboxamide;
N-benzyl-2-[(4-chlorophenyl)(pyridin-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-3-oxo-2-[phenyl(pyridin-2-yl)methyl]isoindoline-1-carboxamide;
2-(2,2-dimethylpropyl)-N-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;
2-(2,2-dimethylpropyl)-N-[(1-methyl-5-phenyl-1H-pyrazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-butyl-2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[(1-methyl-5-phenyl-1H-pyrazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-(biphenyl-2-ylmethyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-5-hydroxy-4-methyl-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;
2-(biphenyl-2ylmethyl)-5-hydroxy-4-methyl-3-oxo-N-propylisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-ethyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[(2',4'-dichlorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[(3',4'-dichlorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[(2'-chlorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[(3'-chloro-4'-fluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[(4'-chlorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[(4'-fluoro-2'-methylbiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(2',4'-difluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(2',5'-difluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(3'-fluorobiphenyl-2-yl)methyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N-butyl-3-oxo-2-(2-phenoxybenzyl)isoindoline-1-carboxamide;

N-[3-(difluoromethoxy)benzyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;

2-(3,3-dimethylbutyl)-3-oxo-N-[3-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide;

N-[3-(difluoromethoxy)benzyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;

6-chloro-2-(diphenylmethyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

6-chloro-2-(diphenylmethyl)-N-(2-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-6-chloro-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-6-chloro-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-6-chloro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-6-chloro-N-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(biphenyl-2-ylmethyl)-6-chloro-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-6-chloro-3-oxoisoindoline-1-carboxamide;

6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

6-chloro-2-[2-(4-chlorophenyl)propyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-6-chloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-4,5-dimethoxy-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;

2-[1-(1,5-dimethyl-1H-pyrazol-4-yl)ethyl]-5,7-dimethoxy-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

5,7-dimethoxy-2-(2-methoxybenzyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-(2-fluorobenzyl)-5,7-dimethoxy-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-(tert-butyl)-5,7-dimethoxy-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;

3-oxo-2-(2-phenoxybenzyl)-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-(3,4-dichlorobenzyl)-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-N-(1H-indol-3-ylmethyl)-3-oxoisoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-3-oxo-N-{2-[3-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-6-fluoro-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(biphenyl-2-ylmethyl)-6-fluoro-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)ethyl]-N-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]-6-fluoro-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)ethyl]-6-fluoro-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(4-chlorophenyl)ethyl]-6-fluoro-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[2-(4-chlorophenyl)ethyl]-6-fluoro-3-oxoisoindoline-1-carboxamide;

6-fluoro-2-[2-(4-fluorophenyl)ethyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

N-benzyl-6-fluoro-2-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-6-fluoro-2-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

6-fluoro-2-[2-(4-fluorophenyl)propyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

N-benzyl-6-fluoro-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-6-fluoro-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-1-methyl-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-4,7-difluoro-1-methyl-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-chlorophenyl)propyl]-1-methyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(diphenylmethyl)-5-methoxy-3-oxoisoindoline-1-carboxamide;
2-(diphenylmethyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-1-methyl-3-oxoisoindoline-1-carboxamide;
N-butyl-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-methoxy-4-methyl-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-1-[(tert-butylamino)carbonyl]-4-methyl-3-oxo-2,3-dihydro-1H-isoindol-5-yl dimethylcarbamate;
2-(biphenyl-2-ylmethyl)-5-hydroxy-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;
5-hydroxy-2-[2-(4-methoxyphenyl)ethyl]-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;
2-(4-chlorobenzyl)-5-hydroxy-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;
N-(4-fluorobenzyl)-5-hydroxy-2-[2-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
2-[2-(3,4-dichlorophenyl)ethyl]-N-(4-fluorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide;
2-(4-chlorobenzyl)-N-(4-fluorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(4-fluorobenzyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(3,4-dichlorophenyl)ethyl]-5-hydroxy-3-oxoisoindoline-1-carboxamide;
N-(3,4-dichlorobenzyl)-2-isobutyl-3-oxoisoindoline-1-carboxamide;
N-[2-(1H-indol-3-yl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;
N-(3-chlorobenzyl)-2-isobutyl-3-oxoisoindoline-1-carboxamide;
N-[4-(difluoromethoxy)benzyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;
2-isobutyl-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;
N-(1H-indol-3-ylmethyl)-2-isobutyl-3-oxoisoindoline-1-carboxamide;
N-[2-(1,3-benzodioxol-5-yl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;
N-[2-(3-fluorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;
2-isobutyl-3-oxo-N-{2-[3-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide;
N-[2-(3,4-dichlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;
N-[2-(4-chlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;
N-[2-(3-chlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;
N-[2-(2-chlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;

N-[2-(2,4-dichlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;
N-[2-(2,6-dichlorophenyl)ethyl]-2-isobutyl-3-oxoisoindoline-1-carboxamide;
2-(3,3-dimethylbutyl)-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-(3-chlorobenzyl)-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
N-(3,4-dichlorobenzyl)-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
2-(3,3-dimethylbutyl)-N-(1H-indol-3-ylmethyl)-3-oxoisoindoline-1-carboxamide;
N-[4-(difluoromethoxy)benzyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
2-(3,3-dimethylbutyl)-N-[2-(3-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-[2-(1,3-benzodioxol-5-yl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
N-[2-(3-cyanophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
2-(3,3-dimethylbutyl)-3-oxo-N-{2-[3-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide;
N-[2-(3-chlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
N-[2-(3,4-dichlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
N-[2-(4-chlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
N-[2-(2-chlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
N-[2-(2,4-dichlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;
2-(2,2-dimethylpropyl)-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-(3-chlorobenzyl)-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
N-[4-(difluoromethoxy)benzyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
2-(2,2-dimethylpropyl)-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;
N-[2-(1,3-benzodioxol-5-yl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
2-(2,2-dimethylpropyl)-N-[2-(3-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-[2-(3-cyanophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
N-[2-(2-chlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
N-[2-(3-chlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
N-[2-(2,4-dichlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;
2-[2-(4-chlorophenyl)ethyl]-N-ethyl-3-oxo-N-(2-pyridin-2-ylethyl)isoindoline-1-carboxamide;
2-[2-(4-chlorophenyl)ethyl]-3-(1,3-dihydro-2H-isoindol-2-ylcarbonyl)isoindolin-1-one;
2-[2-(4-chlorophenyl)ethyl]-N-methyl-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-benzyl-2-[2-(4-chlorophenyl)ethyl]-N-ethyl-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[2-(4-chlorophenyl)ethyl]-N-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-3-oxo-2-{2-[4-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide;
N-butyl-3-oxo-2-{2-[4-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide;
N-benzyl-3-oxo-2-{2-[4-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide;
N-(tert-butyl)-5-hydroxy-2-[2-(1H-indol-3-yl)ethyl]-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(4-fluorophenyl)propyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
2-[3,5-bis(trifluoromethyl)benzyl]-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-(2,2-diphenylethyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-(diphenylmethyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-(9H-fluoren-9-yl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-5-hydroxy-4-methyl-3-oxo-2-{2-[4-(trifluoromethyl)phenoxy]benzyl}isoindoline-1-carboxamide;
2-(biphenyl-3-ylmethyl)-N-(tert-butyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-butyl-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;
N-butyl-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[2-(4-fluorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-[2-(1H-indol-3-yl)ethyl]-3-oxo-2-[4-(piperidin-1-ylcarbonyl)benzyl]isoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(2,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(4-cyano-2,6-difluorobenzyl)-3-oxoisoindoline-1-carboxamide;
N-(2,4-difluorobenzyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;
N-(2-chlorobenzyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;
2-(diphenylmethyl)-N-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-(diphenylmethyl)-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-(2,4-difluorobenzyl)-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide;

N-(2-chlorobenzyl)-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide;

N-[2-(4-fluorophenyl)ethyl]-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide;

N-benzyl-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide;

N-(4-fluorobenzyl)-3-oxo-2-(2-pyridin-3-ylbenzyl)isoindoline-1-carboxamide;

N-butyl-5-methoxy-2-(2-methyl-2-phenylpropyl)-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-butyl-5-methoxy-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-fluorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-chlorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-5-methoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(4-fluorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-methoxy-3-oxoisoindoline-1-carboxamide;

N-benzyl-5-methoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-5-methoxy-2-(2-methyl-2-phenylpropyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(biphenyl-2-ylmethyl)-5-methoxy-3-oxoisoindoline-1-carboxamide;

N-butyl-5,6-dimethoxy-2-(2-methyl-2-phenylpropyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[2-(4-chlorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide;

N-butyl-5,6-dimethoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-fluorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-butyl-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-chlorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-5,6-dimethoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-5,6-dimethoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-5,6-dimethoxy-2-(2-methyl-2-phenylpropyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[2-(4-fluorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(biphenyl-2-ylmethyl)-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(diphenylmethyl)-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[2-(4-chlorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-1-methyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-butyl-1-methyl-3-oxoisoindoline-1-carboxamide;

ethyl N-benzyl-N-({2-[2-(4-chlorophenyl)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;

2-[2-(4-chlorophenyl)ethyl]-N-methyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)ethyl]-N,N-diethyl-3-oxoisoindoline-1-carboxamide;

N-benzyl-N-butyl-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-[2-(2,6-dichlorophenyl)ethyl]-2-(3,3-dimethylbutyl)-3-oxoisoindoline-1-carboxamide;

N-[2-(4-chlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;

N-[2-(2,6-dichlorophenyl)ethyl]-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;

N-butyl-5-methoxy-2-[2-(1-naphthyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[2-(4-fluorophenyl)propyl]-5-methoxy-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5,6-dimethoxy-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(4'-fluoro-2'-methylbiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(4'-methylbiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(4'-methoxybiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(4'-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

methyl N-({2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;

methyl N-({2-[(4'-fluoro-2'-methylbiphenyl-2-yl)methyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;

methyl N-({2-[(4'-fluorobiphenyl-2-yl)methyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;

methyl N-({2-[(4'-methylbiphenyl-2-yl)methyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;

2-[(3',4'-difluorobiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[(4'-fluoro-2'-methylbiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[(4'-methoxybiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[(4'-fluorobiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[(4'-methylbiphenyl-2-yl)methyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-(4-chlorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-5-hydroxy-2-[2-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-7-hydroxy-2-[2-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-3-oxoisoindoline-1-carboxamide;

2-[2-(3,4-dichlorophenyl)ethyl]-5-hydroxy-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-(3,4-difluorobenzyl)-2-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide;

N-(3-chlorobenzyl)-2-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide;

2-(4-hydroxybenzyl)-3-oxo-N-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-[3,5-bis(trifluoromethyl)benzyl]-2-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide;

N-(3-chlorobenzyl)-2-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

N-[3,5-bis(trifluoromethyl)benzyl]-2-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(3-cyanobenzyl)-N-(3,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(3-cyanobenzyl)-3-oxo-N-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-[4-(aminocarbonyl)benzyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-[4-(aminocarbonyl)benzyl]-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide;

2-(3,4-difluorobenzyl)-N-{4-[(dimethylamino)methyl]benzyl}-3-oxoisoindoline-1-carboxamide;

2-(3-chlorobenzyl)-N-{4-[(dimethylamino)methyl]benzyl}-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-{4-[(dimethylamino)methyl]benzyl}-3-oxoisoindoline-1-carboxamide;

2-(3,4-difluorobenzyl)-N-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide;

2-(3-chlorobenzyl)-N-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-(4-hydroxybenzyl)-3-oxoisoindoline-1-carboxamide;

2-(3-chlorobenzyl)-N-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

N-(3-cyanobenzyl)-2-(3,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-(3-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-hydroxy-3-oxoisoindoline-1-carboxamide;

N-{4-[(dimethylamino)methyl]benzyl}-3-oxo-2-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-(4-hydroxybenzyl)-3-oxo-2-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-(3-cyanobenzyl)-3-oxo-2-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-(biphenyl-3-ylmethyl)-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-4-ylmethyl)-N-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

N-butyl-3-oxo-2-[2-(2-phenoxyphenyl)ethyl]isoindoline-1-carboxamide;

N-butyl-2-(2-{4-[(diethylamino)carbonyl]phenyl}ethyl)-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(3-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-3-oxo-2-{2-[2-(trifluoromethoxy)phenyl]ethyl}isoindoline-1-carboxamide;

2-(2-biphenyl-4-ylethyl)-N-butyl-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(3,5-dimethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-3-oxo-2-[2-(4-phenoxyphenyl)ethyl]isoindoline-1-carboxamide;

N-butyl-2-[2-(2-ethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(1,3-benzodioxol-5-yl)ethyl]-N-butyl-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-[2-(2-phenoxyphenyl)ethyl]isoindoline-1-carboxamide

N-(tert-butyl)-3-oxo-2-{2-[2-(trifluoromethoxy)phenyl]ethyl}isoindoline-1-carboxamide;

2-(2-biphenyl-4-ylethyl)-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(3,5-dimethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-[2-(4-phenoxyphenyl)ethyl]isoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(2-ethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(1,3-benzodioxol-5-yl)ethyl]-N-(tert-butyl)-3-oxoisoindoline-1-carboxamide;

N-[2-(1H-indol-3-yl)ethyl]-3-oxo-2-[2-(2-phenoxyphenyl)ethyl]isoindoline-1-carboxamide;

2-(2-{4-[(diethylamino)carbonyl]phenyl}ethyl)-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(3-fluorophenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-[2-(1H-indol-3-yl)ethyl]-3-oxo-2-{2-[2-(trifluoromethoxy)phenyl]ethyl}isoindoline-1-carboxamide;

2-[2-(4-fluorophenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(3,5-dimethoxyphenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-(2-biphenyl-4-ylethyl)-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-[2-(1H-indol-3-yl)ethyl]-3-oxo-2-[2-(4-phenoxyphenyl)ethyl]isoindoline-1-carboxamide;
2-[2-(2-ethoxyphenyl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;
2-[2-(1,3-benzodioxol-5-yl)ethyl]-N-[2-(1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;
(1R)-2-[(1S)-1-(4-fluorophenyl)ethyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;
N-[4-(dimethylamino)benzyl]-2-[2-(dimethylamino)-2-phenylethyl]-3-oxoisoindoline-1-carboxamide;
N-[4-(dimethylamino)benzyl]-2-(2,2-diphenylethyl)-3-oxoisoindoline-1-carboxamide;
2-(1-benzyl-2-fluoroethyl)-N-[(5-methylisoxazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-(2-chloro-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
2-(3,4-difluorobenzyl)-N-(4-fluorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide;
2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;
2-(3,4-difluorobenzyl)-5-hydroxy-3-oxo-4-phenyl-N-(2-phenylethyl)isoindoline-1-carboxamide;
N-(2-chlorobenzyl)-2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;
N-(tert-butyl)-2-(2-chlorobenzyl)-5-hydroxy-3-oxo-4-(trimethylsilyl)isoindoline-1-carboxamide;
N-(tert-butyl)-2-(2-chlorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(tert-butyl)-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide;
2-[3,5-bis(trifluoromethyl)benzyl]-N-(tert-butyl)-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-{3-[(dimethylamino)carbonyl]-4-fluorobenzyl}-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-(4-cyanophenyl)-3-oxoisoindoline-1-carboxamide;

2-(1-benzyl-2-fluoroethyl)-N-butyl-3-oxoisoindoline-1-carboxamide;

2-(1-benzyl-2-fluoroethyl)-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(1-benzyl-2-fluoroethyl)-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide;

N-[4-(aminomethyl)phenyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(4-{[(difluoroacetyl)amino]methyl}phenyl)-3-oxoisoindoline-1-carboxamide;

N-[4-(aminocarbonyl)phenyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-(fluoromethoxy)-4-methyl-3-oxoisoindoline-1-carboxamide;

N-[4-(dimethylamino)benzyl]-3-oxo-2-(4-phenylbutyl)isoindoline-1-carboxamide;

N-[4-(dimethylamino)benzyl]-2-(2-hydroxy-2-phenylethyl)-3-oxoisoindoline-1-carboxamide;

N-[4-(dimethylamino)benzyl]-3-oxo-2-[2-(1H-pyrazol-1-yl)benzyl]isoindoline-1-carboxamide;

N-[4-(dimethylamino)benzyl]-3-oxo-2-(4-phenoxybenzyl)isoindoline-1-carboxamide;

N-[4-(dimethylamino)benzyl]-3-oxo-2-[(1-phenyl-1H-pyrazol-4-yl)methyl]isoindoline-1-carboxamide;

N-[4-(dimethylamino)benzyl]-2-[1-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-[4-(dimethylamino)benzyl]-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

N-[4-(dimethylamino)benzyl]-3-oxo-2-(1-phenylpropyl)isoindoline-1-carboxamide;

N-[4-(methylsulfonyl)benzyl]-3-oxo-2-[2-(1H-pyrazol-1-yl)benzyl]isoindoline-1-carboxamide;

2-(2-hydroxy-2-phenylethyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-(2,2-diphenylethyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-(diphenylmethyl)-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide;

N-[4-(methylsulfonyl)benzyl]-3-oxo-2-(1,2,3,4-tetrahydronaphthalen-1-yl)isoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide;

2-[1-(4-fluorophenyl)ethyl]-3-oxo-N-(pyridin-4-ylmethyl)isoindoline-1-carboxamide;
(1S)-2-[(2R)-2-(4-chlorophenyl)propyl]-N-(3-methoxypropyl)-1-methyl-3-oxoisoindoline-1-carboxamide;
(1R)-2-[(2R)-2-(4-chlorophenyl)propyl]-N-(3-methoxypropyl)-1-methyl-3-oxoisoindoline-1-carboxamide;
2-[2-(4-chlorophenyl)propyl]-N-(3-methoxypropyl)-1-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-hydroxy-3-oxo-4-(trimethylsilyl)isoindoline-1-carboxamide;
N-(tert-butyl)-2-(3,4-difluorobenzyl)-5-hydroxy-3-oxo-4-(trimethylsilyl)isoindoline-1-carboxamide;
N-(tert-butyl)-2-(3,4-difluorobenzyl)-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-(3,4-difluorobenzyl)-5-hydroxy-3-oxo-4-phenylisoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide;
2-(2-chloro-4-fluorobenzyl)-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
2-[3,5-bis(trifluoromethyl)benzyl]-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
N,2-bis(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
N-(3-cyano-4-fluorobenzyl)-3-oxo-2-(2-phenylethyl)isoindoline-1-carboxamide;
N-(3-cyano-4-fluorobenzyl)-2-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
2-benzyl-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
N-(3-cyano-4-fluorobenzyl)-2-(3,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide;
2-(biphenyl-2-ylmethyl)-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
2-[2-(4-chlorophenyl)propyl]-N-(3-cyano-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
2-(2-chloro-4-fluorobenzyl)-N-(3-{[(difluoroacetyl)amino]methyl}-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
2-[2-(4-chlorophenyl)propyl]-N-(3-{[(difluoroacetyl)amino]methyl}-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
N-[3-(aminomethyl)-4-fluorobenzyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-[3-(aminocarbonyl)-4-fluorobenzyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-[3-(aminocarbonyl)-4-fluorobenzyl]-2-(2-chloro-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-(4-phenylbutyl)isoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-(1,2,3,4-tetrahydronaphthalen-1-yl)isoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-(4-phenoxybenzyl)isoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-[2-(1H-pyrazol-1-yl)benzyl]isoindoline-1-carboxamide;

N-(tert-butyl)-2-(2,2-diphenylethyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-(diphenylmethyl)-3-oxoisoindoline-1-carboxamide;

N-(1,3-benzodioxol-5-ylmethyl)-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-N-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-(1,3-benzodioxol-5-ylmethyl)-2-(2-chloro-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-N-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-3-oxo-N-(2-pyridin-4-ylethyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(2-pyridin-4-ylethyl)isoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide;

N-(1,3-benzodioxol-5-ylmethyl)-2-[3,5-bis(trifluoromethyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide;

N-(1-benzylpyrrolidin-3-yl)-2-(2-chloro-4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-(1-benzylpyrrolidin-3-yl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-N-{[5-(2-furyl)isoxazol-3-yl]methyl}-3-oxoisoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-N-{[5-(2-furyl)isoxazol-3-yl]methyl}-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-{[5-(2-furyl)isoxazol-3-yl]methyl}-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[3-(1H-imidazol-1-yl)propyl]-3-oxoisoindoline-1-carboxamide;

2-[3,5-bis(trifluoromethyl)benzyl]-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide;

N-(1-benzylpyrrolidin-3-yl)-2-[3,5-bis(trifluoromethyl)benzyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-[(1-phenyl-1H-tetrazol-5-yl)methyl]isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[3-(dimethylamino)propyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[2-(dimethylamino)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide;

N-[2-(4-benzoylpiperazin-1-yl)ethyl]-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(1-pyridin-3-ylethyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(3-methoxyphenyl)-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(1-pyridin-4-ylethyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(4-cyanophenyl)-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(3-methoxypropyl)-3-oxoisoindoline-1-carboxamide;

N-(1,3-benzodioxol-5-ylmethyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(3,4-dimethoxybenzyl)-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[(3-methyl-5-phenylisoxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-chlorophenyl)propyl]-7-fluoro-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-7-fluoro-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-[2-(phenylsulfonyl)ethyl]isoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(4-fluorophenoxy)propyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-3-oxo-2-(2-phenoxypropyl)isoindoline-1-carboxamide;
N-benzyl-2-[(5-methylisoxazol-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[4-(methylsulfonyl)benzyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-3-oxo-2-[2-(phenylsulfonyl)ethyl]isoindoline-1-carboxamide;
N-benzyl-3-oxo-2-(2-phenoxyethyl)isoindoline-1-carboxamide;
N-benzyl-3-oxo-2-(2-phenoxypropyl)isoindoline-1-carboxamide;
N-benzyl-2-[2-(4-fluorophenoxy)propyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[(1-benzyl-1H-pyrazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[(5-methyl-3-phenylisoxazol-4-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-3-oxo-2-[(3-phenylisoxazol-5-yl)methyl]isoindoline-1-carboxamide;
N-(tert-butyl)-5,6-dichloro-2-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-5,6-dichloro-2-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-5,6-dichloro-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-5,6-dichloro-2-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-5-fluoro-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;
N-(4-fluorobenzyl)-3-oxo-2-(2-pyridin-4-ylethyl)isoindoline-1-carboxamide;
2-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxo-N-[3-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;
N-(2-furylmethyl)-3-oxo-2-(2-phenylpropyl)isoindoline-1-carboxamide;
2-[2-(4-chlorophenyl)ethyl]-N-[(5-methyl-2-furyl)methyl]-3-oxoisoindoline-1-carboxamide;
N-(4-fluorobenzyl)-2-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-(2-chlorobenzyl)-2-[2-(1H-indol-3-yl)-1-methylethyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-5,6-dichloro-2-[2-(4-chloro-2-methylphenyl)-2,2-difluoroethyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-5,6-dichloro-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(4-chloro-2-methylphenyl)-2,2-difluoroethyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[2-(4-chloro-2-methylphenyl)-2,2-difluoroethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-[3-(difluoromethoxy)benzyl]-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide;

N-(2-chlorobenzyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

2-[4-(difluoromethoxy)benzyl]-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide;

N-(2-chlorobenzyl)-2-(2,5-dimethylbenzyl)-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-(2-chlorobenzyl)-2-[(1R)-1-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-(2-chlorobenzyl)-2-[(1R)-1-(3-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-(2-chlorobenzyl)-2-[(1S)-1-(1-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-3-oxo-2-(4-phenoxybenzyl)isoindoline-1-carboxamide;

N-(2-chlorobenzyl)-3-oxo-2-(3-phenylpropyl)isoindoline-1-carboxamide;

N-(2-chlorobenzyl)-3-oxo-2-(2-phenylethyl)isoindoline-1-carboxamide;

N-(2-chlorobenzyl)-3-oxo-2-(1-phenylpropyl)isoindoline-1-carboxamide;

N-(2-chlorobenzyl)-2-(1-methyl-3-phenylpropyl)-3-oxoisoindoline-1-carboxamide;

N-(2-chlorobenzyl)-3-oxo-2-(2-phenylpropyl)isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-(2-chlorobenzyl)-3-oxoisoindoline-1-carboxamide;

3-oxo-2-(1-phenylpropyl)-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

3-oxo-2-(2-phenylpropyl)-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-(1-methyl-3-phenylpropyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

3-oxo-2-(2-phenylethyl)-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-benzyl-2-[2-(5-bromo-2-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

3-oxo-2-(3-phenylpropyl)-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-benzyl-2-[2-(3-bromo-4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-(2-methylbutyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

N-benzyl-2-(2,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(cyclohexylmethyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-(3-fluorobenzyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-(2-ethoxybenzyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

3-oxo-2-[4-(trifluoromethoxy)benzyl]-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-[2-(2-thienyl)ethyl]isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[2-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(2-methoxyethyl)-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[4-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[3-(difluoromethoxy)benzyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-2-(1-naphthylmethyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-cycloheptyl-3-oxoisoindoline-1-carboxamide;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-[2-(4-bromophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(1-ethylpropyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-3-oxo-2-[3-(1H-pyrrol-1-yl)benzyl]isoindoline-1-carboxamide;

N-benzyl-2-(3-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[2-(2-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(2-ethoxybenzyl)-3-oxoisoindoline-1-carboxamide;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-3-oxo-2-(2-phenylpropyl)isoindoline-1-carboxamide;

N-benzyl-2-(4-cyanobenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(3,5-dimethoxybenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[1-(1-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-3-oxo-2-[4-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

ethyl N-({2-[3,5-bis(trifluoromethyl)benzyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)-beta-alaninate;

2-(1-naphthylmethyl)-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide;

ethyl N-({2-[2-(3,4-dichlorophenyl)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)-beta-alaninate;

methyl 4-({1-[(benzylamino)carbonyl]-3-oxo-1,3-dihydro-2H-isoindol-2-yl}methyl)benzoate;

3-oxo-2-[3-(trifluoromethyl)benzyl]-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide;

2-[1-(1-naphthyl)ethyl]-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide;

3-oxo-2-[4-(trifluoromethyl)benzyl]-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide;
2-[2-(4-bromophenyl)ethyl]-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide;
2-(2-chloro-6-phenoxybenzyl)-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide;
2-(3,4-dichlorobenzyl)-3-oxo-N-[(trimethylsilyl)methyl]isoindoline-1-carboxamide;
N-benzyl-2-(1-benzylpyrrolidin-3-yl)-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-(1-benzylpyrrolidin-3-yl)-4,5-dimethoxy-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-(3,4-difluorobenzyl)-4,5-dimethoxy-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[2-(4-chlorophenyl)propyl]-4,5-dimethoxy-3-oxoisoindoline-1-carboxamide;
N-benzyl-4,5-dimethoxy-2-(1-methyl-3-phenylpropyl)-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[(1-methyl-1H-pyrrol-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-3-oxo-2-(1-phenyl-2-pyrrolidin-1-ylethyl)isoindoline-1-carboxamide;
N-benzyl-2-[2-(4-methoxyphenyl)-2-oxoethyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[(1R)-1-(4-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-(3,4-difluorobenzyl)-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[(1R)-1-(3-methoxyphenyl)ethyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-(2,5-dimethylbenzyl)-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-(1-methyl-3-phenylpropyl)-3-oxoisoindoline-1-carboxamide;
N-benzyl-3-oxo-2-{2-[3-(trifluoromethyl)phenyl]ethyl}isoindoline-1-carboxamide;
N-benzyl-2-[3,5-bis(trifluoromethyl)benzyl]-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-[2-(6-chloro-1H-indol-3-yl)ethyl]-3-oxoisoindoline-1-carboxamide;
N,2-dibenzyl-3-oxoisoindoline-1-carboxamide;
N-benzyl-2-(cyclohexylmethyl)-3-oxoisoindoline-1-carboxamide;
N-benzyl-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide;
2-(1,3-benzodioxol-5-ylmethyl)-N-cyclohexyl-3-oxoisoindoline-1-carboxamide;
2-(2-methoxybenzyl)-N-(4-methylcyclohexyl)-3-oxoisoindoline-1-carboxamide;
tert-butyl N-{[3-oxo-2-(3-pyrrolidin-1-ylpropyl)-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;
N-(tert-butyl)-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;
N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(2-bromobenzyl)-3-oxoisoindoline-1-carboxamide;
2-[2-(4-chlorophenyl)ethyl]-N-cyclohexyl-3-oxoisoindoline-1-carboxamide;
N-(2,3-dimethylcyclohexyl)-3-oxo-2-(2-thienylmethyl)isoindoline-1-carboxamide;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide;

2-(2-chlorobenzyl)-N-(4-methylcyclohexyl)-3-oxoisoindoline-1-carboxamide;

N-butyl-2-(2-cyclohex-1-en-1-ylethyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[(2R)-2-hydroxy-1,2-diphenylethyl]-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-butyl-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-isopropyl-3-oxoisoindoline-1-carboxamide;

tert-butyl N-{[2-(2-bromobenzyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;

2-[2-(4-chlorophenyl)propyl]-N-isopropyl-3-oxoisoindoline-1-carboxamide;

methyl N-{[3-oxo-2-(2-phenylethyl)-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;

N-(tert-butyl)-2-[1-(2-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-[1-(2-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(3,4-diethoxyphenyl)ethyl]-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

2-benzyl-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-[4-(dimethylamino)benzyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(3-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-N-cyclopentyl-3-oxoisoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-3-oxo-N-(pyridin-3-ylmethyl)isoindoline-1-carboxamide;

2-(2,5-dimethoxybenzyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-(sec-butyl)-2-[2-(4-chlorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(2,3-difluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(2-chloro-4-fluorobenzyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)ethyl]-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(2-methylbenzyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-(cyclohexylmethyl)-3-oxoisoindoline-1-carboxamide;

2-(1-methyl-3-phenylpropyl)-3-oxo-N-(2-phenylethyl)isoindoline-1-carboxamide;

N-benzyl-2-cyclohexyl-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-(2-cyclohex-1-en-1-ylethyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;

tert-butyl N-{[2-(cyclohexylmethyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-(2-cyclohex-1-en-1-ylethyl)-3-oxoisoindoline-1-carboxamide;

tert-butyl N-{[2-(biphenyl-2-ylmethyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;

N-benzyl-2-(2,2-dimethylpropyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(3-methylbutyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-3-oxo-2-[2-(2-thienyl)ethyl]isoindoline-1-carboxamide;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-3-oxo-2-(2-phenylethyl)isoindoline-1-carboxamide;

N-benzyl-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(2-methylbenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(2-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-3-oxo-2-(2-phenylethyl)isoindoline-1-carboxamide;

N-benzyl-2-[1-(2-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide;

methyl N-({2-[2-(4-chlorophenyl)propyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;

tert-butyl N-({2-[1-(2-naphthyl)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;

N-(1H-1,2,3-benzotriazol-1-ylmethyl)-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[1-(2-naphthyl)ethyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(2-bromobenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(2-cyclohex-1-en-1-ylethyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(biphenyl-2-ylmethyl)-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-chlorophenyl)propyl]-3-oxoisoindoline-1-carboxamide;

N-butyl-2-[2-(4-chlorophenyl)-2-methyl-propyl]-3-oxo-1H-isoindole-1-carboxamide;

N-(tert-butyl)-2-[(4,4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

(1R or 1S)-N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

(1S or 1R)-N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)-2-methylpropyl]-N-[(1-isopropyl-5-oxopyrrolidin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[(1-isopropyl-5-oxopyrrolidin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

1H-isoindole-1-carboxamide, 2-[2-(4-chlorophenyl)propyl]-2,3-dihydro-N-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-oxo-;

N-(tert-butyl)-2-[(4',5-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(5-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(4-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-[(4-fluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

(1R or 1S)-N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

(1S or 1R)-N-(tert-butyl)-2-[(3',4'-difluorobiphenyl-2-yl)methyl]-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-[(1-isopropyl-5-oxopyrrolidin-3-yl)methyl]-3-oxoisoindoline-1-carboxamide;

1H-isoindole-1-carboxamide, 2-[2-(4-chlorophenyl)propyl]-2,3-dihydro-N-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-oxo-;

2-(2,2-dimethylpropyl)-6-fluoro-3-oxo-N-(1-phenylethyl)isoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-6-fluoro-N-(3-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-6-fluoro-N-(2-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-N-(3-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(2,2-dimethylpropyl)-N-(2-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

2-(1-methyl-1-phenylethyl)-3-oxo-N-(1-phenylethyl)isoindoline-1-carboxamide;

6-fluoro-3-oxo-N,2-bis(1-phenylethyl)isoindoline-1-carboxamide;

N-(1-methyl-1-phenylethyl)-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;

3-oxo-N,2-bis(1-phenylethyl)isoindoline-1-carboxamide;

N-(3-fluorobenzyl)-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;

N-(2-fluorobenzyl)-3-oxo-2-(1-phenylethyl)isoindoline-1-carboxamide;

(1R or 1S)-2-[(2S or 2R)-2-(4-chlorophenyl)propyl]-3-oxo-N-propylisoindoline-1-carboxamide;

(1S or 1R)-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-3-oxo-N-propylisoindoline-1-carboxamide;

(1R or 1S)-2-[(2R or 2S)-2-(4-chlorophenyl)propyl]-3-oxo-N-propylisoindoline-1-carboxamide;

(R or S)2-(biphenyl-2-ylmethyl)-6-chloro-N-ethyl-3-oxoisoindoline-1-carboxamide;

(S or R)2-(biphenyl-2-ylmethyl)-6-chloro-N-ethyl-3-oxoisoindoline-1-carboxamide;

N-(4-fluorobenzyl)-2-[1-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[1-(4-chlorophenyl)ethyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-[1-(4-fluorophenyl)ethyl]-3-oxoisoindoline-1-carboxamide;

2-[1-(4-chlorophenyl)-1-methylethyl]-N-(4-fluorobenzyl)-3-oxoisoindoline-1-carboxamide;

N-benzyl-6-fluoro-2-[1-(4-fluorophenyl)-1-methylethyl]-3-oxoisoindoline-1-carboxamide;

2-[1-(4-chlorophenyl)-1-methylethyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

N-(4-fluorobenzyl)-2-[1-(4-fluorophenyl)-1-methylethyl]-3-oxoisoindoline-1-carboxamide;

N-benzyl-6-fluoro-2-(1-methyl-1-phenylethyl)-3-oxoisoindoline-1-carboxamide;

2-[1-(4-fluorophenyl)-1-methylethyl]-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

N-(4-fluorobenzyl)-2-(1-methyl-1-phenylethyl)-3-oxoisoindoline-1-carboxamide;

2-(1-methyl-1-phenylethyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(5-cyanopentyl)-6-fluoro-3-oxoisoindoline-1-carboxamide;

N-benzyl-6-bromo-3-oxo-2-(1-phenylpropyl)isoindoline-1-carboxamide;

N-benzyl-2-[2-(4-chlorophenyl)propyl]-4-fluoro-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-(4,4-difluorobutyl)-4-fluoro-3-oxoisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-4-fluoro-3-oxo-N-propylisoindoline-1-carboxamide;

2-[2-(4-chlorophenyl)propyl]-N-ethyl-4-fluoro-3-oxoisoindoline-1-carboxamide;

N-benzyl-2-(biphenyl-2-ylmethyl)-4-fluoro-3-oxoisoindoline-1-carboxamide;

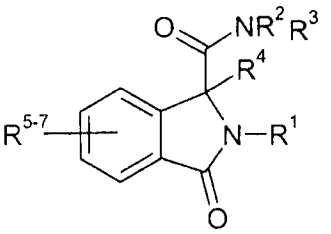
2-(biphenyl-2-ylmethyl)-N-(4,4-difluorobutyl)-4-fluoro-3-oxoisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-4-fluoro-3-oxo-N-propylisoindoline-1-carboxamide;

2-(biphenyl-2-ylmethyl)-N-ethyl-4-fluoro-3-oxoisoindoline-1-carboxamide;
N-benzyl-4-fluoro-3-oxo-2-[(1R)-1-phenylethyl]isoindoline-1-carboxamide;
or a pharmaceutically acceptable salt thereof;

or an enantiomer thereof.

60. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof; wherein

$\mathbf{R^1}$ represents C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, oxo, $-OR^8$, $-COR^9$, $-SR^{10}$, $-COXR^{11}$, $-N(R^{12a})(R^{12b})$, $-N(R^{13a})C(O)OR^{13b}$, $-OC(O)N(R^{14a})(R^{14b})$, $-SO_2R^{15}$, aryl or Het^1); further R^1 represents aryl or Het^2;

R^8 to R^{11}, R^{13a}, R^{13b}, R^{15} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^9 (which C_1-C_6 alkyl, aryl and Het^9 groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{10});

R^{12a} and R^{12b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{11} (which C_1-C_6 alkyl, aryl and Het^{11} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{12}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{14a} and R^{14b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{13} (which C_1-C_6 alkyl, aryl and Het^{13} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{14}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^2 represents C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, $-OR^{16}$, $-COR^{17}$, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, cyano, trialkylsilyl, $-COXR^{18}$, aryl or Het^3);
further R^2 represents $-(CH_2)_kN(R^{19a})(R^{19b})$, $-(CH_2)_kNR^{20a}C(O)N(R^{20b})(R^{20c})$, $-(CH_2)_nNR^{21a}SO_2R^{21b}$, $-(CH_2)_nSO_2R^{22}$, $-(CH_2)_kN(R^{23a})C(O)OR^{23b}$, $-OC(O)N(R^{24a})(R^{24b})$, C_3-C_8 cycloalkyl, aryl or Het^4;

R^{16} to R^{18}, R^{21}, R^{22}, R^{23a}, R^{23b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{15} (which C_1-C_6 alkyl, aryl and Het^{15} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{16});

R^{19a} and R^{19b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{19} (which C_1-C_6 alkyl, aryl and Het^{19} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{20}) or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{20a}, R^{20b} and R^{20c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{21} (which C_1-C_6 alkyl, aryl and Het^{21} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{22});
R^{20b} and R^{20c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^3 represents hydrogen, C_1-C_{12} alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, $-OR^{25}$, $-COR^{26}$, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, trialkylsilyl, $-COXR^{27}$, aryl or Het^5);
further R^3 represents $-(CH_2)_kN(R^{28a})(R^{28b})$, $-(CH_2)_kN(R^{29a})C(O)N(R^{29b})(R^{29c})$, $-(CH_2)_nNR^{30a}SO_2R^{30b}$, $-(CH_2)_nSO_2R^{31}$, $-(CH_2)_kN(R^{32a})C(O)OR^{32b}$, $-OC(O)N(R^{33a})(R^{33b})$, C_3-C_8 cycloalkyl, aryl or Het^6;

R^{25} to R^{27}, R^{30}, R^{31}, R^{32a}, R^{32b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{23} (which C_1-C_6 alkyl, aryl and Het^{23} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{24});

R^{28a} and R^{28b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{25} (which C_1-C_6 alkyl, aryl and Het^{25} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{26}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{33a} and R^{33b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{27} (which C_1-C_6 alkyl, aryl and Het^{27} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{28}) or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{29a}, R^{29b}, and R^{29c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{29} (which C_1-C_6 alkyl, aryl and Het^{29} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{30}); R^{29b} and R^{29c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

$\mathbf{R^4}$ represents hydrogen, –OH, aryl, C_1-C_6 alkyl (which alkyl group is optionally substituted by one or more groups selected from halogen, hydroxy, C_2-C_4 alkenyl, trialkylsilyl), $-OR^{34}$, $-(CH_2)_mR^{35}$;

R^{34} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{31} (which C_1-C_6 alkyl, aryl and Het^{31} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{32});

R^{35} independently represent aryl or Het^{33}(which aryl and Het^{33} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{34});

$\mathbf{R^5}$ to $\mathbf{R^7}$ independently represent, at each occurence, hydrogen, -OH, halogen, cyano, nitro, C_{1-6} alkyl, $-OR^{36}$, $-N(R^{37a})(R^{37b})$, $-C(O)R^{38}$, $-C(O)OR^{39}$, $-C(O)N(R^{40a})(R^{40b})$, $-NC(O)OR^{41}$, $-OC(O)N(R^{42a})(R^{42b})$, $-N(R^{43a})C(O)R^{43b}$, $-N(R^{44a})S(O)_2R^{44b}$, $-S(O)_2R^{45}$, $-OS(O)_2R^{46}$, $-(CH_2)_nN(R^{47a})(R^{47b})$, $-(CH_2)_nNR^{48a}C(O)N(R^{48b})(R^{48c})$, $-(CH_2)_nNR^{49a}SO_2R^{49b}$, trialkylsilyl, aryl or Het^7;

R^{36}, R^{38}, R^{39}, R^{41}, R^{43}, R^{44a}, R^{44b}, R^{45}, R^{46}, R^{49a} and R^{49b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{35} (which C_1-C_6 alkyl, aryl and Het^{35} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{36});

R^{37a} and R^{37b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{37} (which C_1-C_6 alkyl, aryl and Het^{37} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{38}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{40a} and R^{40b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{39} (which C_1-C_6 alkyl, aryl and Het^{39} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{40}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{42a} and R^{42b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{41} (which C_1-C_6 alkyl, aryl and Het^{41} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{42}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{47a} and R^{47b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{43} (which C_1-C_6 alkyl, aryl and Het^{43} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{44}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{48a}, R^{48b} and R^{48c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{45} (which C_1-C_6 alkyl, aryl and Het^{45} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{46}); R^{48b} and R^{48c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

aryl is, at each occurrence, optionally substituted by –OH, halogen, cyano, nitro, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, aryl, Het^8, $-OR^{50}$, $-(CH_2)_mR^{51}$, $-SR^{52}$, $-C(O)R^{53}$, $-COXR^{54}$, $-N(R^{55a})(R^{55b})$, $-SO_2R^{56}$, $-OS(O)_2R^{57}$, $-(CH_2)_mN(R^{58a})(R^{58b})$, $-CH_2)_mNR^{59a}C(O)N(R^{59b})(R^{59c})$, $-C(O)OR^{60}$, $-C(O)N(R^{61a})(R^{61b})$, $-N(R^{62a}C(O)R^{62b}$, $-N(R^{63a})C(O)OR^{63b}$, $-OC(O)N(R^{64a})(R^{64b})$, $-N(R^{65a})S(O)_2R^{65b}$ and $OC(O)R^{66}$;

R^{50} to R^{54}, R^{56}, R^{57}, R^{60}, R^{62a}, R^{62b}, R^{63a}, R^{63b}, R^{65a}, R^{65b} and R^{66} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{47} (which C_1-C_6 alkyl, aryl and Het^{47}

groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{48});

R^{51} independently represent aryl or Het^{49} (which aryl and Het^{49} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{50});

R^{55a} and R^{55b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{51} (which C_1-C_6 alkyl, aryl and Het^{51} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{52}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{58a} and R^{58b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{53} (which C_1-C_6 alkyl, aryl and Het^{53} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{54}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{59a}, R^{59b} and R^{59c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{55} (which C_1-C_6 alkyl, aryl and Het^{55} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{56}); R^{59b} and R^{59c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{61a} and R^{61b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{57} (which C_1-C_6 alkyl, aryl and Het^{57} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{58}); or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{64a} and R^{64b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{59} (which C_1-C_6 alkyl, aryl and Het^{59} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{60});

Het^1 to Het^{60} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, a further Het, $-OR^{67}$, $-(CH_2)_mR^{68}$, $-SR^{69}$, $-COXR^{70}$, $-N(R^{71a})(R^{71b})$, $-SO_2R^{72}$, $-(CH_2)_mN(R^{73a})(R^{73b})$, $-(CH_2)_mNR^{74a}C(O)N(R^{74b})(R^{74c})$, $-C(O)R^{75}$, $-C(O)OR^{76}$, $-C(O)N(R^{77a})(R^{77b})$, $-N(R^{78a})C(O)R^{78b}$, $-N(R^{79a})S(O)_2R^{79b}$, $OC(O)R^{80}$, $-NC(O)OR^{81}$, $-OC(O)N(R^{82a})(R^{82b})$;

R^{67}, R^{69}, R^{70}, R^{72}, R^{75}, R^{76}, R^{78a}, R^{78b}, R^{79a}, R^{79b}, R^{80} or R^{81} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{61} (which C_1-C_6 alkyl, aryl and Het^{61} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{62});

R^{68} represents aryl or Het^{63} (which aryl and Het^{63} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{64});

R^{71a} and R^{71b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{65} (which C_1-C_6 alkyl, aryl and Het^{65} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{66}), or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{73a} and R^{73b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{67} (which C_1-C_6 alkyl, aryl and Het^{67} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{68}); or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{74a}, R^{74b} and R^{74c} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{69} (which C_1-C_6 alkyl, aryl and Het^{69} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{70}); R^{74b} and R^{74c} may together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

R^{77a}, and R^{77b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{71} (which C_1-C_6 alkyl, aryl and Het^{71} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{72}); or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

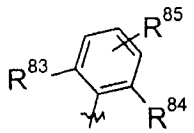
R^{82a}, and R^{82b} independently represent, at each occurrence, hydrogen, C_1-C_6 alkyl, aryl or Het^{73} (which C_1-C_6 alkyl, aryl and Het^{73} groups are optionally substituted with one or more substituents selected from –OH, halogen, cyano, nitro, C_1-C_6 alkyl, aryl and Het^{74}) or together represent C_3-C_6 alkylene, optionally interrupted by an O atom;

Het^{61} to Het^{74} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl;

X represents a nitrogen or oxygen atom;
m is an integer of 0 to 10;
n is an integer of 0 to 4;
k is an integer of 1 to 5;

provided that

a) R^2 or R^3 do not represent a fragment of formula



wherein

R^{83} and R^{84} represent independently, at each occurrence, halogen, C_1-C_{12} alkyl, C_1-C_{12} alkoxy, C_1-C_{12} haloalkyl, C_1-C_{12} haloalkoxy, cyano, $-SR^{86}$, $-N(R^{87a})R^{87b}$, C_2-C_6 alkynyl, aryl or Het^{75};

R^{85} represents hydrogen, C_1-C_{12} alkyl group or C_1-C_{12} alkoxy group (which C_1-C_{12} alkyl and C_1-C_{12} alkoxy groups are optionally substituted by one or more groups selected from halogen, C2-C6 alkenyl, C_2-C_6 alkynyl, cyano, oxo, aryl, Het^{76}, $-OR^{88}$, $-SR^{89}$, $-COXR^{90}$, $-N(R^{91a})R^{91b}$, $-SO_2R^{92}$);

Het^{75} to Het^{76} independently represent, at each occurence, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryloxy, $-N(R^{93a})R^{93b}$, $-C(O)R^{93c}$, $-C(O)OR^{93d}$, $-C(O)N(R^{93e})R^{93f}$, $-N(R^{93g})C(O)R^{93h}$ and $-N(R^{93i})S(O)_2R^{93j}$, $OC(O)R^{93k}$ and a further Het;

R^{86} to R^{93} represent independently, at each occurrence, hydrogen or C_{1-6} alkyl; and

c) the compound is not:

2-(2-ethoxyethyl)-N-isopropyl-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-(3-pyrrolidin-1-ylpropyl)isoindoline-1-carboxamide;

N-(tert-butyl)-3-oxo-2-(tetrahydrofuran-2-ylmethyl)isoindoline-1-carboxamide;

2-[1-(hydroxymethyl)butyl]-N-isopropyl-3-oxoisoindoline-1-carboxamide;

N-isopropyl-2-(3-methylbutyl)-3-oxoisoindoline-1-carboxamide;

N-(tert-butyl)-2-cyclohexyl-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-(3-methylbutyl)-3-oxoisoindoline-1-carboxamide;
methyl N-{[2-(3-methylbutyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;
tert-butyl N-({2-[1-(hydroxymethyl)butyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;
tert-butyl N-{[2-(3-methylbutyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;
N-(tert-butyl)-2-[1-(methoxymethyl)propyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[2-(diethylamino)ethyl]-3-oxoisoindoline-1-carboxamide;
N-(tert-butyl)-2-[1-(hydroxymethyl)butyl]-3-oxoisoindoline-1-carboxamide;
tert-butyl N-{[3-oxo-2-(2-thienylmethyl)-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate;
tert-butyl N-({2-[2-(methylthio)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-1-yl}carbonyl)glycinate;
methyl N-{[2-(cyclopropylmethyl)-3-oxo-2,3-dihydro-1H-isoindol-1-yl]carbonyl}glycinate; or
2-(2,2-dimethylpropyl)-3-oxo-N-(4,4,4-trifluorobutyl)isoindoline-1-carboxamide.
for use in therapy.

61. Use of the compound of formula I according to any of claims 1 to 60, in the manufacture of a medicament for treatment of arrhythmias.

62. Use of the compound of formula I according to any of claims 1 to 60, in the manufacture of a medicament for treatment of atrial or ventricular arrhythmias.

63. A pharmaceutical composition comprising as active ingredient a therapeutically effective amount of the compound according to any of claims 1 to 60 in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

64. The pharmaceutical composition according to claim 63, for use in the treatment of arrhythmias.

65. A method of treatment of arrhythmias, comprising administering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compounds of formula I, according to any of claims 1 to 60.

66. An agent for the treatment of arrhythmias, which comprises as active ingredient a compound of formula I, according to any of claims 1 to 60.

67. Compound according to any of claims 1 to 60 for use in the treatment of arrhythmias.

68. A process for preparing a compound of formula I as described herein.

(12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual
Bureau International

(43) Fecha de publicación internacional
17 de Enero de 2008 (17.01.2008)

PCT

(10) Número de Publicación Internacional
WO 2008/008022 A1

(51) Clasificación Internacional de Patentes:
C07D 209/46 (2006.01) *A61P 9/04* (2006.01)
A61K 31/40 (2006.01) *A61P 9/06* (2006.01)
A61K 31/4035 (2006.01) *C07D 401/00* (2006.01)
A61K 31/41 (2006.01) *C07D 403/00* (2006.01)
A61K 31/435 (2006.01) *C07D 413/00* (2006.01)
A61K 31/495 (2006.01)

(21) Número de la solicitud internacional:
PCT/SE2007/000683

(22) Fecha de presentación internacional: 12 de Julio de 2007 (12.07.2007)

(25) Idioma de presentación: Inglés

(26) Idioma de publicación: Inglés

(30) Datos relativos a la prioridad:
60/830,243 12 de Julio de 2006 (12.07.2006) US
60/913,367 23 de Abril de 2007 (23.04.2007) US

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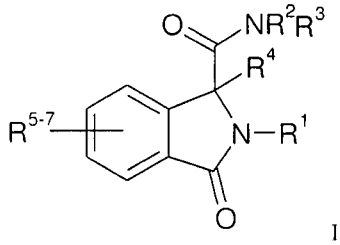
(81) Estados designados *(a menos que se indique otra cosa, para toda clase de protección nacional admisible)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Estados designados *(a menos que se indique otra cosa, para toda clase de protección regional admisible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicada:
- *con informe de búsqueda internacional*

Para códigos de dos letras y otras abreviaturas, véase la sección "Guidance Notes on Codes and Abbreviations" que aparece al principio de cada número regular de la Gaceta del PCT.

(54) Title: ISOINDOLINE DERIVATIVES FOR THE TREATMENT OF ARRHYTHMIAS
(54) Título: DERIVADOS DE ISOINDOLINA PARA EL TRATAMIENTO DE ARRITMIAS



I

(57) Abstract: There is provided compounds of formula I, wherein R^1 to R^7 have meanings given in the description, which are useful in the prophylaxis and in the treatment of arrhythmias, in particular atrial and ventricular arrhythmias

(57) Resumen: Se estipulan compuestos de fórmula I, donde R^1 a R^7 tienen los significados dados en la descripción, los cuales son útiles en la profilaxis y el tratamiento de arritmias, en particular las arritmias auriculares y ventriculares.

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DERIVADOS DE ISOINDOLINA PARA EL TRATAMIENTO DE ARRITMIAS

COMPUESTOS NUEVOS I/418

Campo de la invención

Esta invención se refiere a compuestos 3-oxoisoindolina-1-carboxamida nuevos, útiles desde el punto de vista farmacéutico, en particular compuestos que son útiles en el tratamiento de las arritmias cardíacas.

Antecedentes

Las arritmias cardíacas se pueden definir como anormalidades en la velocidad, la regularidad o el sitio de origen del impulso cardíaco o como trastornos en la conducción que causa una secuencia anormal de la activación. Las arritmias se pueden clasificar clínicamente mediante el presunto sitio de origen (es decir como supraventricular, incluidas las arritmias auriculares y auriculoventriculares y las arritmias ventriculares) y/o mediante la velocidad (es decir bradiarritmias (lento) y taquiarritmias (rápido)).

En el tratamiento de las arritmias cardíacas, el resultado negativo en los ensayos clínicos (consulte, por ejemplo, el resultado del ensayo Cardiac Arrythmia Suppression Trial (CAST) publicado en el New England Journal of Medicine, 321, 406 (1989)) con antiarrítmicos "tradicionales", que actúan principalmente reduciendo la velocidad de conducción (antiarrítmicos clase I), ha impulsado el desarrollo de medicamentos hacia los compuestos que retardan selectivamente la repolarización cardíaca, prolongando de ese modo el intervalo QT. Los antiarrítmicos clase III se pueden definir como fármacos que prolongan la duración del potencial de acción transmembrana (que puede ser causado por un bloqueo de corrientes de K^+ externas o por un aumento de las corrientes iónicas internas) y la refractariedad, sin afectar la conducción cardíaca. Las corrientes de potasio rectificadoras tardías de activación rápida y lenta I_{Kr} e I_{Ks}, respectivamente, son las principales corrientes que participan en el proceso de repolarización general durante la meseta del potencial de acción y la mayoría de los agentes clase III bloquean predominantemente a I_{Kr}.

Una de las desventajas clave de los fármacos conocidos hasta ahora que actúan retardando la repolarización por un bloqueo de I_{Kr} (clase III u otros) es se sabeque casi todas presentan una forma única de proarritmia ventricular conocida como *torsades de pointes* (torneado de los puntos), que ocasionalmente puede ser fatal. Desde el punto de vista de la seguridad, la reducción al mínimo de este fenómeno (que también se ha demostrado que se presenta como resultado de la administración de fármacos no cardíacos como fenotiacinas, antidepresivos tricíclicos, antihistamínicos y antibióticos) es un problema clave a ser resuelto a la hora de proveer de fármacos antiarrítmicos eficaces.

En los miocitos auriculares humanos, se identificó una corriente de potasio rectificadora tardía de activación ultrarrápida, I_{Kur} también conocida como I_{so} o I_{sus}. Se identificó el gen que es más probable que codifique la proteína de canal I_{Kur} y se denomina Kv1.5 (Wang et al (1993) Circ Res73:1061-0176, Feng et al (1997) Circ Res 80:572-579). Debido a la inactivación lenta de la corriente, I_{Kur} persiste durante la fase de meseta y contribuye significativamente a la repolarización del potencial de acción en los miocitos auriculares. De manera muy interesante, los estudios de pinza de voltaje que investigan las corrientes repolarizantes no han logrado demostrar la presencia de I_{Kur} en los miocitos ventriculares humanos (Amos et al J Physiol (1996) 491(1):31-50). Por lo tanto, un bloqueador selectivo de I_{Kur}, que es un compuesto que bloquea Kv1.5, es de gran interés para la terapia de la arritmia auricular, ya que tal agente debería retardar la repolarización únicamente en el miocardio auricular humano, eludiendo las proarritmias ventriculares (es decir *torsades de pointes*,) asociadas con la repolarización ventricular retardada.

Se han descrito bloqueadores de Kv1.5 que presentan estas propiedades (Peukert et al J Med Chem (2003) 46:486-498; Knobloch et al Naunyn-Schmiedeberg's Arch Pharmacol (2002) 366:482-487).

Se conocen algunos derivados de 3-oxoisoindolina-1-carboxamida. Los derivados de 3-oxoisoindolina-1-carboxamida son el blanco ideal de las reacciones multicomponente (MCR, por sus siglas en inglés). Tetrahedron Letters (1998), 39(18), 2.725-2.728 divulga algunos derivados de 3-oxoisoindolina-1-carboxamida preparados mediante las reacciones denominadas de Ugi (N-terc-butil-3-oxo-2-propilisoindolina-1-carboxamida; N-terc-butil-1-metil-3-oxo-2-propilisoindolina-1-carboxamida; N,1-dimetil-3-oxo-2-propilisoindolina-

1-carboxamida; N-ciclohexil-3-oxo-2-propilisoindolina-1-carboxamida; 2-bencil-N-terc-butil-3-oxoisoindolina-1-carboxamida; 2-bencil-N,1-dimetil-3-oxoisoindolina-1-carboxamida; 2-bencil-N-terc-butil-1-metil-3-oxoisoindolina-1-carboxamida; 2-bencil-N,1-dimetil-3-oxoisoindolina-1-carboxamida.

También el Journal of Organic Chemistry (1999), 64(3), 1.074-1.076 divulga tales compuestos {4-[1-(terc-butilcarbamoil)-3-oxo-1,3-dihidro-2H-isoindol-2-il]butil}carbamato de terc-butilo; 2-bencil-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida; 2-bencil-N-butil-3-oxoisoindolina-1-carboxamida; 2-bencil-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida; 2-(2-hidroxietil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida; N-butil-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida; 2-(2-hidroxietil)-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida; 2-[3-(1H-imidazol-1-il)propil]-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida; N-butil-2-[3-(1H-imidazol-1-il)propil]-3-oxoisoindolina-1-carboxamida; 2-[3-(1H-imidazol-1-il)propil]-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida; 2-ciclohexil-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida; N-butil-2-ciclohexil-3-oxoisoindolina-1-carboxamida; 2-ciclohexil-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida) y en Bioorganic & Medicinal Chemistry Letters (2002), 12(14), 1.813-1.816 (2-ciclohexil-N-hexil-3-oxoisoindolina-1-carboxamida; N,2-dihexil-3-oxoisoindolina-1-carboxamida; N-hexil-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida; N-hexil-2-(4-hidroxibutil)-3-oxoisoindolina-1-carboxamida; N,2-diciclohexil-3-oxoisoindolina-1-carboxamida; N-ciclohexil-2-hexil-3-oxoisoindolina-1-carboxamida; N-ciclohexil-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida; N-ciclohexil-2-(4-hidroxibutil)-3-oxoisoindolina-1-carboxamida; {4-[1-(ciclohexicarbamoil)-3-oxo-1,3-dihidro-2H-isoindol-2-il]butil}carbamato de terc-butilo; N-adamantan-1-il-2-ciclohexil-3-oxoisoindolina-1-carboxamida; N-adamantan-1-il-2-hexil-3-oxoisoindolina-1-carboxamida; N-adamantan-1-il-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida; N-adamantan-1-il-2-(2-morfolin-4-iletil)-3-oxoisoindolina-1-carboxamida; N-(2,6-dimetilfenil)-2-hexil-3-oxoisoindoline-1-carboxamida). También Tetrahedron, vol. 53, N° 19, 6.653-6.679 divulga derivados de 3-oxoisoindolina-1-carboxamida preparados mediante reacciones denominadas de Ugi ácido (6-{[(2-alil-1-metil-3-oxo-2,3-dihidro-1H-isoindol-1-il)carbonil]amino}hexanoico). En esas referencias no se contempla ningún uso farmacéutico de los compuestos preparados. Tetrahedron Letters (2002), 43(6), 943-946 divulga algunos

derivados de 3-oxoisoindolina-1-carboxamida preparados mediante reacciones intramoleculares del tipo Diels-Alder (N,2-dibencil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida; N-bencil-2-terc-butil-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida; N-bencil-2-terc-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida; N,2-dibencil-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida; N-bencil-2-terc-butil-5-hidroxi-3-oxoisoindolina-1-carboxamida). También el Journal of Organic Chemistry (2004), 69(4), 1.207-1.214 divulga el compuesto (N,2-dibencil-5-{[(2-nitrofenil)sulfonil]amino}-3-oxoisoindolina-1-carboxamida). No se contempla ningún uso farmacéutico del compuesto preparado.

El Journal of Heterocyclic Chemistry (1997), 34(4), 1.371-1.374 divulga algunos derivados de 3-oxoisoindolina-1-carboxamida simétricamente sustituidos preparados mediante ciclación carbonilativa de 2-bromobenzaldehído con aminas primarias (N,2-dibencil-3-oxoisoindolina-1-carboxamida; N,2-dietil-3-oxoisoindolina-1-carboxamida; N,2-dibutil-3-oxoisoindolina-1-carboxamida; N,2-didodecil-3-oxoisoindolina-1-carboxamida; N,2-bis(4-metoxibencil)-3-oxoisoindolina-1-carboxamida; 3-oxo-N,2-dipropilisoindolina-1-carboxamida; N,2-diheptil-3-oxoisoindolina-1-carboxamida; 3-oxo-N,2-difenilisoindolina-1-carboxamida). No se contempla ningún uso farmacéutico de los compuestos preparados. Algunos otros derivados de 3-oxoisoindolina-1-carboxamida se divulgan en Zhurnal Obshchei Khimii (1965), 1(7), 1.292-7; Yakugaku Zasshi (1969), 89(3), 418-21; Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1980), (4), 846-8 (2-(4-nitrofenil)-3-(pirrolidin-1-ilcarbonil)isoindolin-1-ona); EP1566378 A1 (2-(3-fluorofenil)-5,6-dimetil-3-[(4-metilpiperazin-1-il)-carbonil]isoindolin-1-ona); EP 1661898; CHEMCATS (Chemical Catalogs Online provisto por STN) (N-[2-(3,4-dimetoxifenil)etil]-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida; N-ciclopentil-2-(3-metoxibencil)-3-oxoisoindolina-1-carboxamida; 2-(1,3-benzodioxol-5-ilmetil)-N-{[(4-metilfenil)sulfonil]metil}-3-oxoisoindolina-1-carboxamida; N-ciclohexil-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida; 2-bencil-N-ciclohexil-3-oxoisoindolina-1-carboxamida; N-{[(4-metilfenil)sulfonil]metil}-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida; 2-(4-clorobencil)-N-{[(4-metilfenil)sulfonil]metil}-3-oxoisoindolina-1-carboxamida; N-ciclohexil-2-(2-furilmetil)-3-oxoisoindolina-1-carboxamida; 2-(4-clorobencil)-N-ciclohexil-3-oxoisoindolina-1-carboxamida; WO03/040096 ({1-bencil-2-hidroxi-3-[(2-hidroxi-3-{[(3-oxo-2,3-dihidro-1H-isoindol-1-

il)carbonil]amino}-4-fenilbutil)amino]propil}carbamato de terc-butilo); US5559256; Chemical & Pharmaceutical Bulletin (1988), 36(1), 190-201; Journal of the Chemical Society (1972-1999), (1972), (6), 835-840; Justus Liebigs Annalen Der Chemie (1978), vol 2, 283-288 (1-hidroxi-2-metil-3-oxo-N-(piridin-2-ilmetil)isoindolina-1-carboxamida; N-[3-(dimetilamino)propil]-1-hidroxi-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida; N-(3-azepan-1-ilpropil)-1-hidroxi-3-oxo-2-fenilisoindolina-1-carboxamida, 1-hidroxi-2-metil-3-oxoisoindolina-1-carbohidrazida; 1-hidroxi-3-oxo-fenilisoindolina-1-carbohidrazida); Zeitschrift for Naturforschung. B, 1993, vol 48:8, 1.094-1.104 (2-benzoil-1-hidroxi-3-oxo-N-fenilisoindolina-1-carboxamida); J. Prakt. Chem. 2, 159, 1941, 241, 244, 254; Heterocycles Vol 38; No 8; 1994, 1.828-1.838; J. Org. Chem. 17, 1952, 4, 8, 1-13; Tetrahedron, EN, 53, 19, 1997, 6.653-6.680; Tetrahedron Letters, vol 38, No 3, 1997, 359-362 ácido (6-{[(2-alil-1-metil-3-oxo-2,3-dihidro-1H-isoindol-1-il)carbonil]amino} hexanoico y ácido 6-{[(1-metil-2-octil-3-oxo-2,3-dihidro-1H-isoindol-1-il)carbonil]amino} hexanoico). EP1566378 A1 divulga derivados de isoindolina que tienen efectos anestésicos, EP 1661898 A1 derivados de isoindolina para usar en el tratamiento del cáncer, y EP 1749817 A1 derivados de isoindolina para controlar el dolor neuropático. US 2007/0099930 divulga dihidroisoindolonas sustituidas que tienen efecto como moduladores de la glucocinasa. Otros derivados de isoindolina se describen en SYNTHESIS 2006, No 23, pp. 4.046-4.052 ([1-(terc-butilcarbamoil)-3-oxo-1,3-dihidro-2H-isoindol-2-il]acetato de metilo); y en J. Org. Chem 2006, 71, 9.544-9.547 (N1-ciclopentil-N4-(2,6-difluorofenil)-2-(2,4-dimetilfenil)-5-metil-3-oxoisoindolina-1,4-dicarboxamida).

Los compuestos divulgados en los documentos indicados antes se reivindican a partir de las reivindicaciones de compuestos de la presente solicitud por el requisito b). Los compuestos de del requisito c) no demuestran actividad a las concentraciones a las cuales se analizaron.

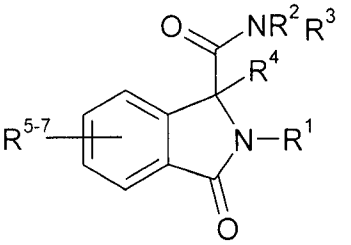
El caso copendiente Nº US 60/830186 describe el requisito a).

Además, el compuesto siguiente figura en el Chemical Abstracts pero no se da ninguna referencia: 3-oxo-N,2-difenilisoindolina-1-carboxamida.

Hemos encontrado con sorpresa que un nuevo grupo de compuestos de 3-oxoisoindolina-1-carboxamida tiene actividad electrofisiológica, preferentemente actividad bloqueante Kv1.5; y por consiguiente se espera que sean útiles en el tratamiento de las arritmias cardíacas.

Divulgación de la invención

De acuerdo con la invención se estipula un compuesto de fórmula I,



I

o una de sus sales farmacéuticamente aceptables

donde

R^1 representa C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, $-OR^8$, $-COR^9$, $-SR^{10}$, $-COXR^{11}$, $-N(R^{12a})(R^{12b})$, $-N(R^{13a})C(O)OR^{13b}$, $-OC(O)N(R^{14a})(R^{14b})$, $-SO_2R^{15}$, arilo o Het^1); además R^1 representa arilo o Het^2;

R^8 a R^{11}, R^{13a}, R^{13b}, R^{15} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^9 (donde los grupos C_1-C_6 alquilo, arilo y Het^9 están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{10});

R^{12a} y R^{12b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{11} (donde los grupos C_1-C_6 alquilo, arilo y Het^{11} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{12}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{14a} y R^{14b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{13} (donde los grupos C_1-C_6 alquilo, arilo y Het^{13} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{14}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

$\mathbf{R^2}$ representa C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, $-OR^{16}$, $-COR^{17}$, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, trialquilsililo, $-COXR^{18}$, arilo o Het^3);
además R^2 representa $-(CH_2)_kN(R^{19a})(R^{19b})$, $-(CH_2)_kNR^{20a}C(O)N(R^{20b})(R^{20c})$, $-(CH_2)_nNR^{21a}SO_2R^{21b}$, $-(CH_2)_nSO_2R^{22}$, $-(CH_2)_kN(R^{23a})C(O)OR^{23b}$, $-OC(O)N(R^{24a})(R^{24b})$, C_3-C_8 cicloalquilo, arilo o Het^4;

R^{16} a R^{18}, R^{21}, R^{22}, R^{23a}, R^{23b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{15} (donde los grupos C_1-C_6 alquilo, arilo y Het^{15} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{16});

R^{19a} y R^{19b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{19} (donde los grupos C_1-C_6 alquilo, arilo y Het^{19} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{20}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{20a}, R^{20b} y R^{20c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{21} (donde los grupos C_1-C_6 alquilo, arilo y Het^{21} están opcionalmente sustituidos con uno o más sustituyentes selecionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{22}); R^{20b} y R^{20c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^3 representa hidrógeno, C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, $-OR^{25}$, $-COR^{26}$, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, trialquilsililo, $-COXR^{27}$, arilo o Het^5);
además R^3 representa $-(CH_2)_kN(R^{28a})(R^{28b})$, $-(CH_2)_kN(R^{29a})C(O)N(R^{29b})(R^{29c})$, $-(CH_2)_nNR^{30a}SO_2R^{30b}$, $-(CH_2)_nSO_2R^{31}$, $-(CH_2)_kN(R^{32a})C(O)OR^{32b}$, $-OC(O)N(R^{33a})(R^{33b})$, C_3-C_8 cicloalquilo, arilo o Het^6;

R^{25} a R^{27}, R^{30}, R^{31}, R^{32a}, R^{32b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{23} (donde los grupos C_1-C_6 alquilo, arilo y Het^{23} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{24});

R^{28a} y R^{28b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{25} (donde los grupos C_1-C_6 alquilo, arilo y Het^{25} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{26}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{33a} y R^{33b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{27} (donde los grupos C_1-C_6 alquilo, arilo y Het^{27} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{28}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{29a}, R^{29b} y R^{29c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{29} (donde los grupos C_1-C_6 alquilo, arilo y Het^{29} pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{30}); R^{29b} y R^{29c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

$\mathbf{R^4}$ representa hidrógeno, –OH, arilo, C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, hidroxi, C_2-C_4 alquenilo, trialquilsililo), $-OR^{34}$, $-(CH_2)_mR^{35}$;

R^{34} representa independientemente, cada vez que aparece, hidrógeno, C_1-C_6 alquilo, arilo o Het^{31} (donde los grupos C_1-C_6 alquilo, arilo y Het^{31} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{32});

R^{35} representa independientemente arilo o Het^{33}(donde los grupos arilo y Het^{33} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{34});

$\mathbf{R^5}$ **a** $\mathbf{R^7}$ representan independientemente, cada vez que aparecen, hidrógeno, -OH, halógeno, ciano, nitro, C_{1-6} alquilo, $-OR^{36}$, $-N(R^{37a})(R^{37b})$, $-C(O)R^{38}$, $-C(O)OR^{39}$, $-C(O)N(R^{40a})(R^{40b})$, $-NC(O)OR^{41}$, $-OC(O)N(R^{42a})(R^{42b})$, $-N(R^{43a})C(O)R^{43b}$, $-N(R^{44a})S(O)_2R^{44b}$, $-S(O)_2R^{45}$, $-OS(O)_2R^{46}$, $-(CH_2)_nN(R^{47a})(R^{47b})$, $-(CH_2)_nNR^{48a}C(O)N(R^{48b})(R^{48c})$, $-(CH_2)_nNR^{49a}SO_2R^{49b}$, trialquilsililo, arilo o Het^7;

R^{36}, R^{38}, R^{39}, R^{41}, R^{43}, R^{44a}, R^{44b}, R^{45}, R^{46}, R^{49a} y R^{49b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{35} (donde los grupos C_1-C_6 alquilo, arilo y Het^{35} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{36});

R^{37a} y R^{37b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{37} (donde los grupos C_1-C_6 alquilo, arilo y Het^{37} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{38}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{40a} y R^{40b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{39} (donde los grupos C_1-C_6 alquilo, arilo y Het^{39} están opcionalmente

sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{40}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{42a} y R^{42b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{41} (donde los grupos C_1-C_6 alquilo, arilo y Het^{41} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{42}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{47a} y R^{47b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{43} (donde los grupos C_1-C_6 alquilo, arilo y Het^{43} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{44}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{48a}, R^{48b} y R^{48c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{45} (donde los grupos C_1-C_6 alquilo, arilo y Het^{45} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{46}) R^{48b} y R^{48c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

arilo está, cada vez que aparece, opcionalmente sustituido con –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, C_3-C_8 cicloalquilo, C_2-C_6 alquenilo, arilo, Het^8, $-OR^{50}$, $-(CH_2)_mR^{51}$, $-SR^{52}$, $-C(O)R^{53}$, $-COXR^{54}$, $-N(R^{55a})(R^{55b})$, $-SO_2R^{56}$, $-OS(O)_2R^{57}$, $-(CH_2)_mN(R^{58a})(R^{58b})$, $-CH_2)_mNR^{59a}C(O)N(R^{59b})(R^{59c})$, $-C(O)OR^{60}$, $-C(O)N(R^{61a})(R^{61b})$, $-N(R^{62a}C(O)R^{62b}$, $-N(R^{63a})C(O)OR^{63b}$, $-OC(O)N(R^{64a})(R^{64b})$, $-N(R^{65a})S(O)_2R^{65b}$ y $OC(O)R^{66}$;

R^{50} a R^{54}, R^{56}, R^{57}, R^{60}, R^{62a}, R^{62b}, R^{63a}, R^{63b}, R^{65a}, R^{65b} y R^{66} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{47} (donde los grupos C_1-C_6 alquilo, arilo y Het^{47} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{48});

R^{51} representa independientemente arilo o Het^{49} (donde los grupos arilo y Het^{49} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{50});

R^{55a} y R^{55b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{51} (donde los grupos C_1-C_6 alquilo, arilo y Het^{51} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{52}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{58a} y R^{58b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{53} (donde los grupos C_1-C_6 alquilo, arilo y Het^{53} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{54}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{59a}, representa independientemente, cada vez que aparece, hidrógeno, C_1-C_6 alquilo, arilo o Het^{55} (donde los grupos C_1-C_6 alquilo, arilo y Het^{55} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{56}); R^{59b} y R^{59c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{61a} y R^{61b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{57} (donde los grupos C_1-C_6 alquilo, arilo y Het^{57} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{58}); o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{64a} y R^{64b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{59} (donde los grupos C_1-C_6 alquilo, arilo y Het^{59} están opcionalmente

sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{60});

Het^1 a Het^{60} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde esos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro, C_{1-6} alquilo, C_{2-6} alquenilo, arilo, otro Het, $-OR^{67}$, $-(CH_2)_mR^{68}$, $-SR^{69}$, $-COXR^{70}$, $-N(R^{71a})(R^{71b})$, $-SO_2R^{72}$, $-(CH_2)_mN(R^{73a})(R^{73b})$, $-(CH_2)_mNR^{74a}C(O)N(R^{74b})(R^{74c})$, $-C(O)R^{75}$, $-C(O)OR^{76}$, $-C(O)N(R^{77a})(R^{77b})$, $-N(R^{78a})C(O)R^{78b}$, $-N(R^{79a})S(O)_2R^{79b}$, $OC(O)R^{80}$, $-NC(O)OR^{81}$, $-OC(O)N(R^{82a})(R^{82b})$;

R^{67}, R^{69}, R^{70}, R^{72}, R^{75}, R^{76}, R^{78a}, R^{78b}, R^{79a}, R^{79b}, R^{80} o R^{81} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{61} (donde los grupos C_1-C_6 alquilo, arilo y Het^{61} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{62});

R^{68} representa independientemente arilo o Het^{63}(donde los grupos arilo y Het^{63} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{64});

R^{71a} y R^{71b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{65} (donde los grupos C_1-C_6 alquilo, arilo y Het^{65} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{66}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{73a} y R^{73b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{67} (donde los grupos C_1-C_6 alquilo, arilo y Het^{67} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{68}); o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{74a}, R^{74b} y R^{74c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{69} (donde los grupos C_1-C_6 alquilo, arilo y Het^{69} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{70}); R^{74b} y R^{74c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

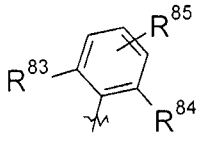
R^{77a} y R^{77b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{71} (donde los grupos C_1-C_6 alquilo, arilo y Het^{71} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{72}); o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{82a} y R^{82b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{73} (donde los grupos C_1-C_6 alquilo, arilo y Het^{73} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{74}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

Het^{61} a Het^{74} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde los grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro y C_{1-6} alquilo;

X representa un átomo de nitrógeno u oxígeno;
m es un número entero entre 0 y 10;
n es un número entero entre 0 y 4;
k es un número entero entre 1 y 5;
siempre que:

a) R^2 o R^3 no representen un fragmento de fórmula



donde

R^{83} y R^{84} representan independientemente, cada vez que aparecen, halógeno, C_1-C_{12} alquilo, C_1-C_{12} alcoxi, C_1-C_{12} haloalquilo, C_1-C_{12} haloalcoxi, ciano, $-SR^{86}$, $-N(R^{87a})R^{87b}$, C_2-C_6 alquinilo, arilo o Het^{75};

R^{85} representa hidrógeno, un grupo C_1-C_{12} alquilo o un grupo C_1-C_{12} alcoxi (donde los grupos C_1-C_{12} alquilo y C_1-C_{12} alcoxi están opcionalmente sustituidos con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_2-C_6 alquinilo, ciano, oxo, arilo, Het^{76}, $-OR^{88}$, $-SR^{89}$, $-COXR^{90}$, $-N(R^{91a})R^{91b}$ y $-SO_2R^{92}$);

Het^{75} a Het^{76} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde esos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro, C_{1-6} alquilo, C_{1-6} alcoxi, arilo, ariloxi, $-N(R^{93a})R^{93b}$, $-C(O)R^{93c}$, $-C(O)OR^{93d}$, $-C(O)N(R^{93e})R^{93f}$, $-N(R^{93g})C(O)R^{93h}$ y $-N(R^{93i})S(O)_2R^{93j}$, $OC(O)R^{93k}$ y otro Het;

R^{86} a R^{93} representan independientemente, cada vez que aparecen, hidrógeno o C_{1-6} alquilo;

X representa O o N;

b) el compuesto no es:

2-(4-nitrofenil)-3-(pirrolidin-1-ilcarbonil)isoindolin-1-ona;

N,2-dibencil-3-oxoisoindolina-1-carboxamida;

N,2-dietil-3-oxoisoindolina-1-carboxamida;

N,2-dibutil -3-oxoisoindolina-1-carboxamida;

N,2-didodecil-3-oxoisoindolina-1-carboxamida;

N,2-bis(4-metoxibencil)-3-oxoisoindolina-1-carboxamida;

3-oxo-N,2-dipropilisoindolina-1-carboxamida;

N,2-diheptil-3-oxoisoindolina-1-carboxamida;

3-oxo-N,2-difenilisoindolina-1-carboxamida;

N-(terc-butil)-3-oxo-2-propilisoindolina-1-carboxamida;

N-(terc-butil)-1-metil-3-oxo-2-propilisoindolina-1-carboxamida;

N,1-dimetil-3-oxo-2-propilisoindolina-1-carboxamida;

N-ciclohexil-3-oxo-2-propilisoindolina-1-carboxamida;

N-(fenil)-3-oxo-2-propilisoindolina-1-carboxamida;

2-bencil-N-terc-butil-3-oxoisoindolina-1-carboxamida:

2-bencil-N,1-dimetil-3-oxoisoindolina-1-carboxamida;

2-bencil-N-terc-butil-1-metil-3-oxoisoindolina-1-carboxamida;

2-bencil-N,1-dimetil-3-oxoisoindolina-1-carboxamida;

(4-{1-[(terc-butilamino)carbonil]-3-oxo-1,3-dihidro-2H-isoindol-2-il}butil)carbamato de terc-butilo:

2-bencil-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;

2-bencil-N-butil-3-oxoisoindolina-1-carboxamida;

2-bencil-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida;

2-(2-hidroxietil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;

N-butil-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida;

2-(2-hidroxietil)-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida;

2-(3-(1H-imidazol-1-il)propil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;

N-butil-2-[3-(1H-imidazol-1-il)propil]-3-oxoisoindolina-1-carboxamida;

2-[3-(1H-imidazol-1-il)propil]-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida

2-(ciclohexil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;

N-butil-2-ciclohexil-3-oxoisoindolina-1-carboxamida;

2-ciclohexil-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida;

N,2-dibencil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;

N-bencil-2-terc-butil-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida;

N-bencil-2-terc-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;

N,2-dibencil-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida;

N-bencil-2-terc-butil-5-hidroxi-3-oxoisoindolina-1-carboxamida;

2-ciclohexil-N-hexil-3-oxoisoindolina-1-carboxamida;

N,2-dihexil-3-oxoisoindolina-1-carboxamida;

N-hexil-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida;

N-hexil-2-(4-hidroxibutil)-3-oxoisoindolina-1-carboxamida;
N,2-diciclohexil-3-oxoisoindolina-1-carboxamida;
N-ciclohexil-2-hexil-3-oxoisoindolina-1-carboxamida;
N-ciclohexil-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida;
N-ciclohexil-2-(4-hidroxibutil)-3-oxoisoindolina-1-carboxamida;
(4-{1-[(ciclohexilamino)carbonil]-3-oxo-1,3-dihidro-2H-isoindol-2-il}butil)carbamato de terc-butilo;
N-adamantan-1-il-2-ciclohexil-3-oxoisoindolina-1-carboxamida;
N-adamantan-1-il-2-hexil-3-oxoisoindolina-1-carboxamida;
N-adamantan-1-il-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida;
N-adamantan-1-il-2-(2-morfolin-4-iletil)-3-oxoisoindolina-1-carboxamida
N,2-dibencil-5-{[(2-nitrofenil)sulfonil]amino}-3-oxoisoindolina-1-carboxamida;
[1-(terc-butilcarbamoil)-3-oxo-1,3-dihidro-2H-isoindol-2-il]acetato de etilo;
N-[2-(3,4-dimetoxifenil)etil]-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida
N-ciclopentil-2-(3-metoxibencil)-3-oxoisoindolina-1-carboxamida;
2-(1,3-benzodioxol-5-ilmetil)-N-{[(4-metilfenil)sulfonil]metil}-3-oxoisoindolina-1-carboxamida;
N-ciclohexil-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida;
2-bencil-N-ciclohexil-3-oxoisoindolina-1-carboxamida;
N-{[(4-metilfenil)sulfonil]metil}-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida;
2-(4-clorobencil)-N-{[(4-metilfenil)sulfonil]metil}-3-oxoisoindolina-1-carboxamida;
N-ciclohexil-2-(2-furilmetil)-3-oxoisoindolina-1-carboxamida;
2-(4-clorobencil)-N-ciclohexil-3-oxoisoindolina-1-carboxamida;
2-benzoil-1-hidroxi-3-oxo-N-fenilisoindolina-1-carboxamida; 3-oxo-N,2-difenilisoindolina-1-carboxamida; ácido 6-{[(1-metil-2-octil-3-oxo-2,3-dihidro-1H-isoindol-1-il)carbonil]amino}hexanoico; N-(metil)-2-benzoil-1-hidroxi-3-oxoindolina-1-carboxamida; N-(fenil)-2-benzoil-1-hidroxi-3-oxoisoindolina-1-carboxamida;ácido 6-[(2-alil-1-metil-3-oxoisoindolina-1-carbonil)-amino]-hexanoico; N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-etil-3-oxoisoindolina-1-carboxamida;
N1-ciclopentil-N4-(2,6-diclorofenil)-2-(2,4-dimetilfenil)-5-metil-3-oxoisoindolina-1,4-dicarboxamida;

[1-(terc-butilcarbamoil)-3-oxo-1,3-dihidro-2H-isoindol-2-il]acetato de metilo;
1-hidroxi-2-metil-3-oxoisoindolina-1-carbohidrazida;
1-hidroxi-3-oxo-fenilisoindolina-1-carbohidrazida;
o una de sus sales farmacéuticamente aceptables;

c) el compuesto no es:
2-(2-etoxietil)-N-isopropil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-(3-pirrolidin-1-ilpropil)isoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-(tetrahidrofuran-2-ilmetil)isoindolina-1-carboxamida;
2-[1-(hidroximetil)butil]-N-isopropil-3-oxoisoindolina-1-carboxamida;
N-isopropil-2-(3-metilbutil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-ciclohexil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(3-metilbutil)-3-oxoisoindolina-1-carboxamida;
N-{[2-(3-metilbutil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de metilo;
N-({2-[1-(hidroximetil)butil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de terc-butilo;
N-{[2-(3-metilbutil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
N-(terc-butil)-2-[1-(metoximetil)propil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(dietilamino)etil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[1-(hidroximetil)butil]-3-oxoisoindolina-1-carboxamida;
N-{[3-oxo-2-(2-tienilmetil)-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
N-({2-[2-(metiltio)etil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de terc-butilo;
N-{[2-(ciclopropilmetil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de metilo;
o
2-(2,2-dimetilpropil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida.
o una de sus sales farmacéuticamente aceptables.

De aquí en adelante se hará referencia a los compuestos de fórmula I como los definidos antes como "los compuestos de la invención".

En una realización R^1 representa C_1-C_7 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, -OR^8, -$COXR^{11}$, arilo o Het^1); además R^1 representa Het^2.

En una realización R^1 representa C_1-C_7 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, -OR^8, -$COXR^{11}$, fenilo, naftalenilo o Het^1).

En una realización R^1 representa

(1-bencilpirrolidin-3-ilo); (1-fluoro-3-fenilpropan-2-ilo); (1-metil-5-fenilpirazol-3-il)metilo; (1-metilpirrol-2-il)metilo; (2,3-difluorofenil)metilo; (2,4-difluorofenil)metilo; (2,5-dimetoxifenil)metilo; (2,5-dimetilfenil)metilo; (2-bromofenil)metilo; (2-cloro-4-fluorofenil)metilo; (2-cloro-6-fenoxifenil)metilo; (2-clorofenil)metilo; (2-dimetilamino-2-feniletilo); (2-etoxifenil)metilo; (2-fluorofenil)metil; (2-metoxifenil)metilo; (2-metil-2-fenilpropilo); (2-metilfenil)metilo; (2-fenoxifenil)metilo; (2-fenilfenil)metilo; (2-piridin-3-ilfenil)metilo; (3,4-diclorofenil)metilo; (3,4-difluorofenil)metilo; (3,5-dimetoxifenil)metilo; (3-clorofenil)metilo; (3-ciano-4-fluorofenil)metilo; (3-cianofenil)metilo; (3-fluorofenil)metilo; (3-hidroxi-2,2-dimetilpropilo); (3-metoxifenil)metilo; (3-fenil1,2-oxazol-5-il)metilo; (3-fenilfenil)metilo; (3-pirrol-1-ilfenil)metilo; (4-clorofenil)metilo; (4-dimetilaminofenil)metilo; (4-fluorofenil)metilo; (4-hidroxifenil)metilo; (4-metoxicarbonilfenil)metilo; (4-fenoxifenil)metilo; (4-fenilfenil)metilo; (5-metil-2-fenil-1,3-oxazol-4-il)metilo; (5-metil-3-fenil-1,2-oxazol-4-il)metilo; (fenilpiridin-2-il-metilo); [(1R)-1-(4-metoxifenil)etilo]; [(1S)-1-feniletilo; [(1R)-1-feniletilo]; [(1R)-2-(4-clorofenil)-1-(4,4,4- trifluorobutilcarbamoil)etilo]; [(1R)-2-(4-clorofenil)-1-metoxicarbonil-etilo]; [(1S)-1-naftalen-1-iletilo]; [(2R)-2-(4-clorofenil)propilo]; [(2S)-2-(4- clorofenil)propilo]; [(4-clorofenil)-piridin-4-il-metilo]; [(4-fluorofenil)-piridin-3-il-metilo]; [(4-fluorofenil)-piridin-3-il-metilo]; [(4-fluorofenil)-piridin-3-il-metilo]; [2-(2,4-diclorofenil)fenil]metilo; [2-(2,4-difluorofenil)fenil]metilo; [2-(2,5-difluorofenil)fenil]metilo; [2-(2-clorofenil)fenil]metilo; [2-(3,4-diclorofenil)fenil]metilo; [2-(3,4-difluorofenil)fenil]metilo; [2-(3-cloro-4-fluorofenil)fenil]metilo; [2-(3-fluorofenil)fenil]metilo; [2-(4-cloro-2-metilfenil)-2,2-difluoroetilo]; [2-(4-clorofenil)fenil]metilo; [2-(4-fluoro-2-metilfenil)fenil]metilo; [2-(4-

fluorofenoxi)fenil]metilo; [2-(4-fluorofenil)fenil]metilo; [2-(4-metoxifenil)-2-oxo-etilo]; [2-(4-metoxifenil)fenil]metilo; [2-(4-metilfenil)fenil]metilo; [2-(trifluorometil)fenil]metilo; [2-[4-(trifluorometil)fenoxi]fenil]metilo; [3-(difluorometoxi)fenil]metilo; [3,5-bis(trifluorometil)fenil]metilo; [4-(difluorometoxi)fenil]metilo; [4-(trifluorometil)fenil]metilo; 1-(1H-indol-3-il)propan-2-ilo; 1-(4-fluorofenil)etilo; 1-naftalen-1-iletilo; 1-naftalen-2-iletilo; 1-feniletilo; 1-fenilpropilo; 2-(1-ciclohexenil)etilo; 2-(2-etoxifenil)etilo; 2-(2-metoxifenil)etilo; 2-(2-fenoxifenil)etilo; 2-(3,4-diclorofenil)etilo; 2-(3,5-dimetoxifenil)etilo; 2-(3-bromo-4-metoxifenil)etilo; 2-(3-fluorofenil)etilo; 2-(4-bromofenil)etilo; 2-(4-clorofenil)etilo; 2-(4-clorofenil)propilo; 2-(4-fluorofenoxi)propilo; 2-(4-fluorofenil)etilo; 2-(4-fluorofenil)propilo; 2-(4-fenoxifenil)etilo; 2-(4-metoxifenil)etilo; 2-(4-metoxifenil)etilo; 2-(4-fenilfenil)etilo; 2-(5-bromo-2-metoxifenil)etilo; 2-(6-cloro-1H-indol-3-il)etilo; 2,2-dimetilpropilo; 2,2-difeniletilo; 2-[2-(trifluorometoxi)fenil]etilo; 2-[3-(trifluorometil)fenil]etilo; 2-[4-(dietilcarbamoil)fenil]etilo; 2-[4-(trifluorometil)fenil]etilo; 2-benzo[1,3]dioxol-5-iletilo; 2-metilbutilo; 2-metilpropilo; 2-naftalen-1-ilpropilo; 2-fenoxipropilo; 2-fenilpropilo; 2-tiofen-2-iletilo; 3,3-dimetilbutilo; 3-fenilpropilo; 3-pirrolidin-1-ilpropilo; 4-fenilbutan-2-ilo; 4-fenilbutilo; 9H-fluoren-9-ilo; benzhidrilo; bencilo; cicloheptilo; ciclohexilo; ciclohexilmetilo; naftalen-1-ilmetilo; pentan-3-ilo; fenetilo; tiofen-2-ilmetilo; 2-fenilpropan-2-ilo; 1-fenilpropilo; [2-(4-clorofenil)-2-metilpropilo]; [4-fluoro-2-(4-fluorofenil)fenil]metilo; (4-fluoro-2-fenilfenil)metilo; [5-fluoro-2-(4-fluorofenil)fenil]metilo; (5-fluoro-2-fenilfenil)metilo; 1-(4-fluorofenil)etilo; 2-(4-clorofenil)propan-2-ilo; 2-(4-fluorofenil)propan-2-ilo o 1-(4-clorofenil)etilo.

(Para la denominación de los radicales se usó un programa del paquete Lexichem de Openeye, versión 4.)

En una realización R^2 representa C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, $-COR^{17}$, trimetilsililo, $-COXR^{18}$, arilo o Het^3); además R^2 representa arilo o Het^4.

En una realización R^2 representa

(1-bencilpirrolidin-3-ilo); (1-metilpirrol-2-il)metilo; (2,2-difluorobenzo[1,3]dioxol-5-il)metilo; (2,3-dimetilciclohexilo); (2,4-difluorofenil)metilo; (2-cloro-4-metilsulfonilfenil)metilo; (2-clorofenil)metilo; (2-fluoro-4-metilsulfonilfenil)metilo; (2-hidroxifenil)metilo; (2-metilpropan-2-il)oxicarbonilmetilo; (3,4-diclorofenil)metilo; (3,4-difluorofenil)metilo; (3,4-metoxifenil)metilo; (3-carbamoil-4-fluorofenil)metilo; (3-clorofenil)metilo; (3-ciano-4-fluorofenil)metilo; (3-cianofenil)metilo; (3-metoxifenilo); (3-metil-5-fenil-1,2-oxazol-4-il)metilo; (4-amino-2-metilpirimidin-5-il)metilo; (4-carbamoilfenilo); (4-carbamoilfenil)metilo; (4-ciano-2,6-difluorofenil)metilo; (4-cianofenilo); (4-cianofenil)metilo; (4-dimetilaminofenil)metilo; (4-fluorofenil)metilo; (4-hidroxifenil)metilo; (4-metilciclohexilo); (4-metilsulfonilfenil)metilo; (5-metil-1,2-oxazol-3-il)metilo; (5-metil-2-furil)metilo; (5-metil-2-fenil-1,3-oxazol-4-il)metilo; (5-metilpirazin-2-il)metilo; [2-(trifluorometil)fenil]metilo; [3-(aminometil)-4-fluorofenil]metilo; [3-(difluorometoxi)fenil]metilo; [3-(dimetilcarbamoil)-4-fluorofenil]metilo; [3-(trifluorometil)fenil]metilo; [3,5-bis(trifluorometil)fenil]metilo; [3-[[(2,2-difluoroacetil)amino]metil]-4-fluorofenil]metilo; [4-(acetamidometil)fenil]metilo; [4-(aminometil)fenilo]; [4-(difluorometoxi)fenil]metilo; [4-(trifluorometil)fenil]metilo; [4-[[(2,2-difluoroacetil)amino]metil]fenilo]; [4-[[(2-fluoroacetil)amino]metil]fenil]metilo; [5-(2-furil)1,2-oxazol-3-il]metilo; [6-(trifluorometil)piridin-3-il]metilo; 1H-indol-3-ilmetilo; 1-piridin-4-iletilo; 2-(1H-indol-3-il)etilo; 2-(2,4-diclorofenil)etilo; 2-(2,6-diclorofenil)etilo; 2-(2-clorofenil)etilo; 2-(3,4-diclorofenil)etilo; 2-(3,4-dimetoxifenil)etilo; 2-(3-clorofenil)etilo; 2-(3-fluorofenil)etilo; 2-(4-benzoilpiperazin-1-il)etilo; 2-(4-clorofenil)etilo; 2-(4-fluorofenil)etilo; 2-(4-metoxifenil)etilo; 2-[3-(trifluorometil)fenil]etilo; 2-benzo[1,3]dioxol-5-iletilo; 2-etoxicarboniletilo; 2-furilmetilo; 2-metoxietilo; 2-piridin-2-iletilo; 2-piridin-4-iletilo; 2-tiofen-2-iletilo; 3-imidazol-1-ilpropilo; 3-metoxipropilo; 4,4,4-trifluorobutilo; 4,4-difluorobutilo; benzo[1,3]dioxol-5-ilmetilo; benzotriazol-1-ilmetilo; bencilo; butilo; ciclohexilo; etilo; metoxicarbonilmetilo; fenetilo; propan-2-ilo; propilo; piridin-3-ilmetilo; piridin-4-ilmetilo; terc-butilo; trimetilsililmetilo; (5-oxo-1-propan-2-il-pirrolidin-3-il)metilo; propan-2-ilcarbamoilmetilo, (2-fluorofenil)metilo; (3-fluorofenil)metilo; 1-feniletilo; 2-fenilpropan-2-ilo; o 5-cianopentilo.

(Para ponerle nombre a los radicales se usó un programa del paquete Lexichem de Openeye, versión 4.)

En una realización R^1 representa C_1-C_7 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, -OR^8, -$COXR^{11}$, arilo o Het^1); además R^1 representa Het^2; y R^2 representa C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_7 cicloalquilo, –COR^{17}, trimetilsililo, –$COXR^{18}$, arilo o Het^3); además R^2 representa arilo o Het^4.

En una realización R^1 representa C_3-C_8 cicloalquilo (donde el grupo cicloalquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, -OR^8, -$COXR^{11}$, arilo, o Het^1); y R^2 representa C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_7 cicloalquilo, –COR^{17}, trimetilsililo, –$COXR^{18}$, arilo o Het^3); además R^2 representa arilo o Het^4.

En una realización R^3 representa hidrógeno, C_1-C_4 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre fluoro, C_2-C_6 alquenilo, trialquilsililo, –$COXR^{27}$, arilo o Het^5).

En una realización R^3 representa hidrógeno.

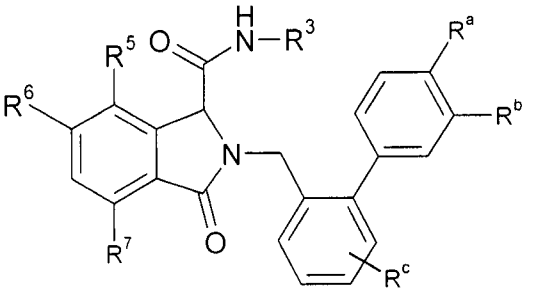
En una realización R^4 representa hidrógeno.

En una realización R^5 a R^7 representan independientemente, cada vez que aparecen, hidrógeno, -OH, halógeno, ciano, C_{1-6} alquilo, -OR^{36}, -$C(O)N(R^{40a})(R^{40b})$ o -$N(R^{44a})S(O)_2R^{44b}$.

En una realización arilo está, independientemente, cada vez que aparece, opcionalmente sustituido con –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, -OR^{50}, C_2-C_6 alquenilo, fenilo, Het^8; donde R^{50} representa C_1-C_6 alquilo o arilo.

En una realización arilo es, cada vez que aparece, fenilo.

En una realización de esta invención el compuesto de fórmula I es



en la cual R^a es hidrógeno o fluoro;

R^b es hidrógeno o fluoro;

R^c es hidrógeno o fluoro;

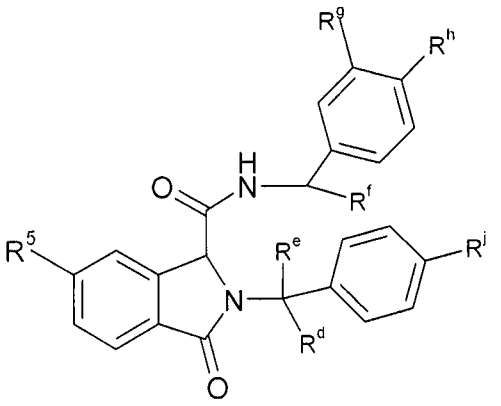
R^3 es C_{1-4} alquilo opcionalmente terminalmente sustituido con 1, 2 ó 3 fluoro;

R^5 es hidrógeno o C_{1-4} alquilo,

R^6 es hidrógeno, OH, halo o C_{1-4} alcoxi;

R^7 es hidrógeno o halo.

En una realización de esta invención el compuesto de fórmula I es



en la cual

R^d es hidrógeno o C_{1-4} alquilo;

R^e es hidrógeno o C_{1-4} alquilo;

R^f es hidrógeno o C_{1-4} alquilo;

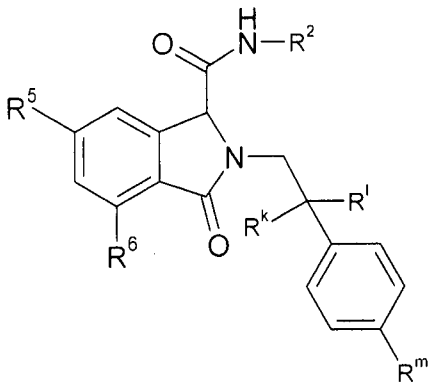
R^g es hidrógeno o halo;

R^h es hidrógeno o halo;

R^i es hidrógeno o halo;

R^5 es hidrógeno o halo.

En una realización de esta invención el compuesto de fórmula I es



en la cual

R^k es hidrógeno o C_{1-4} alquilo;

R^l es hidrógeno o C_{1-4} alquilo;

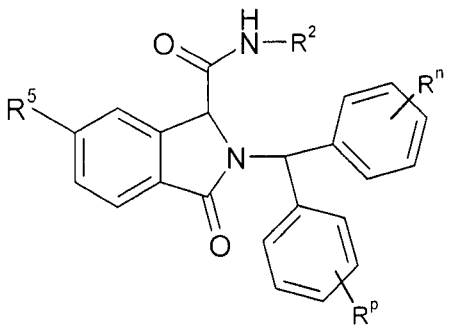
R^m es hidrógeno o halo;

R^2 es C_{3-6} alquilo;

R^5 es hidrógeno o halo;

R^6 es hidrógeno o halo.

En una realización de esta invención el compuesto de fórmula I es



en la cual

R^n es hidrógeno o halo;

R^p es hidrógeno o halo;

R^2 es C_{3-6} alquilo o bencilo, opcionalmente sustituido con halo en el anillo fenilo;

R^5 es hidrógeno o halo.

En una realización de esta invención R^1 es (2-fenilfenil)metilo (bifenilmetilo), opcionalmente sustituido con uno a tres fluoro;

R^2 se selecciona entre etilo, propilo, n-butilo, terc-butilo, 4,4,4-trifluorobutilo, 4,4-difluorobutilo, 4-fluorobutilo, benzo[1,3]dioxol-5-il-metilo, (2,2-difluorobenzo[1,3]dioxol-5-il)metilo, bencilo, (2-clorofenil)metilo, (4-fluorofenil)metilo, (2-trifluorometilfenil)metilo, (3-cianofenil)metilo, (4-cianofenil)metilo, (3-ciano-4-fluorofenil)metilo, (4-carbamoilfenil)metilo, (5-metilpirazin-2-il)metilo, piridin-3-ilmetilo, (4-amino-2-metilpirimidin-5-il)metilo, [6-(trifluorometil)piridin-3-il]metilo, piridin-3-ilmetilo [6-(trifluorometil)piridin-3-il]metilo, piridin-4-ilmetilo, [4-[[(2,2-difluoroacetil)amino]metil]fenil]metilo, [4-(acetamidometil)fenil]metilo, [4-[[(2-fluoroacetil)amino]metil]fenil]metilo, 2-feniletilo o 2-(4-fluorofenil)etilo;

R^5 a R^7 se seleccionan independientemente entre –OH, metilo, metoxi, cloro, fluoro, ciano, metilsulfonilamino, fluorometoxi, difluorometoxi, trifluorometanosulfonato;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, metoxi, fluoro o cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^1 es benzhidrilo (difenilmetilo), opcionalmente sustituido con uno o más sustituyentes seleccionados entre fluoro o cloro;
R^2 se selecciona entre etilo, propilo, butilo, terc-butilo, 4,4-difluorobutilo, 4,4,4-trifluorobutilo, bencilo, (2-cloro-4-metilsulfonilfenil)metilo, (4-metilsulfonilfenil)metilo, (2-fluoro-4-metilsulfonilfenil)metilo, (4-metilsulfonilfenil)metilo, (2-hidroxifenil)metilo, [2-(trifluorometil)fenil]metilo, (2,4-difluorofenil)metilo, (2-clorofenil)metilo, 2-(4-fluorofenil)etilo
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, metoxi, fluoro o cloro:
o uno de sus enantiómeros.

En una realización de esta invención R^1 es 4-fenilbutan-2-ilo, opcionalmente sustituido con uno o más sustituyentes seleccionados entre fluoro o cloro;
R^2 se selecciona entre (2-clorofenil)metilo, [2-(trifluorometil)fenil]metilo, bencilo, 2-feniletilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, metoxi, fluoro o cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^1 es 3,3-dimetilbutilo;
R^2 se selecciona entre [3-(difluorometoxi)fenil]metilo, [3-(trifluorometoxi)fenil]metilo, 2-(1H-indol-3-il)etilo, 1H-indol-3-ilmetilo, (3-clorofenil)metilo, (3;4-diclorofenil)metilo, [4-(difluorometoxi)fenil]metilo, 2-(3-fluorofenil)etilo, 2-benzo[1,3]dioxol-5-iletilo, 2-[3-(trifluorometil)fenil]etilo, 2-(3,4-diclorofenil)etilo, 2-(2,4-diclorofenil)etilo, 2-(2,6-diclorofenil)etilo, 2-(4-clorofenil)etilo, 2-(3-clorofenil)etilo o 2-(2-clorofenil)etilo;
R^3 es hidrógeno;
R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, metoxi, fluoro o cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^1 es bencilo (fenilmetilo), opcionalmente sustituido con uno o más sustituyentes seleccionados entre fluoro, cloro y ciano;
R^2 se selecciona entre etilo, n-propilo, isopropilo, n-butilo, sec-butilo, terc-butilo, benzo[1,3]dioxol-5-il-metilo, bencilo, 1-feniletilo, 2-feniletilo, ciclopentilo, donde esos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre fluoro, cloro, ciano y trifluorometilo; además R^2 representa piridin-3-ilmetilo, piridin-4-ilmetilo, [3-[[(2,2-difluoroacetil)amino]metilo]-4-fluorofenil]metilo, [4-(difluorometoxi)fenil]metilo, (4-dimetilaminofenil)metilo, [5-(2-furil)1,2-oxazol-3-il]metilo, [5-(2-furil)1,2-oxazol-3-il]metilo, 2-(3,4-dimetoxifenil)etilo, butan-2-ilo, ciclopentilo, (2,3-dilmetilciclohexilo), (4-hidroxifenil)metilo, [2-(trifluorometil)fenil] metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, metoxi, bromo, cloro, fluoro, trimetilsililo;
o uno de sus enantiómeros.

En una realización de esta invención R^1 es (2-ciclopentilfenil)metilo;
R^2 se selecciona entre 4,4-difluorobutilo y metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre bromo, fluoro, cloro o ciano;
o uno de sus enantiómeros.

En una realización de esta invención R^1 es 1-feniletilo, opcionalmente sustituido con uno o más sustituyentes seleccionados entre fluoro, cloro, ciano y metoxi;

R^2 se selecciona entre etilo, propilo, terc-butilo, 4,4-difluorobutilo, 4,4,4-trifluorobutilo, 4-metilsulfonilo, bencilo, donde el grupo bencilo está opcionalmente sustituido con uno o más sustituyentes seleccionados entre fluoro, cloro y ciano;
además R^2 representa piridinmetilo, ((2,2-difluoroacetil)amino)metilo, difluorometoxi, dimetilamino, 5-(2-furil)1,2-oxazol-3-il-metilo o ciclopentilo
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre bromo, fluoro, cloro o ciano;
o uno de sus enantiómeros.

En una realización de esta invención R^1 es 3-hidroxi-2,2-dimetilpropilo;
R^2 se selecciona entre [3-(difluorometoxi)fenil]metilo, (3,4-diclorofenil)metilo, (3-clorofenil)metilo, [3-(trifluorometil)fenil]metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, fluoro, cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^1 es 2-(4-clorofenil)propilo;
R^2 se selecciona entre metilo, etilo, n-propilo, propan-2-ilo, butilo, (4-amino-2-metilpirimidin-5-il)metilo, (5-metilpirazin-2-il)metilo, piridin-3-ilmetilo, [6-(trifluorometil)piridin-3-il]metilo, (4-amino-2-metilpirimidin-5-il)metilo, [6-(trifluorometil)piridin-3-il]metilo, (5-metil-2-fenil-1,3-oxazol-4-il)metilo, 4,4,4-trifluorobutilo, (4-metilsulfonilfenil)metilo, bencilo, (2,2-difluorobenzo[1,3]dioxol-5-il)metilo, (4-metilsulfonilfenil)metilo, butinilo, 2-(1H-indol-3-il)etilo; (4-carbamoilfenil)metilo, (4-cianofenil)metilo, [3-(dimetilcarbamoil)-4-fluorofenil]metilo, [3-(dimetilcarbamoil)-4-fluorofenil]metilo, [4-(aminometil)fenilo], [4-[[(2,2-difluoroacetil)amino]metil]fenilo], (4-carbamoilfenilo), piridin-4-ilmetilo, 3-metoxipropilo, (3-ciano-4-fluorofenil)metilo, [3-[[(2,2-difluoroacetil)amino]metil]-4-fluorofenil]metilo, [3-(aminometil)-4-fluorofenil]metilo, (3-carbamoil-4-fluorofenil)metilo, 2-piridin-4-iletilo, (1-metilpirrol-2-il)metilo, [4-(difluorometoxi)fenil]metilo, (1-bencilpirrolidin-3-ilo), 3-imidazol-1-ilpropilo, (4-

dimetilaminofenil)metilo, (4-metilsulfonilfenil)metilo, 3-metilaminopropilo, 1-piridin-3-iletilo, (3-metoxifenilo), 1-piridin-4-iletilo, (4-cianofenilo), 3-metoxipropilo, benzo[1,3]dioxol-5-ilmetilo, (3,4-dimetoxifenil)metilo, (3-metil-5-fenil-1,2-oxazol-4-il)metilo, (5-metil 1,2-oxazol-3-il)metilo, [2-(trifluorometil)fenil]metilo, (2-clorofenil)metilo, 2-(3,4-dimetoxifenil)etilo, 2-tiofen-2-iletilo, 2-(4-metoxifenil)etilo, 2-feniletilo, 2-metoxietilo, (4-fluorofenil)metilo, metoxicarbonilmetilo o benzotriazol-1-ilmetilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^1 es 2-(4-clorofenil)propilo;

R^2 representa terc-butilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, -OH, bromo, fluoro, cloro, metilo, $-OCH_3$, $-OCH_2F$ y trimetilsililo;

o uno de sus enantiómeros.

En una realización de esta invención R^1 es 2-(4-fluorofenil)propilo;

R^2 representa 4,4,4-trifluorobutilo, bencilo, terc-butilo o butilo,

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, -OH, bromo, fluoro, cloro, metoxi;

o uno de sus enantiómeros.

En una realización de esta invención R^1 es 2,2-dimetilpropilo;

R^2 representa [3-(trifluorometoxi)fenil]metilo [3-(difluorometoxi)fenil]metilo, (3,4-diclorofenil)metilo, 2-[3-(trifluorometil)fenil]etilo, 2-(1H-indol-3-il)etilo, (3-clorofenil)metilo, [4-(difluorometoxi)fenil]metilo, [3-

(trifluorometil)fenil]metilo, 2-(3-fluorofenil)etilo, 2-(2-clorofenil)etilo, 2-(3-clorofenil)etilo, 2-(2,4-diclorofenil)etilo, 2-(4-clorofenil)etilo, 2-(2,6-diclorofenil)etilo, benzo[1,3]dioxol-5-ilmetilo, o bencilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro,

o uno de sus enantiómeros.

En una realización de esta invención R^1 es 2-fenilpropan-2-ilo;

R^2 representa bencilo, 1-feniletilo, (4-fluorofenil)metil,4,4,4-trifluorobutilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro,

o uno de sus enantiómeros.

En una realización de esta invención R^1 es 1-fenilpropilo;

R^2 es bencilo, (2-clorofenil)metilo, [2-(trifluorometil)fenil]metilo o (4-dimetilaminofenil)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^1 es [2-(4-clorofenil)-2-metilpropilo];

R^2 representa n-butilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro o cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es (2-clorofenil)metilo;

R^1 representa benzhidrilo, (2-piridin-3-ilfenil)metilo, (3,4-difluorofenil)metilo,

1-(1H-indol-3-il)propan-2-ilo, 2-(4-clorofenil)propilo, (2,5-dimetilfenil)metilo, [(1R)-1-(4-metoxifenil)etilo], 2-(1H-indol-3-il) propilo, [(1R)-1-(3-metoxifenil)etilo], [(1S)-1-naftalen-1-iletilo], 1-fenilpropilo, 2-fenilpropilo, 3-fenilpropilo, 2-feniletilo, 4-fenilbutan-2-ilo, (2-fenilfenil)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es (3,4-diclorofenil)metilo;

R^1 es (3-hidroxi-2,2-dimetilpropilo), 2,2-dimetilpropilo, 2-metilpropilo o 3,3-dimetilbutilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es (3-clorofenil)metilo;

R^1 representa (3-hidroxi-2,2-dimetilpropilo), 2-metilpropilo, 2,2-dimetilpropilo, 3,3-dimetilbutilo, (4-hidroxifenil)metilo o (3-cianofenil)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es (3-ciano-4-fluorofenil)metilo;

R^1 es (2-cloro-4-fluorofenil)metilo, [3,5-bis(trifluorometil)fenil]metilo, (3-ciano-4-fluorofenil)metilo, 2-feniletilo, bencilo, (3,4-difluorofenil)metilo, (2-fenilfenil)metilo o 2-(4-clorofenil)propilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es (3-cianofenil)metilo;
R^1 es (2-fenilfenil)metilo, (3-clorofenil)metilo, (3,4-difluorofenil)metilo, [3,5-bis(trifluorometil)fenil]metilo o [4-(trifluorometil)fenil]metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es (4-fluorofenil)metilo;
R^1 es [(4-clorofenil)-piridin-4-il-metilo], [(4-fluorofenil)-piridin-3-il-metilo], (fenil-piridin-2-il-metilo), 2-(4-metoxifenil)etilo, (4-clorofenil)metilo, (2-fenilfenil)metilo, benzhidrilo, (2-piridin-3-ilfenil)metilo, (3,4-difluorofenil)metilo, (1-fluoro-3-fenil-propan-2-ilo), (1-metilpirrol-2-il)metilo, (2-fenilfenil)metilo, 2-(4-clorofenil)propilo, 1-(4-clorofenil)etilo, 2-(4-clorofenil)propan-2-ilo, 2-(4-fluorofenil)propan-2-ilo, 2-fenilpropan-2-ilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es (4-hidroxifenil)metilo;
R^1 es (3,4-difluorofenil)metilo, (3-clorofenil)metilo, [3,5-bis(trifluorometil)fenil]metilo o [4-(trifluorometil)fenil]metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es [(2-trifluorometil)fenil]metilo;
R^1 es (2-metoxifenil)metilo, (2-fluorofenil)metilo, benzhidrilo, 2-(4-clorofenil)etilo, [4-(piperidina-1-carbonil)fenil]metilo, 2-(4-clorofenil)propilo, (2-fenilfenil)metilo, 1-fenilpropilo, 2-fenilpropilo, 4-fenilbutan-2-ilo, 2-feniletilo, 3-fenilpropilo, 2-metilbutilo,

ciclohexilmetilo, (3-fluorofenil)metilo, (2-etoxifenil)metilo, [4-(trifluorometoxi) fenil]metilo o (3,4-difluorofenil)metilo

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, metoxi o metilo;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es [(3-difluorometoxi)fenil]metilo;

R^1 is 1-feniletilo, (3-hidroxi-2,2-dimetilpropilo), 3,3-dimetilbutilo o 2,2-dimetilpropilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es [(3-trifluorometoxi)fenil]metilo;

R^1 representa 3,3-dimetilbutilo o 2,2-dimetilpropilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es [(3-trifluorometil)fenil]metilo;

R^1 es (3-hidroxi-2,2-dimetilpropilo), 2-metilpropilo, 3,3-dimetilbutilo, 2,2-dimetilpropilo o (1-metilpirrol-2-il)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es [(4-difluorometoxi)fenil]metilo;

R^1 es 2-metilpropilo, 3,3-dimetilbutilo, 2,2-dimetilpropilo, (2-cloro-4-fluorofenil)metilo, 2-(4-clorofenil)propilo o [3,5-bis(trifluorometil)fenil]metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es [(6-trifluorometil)piridin-3-il]metilo;
R^1 es 2-(4-clorofenil)propilo o (2-fenilfenil)metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es 2-(1H-índol-3-il)etilo;
R^1 es 2-(4-clorofenil)propilo, 2-(2-fenoxifenil)etilo, 2-[4-(dietilcarbamoil)fenil]etilo, 2-(3-fluorofenil)etilo, 2-[2-(trifluorometoxi)fenil]etilo, 2-(4-fluorofenil)etilo, 2-(3,5-dimetoxifenil)etilo, 2-(4-fenilfenil)etilo, 2-(4-fenoxifenil)etilo, 2-(2-etoxifenil)etilo o 2-benzo[1.3]dioxol-5-iletilo, 2,2-dimetilpropilo o 3,3-dimetilbutilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es 2-(2,4-diclorofenil)etilo;
R^1 es 2-metilpropilo, 3,3-dimetilbutilo o 2,2-dimetilpropilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es 2-(2,6-diclorofenil)etilo;

R^1 es 2-metilpropilo, 3,3-dimetilbutilo o 2,2-dimetilpropilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es 4,4,4-trifluorobutilo;
R^1 es [2-(trifluorometil)fenil]metilo, [(1R)-1-feniletilo], benzhidrilo, 2-(4-clorofenil)propilo, (2-fenilfenil)metilo, (2-fenoxifenil)metilo, (2-fenilfenil)metilo, 2-(4-clorofenil)etilo, 2-(4-fluorofenil)etilo, 2-(4-fluorofenil)propilo, 2-(4-clorofenil)propan-2-ilo, 2-(4-fluorofenil)propan-2-ilo o 2-fenilpropan-2-ilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es 4,4-difluorobutilo;
R^1 es (2-ciclopentilfenil)metilo, [2-(trifluorometil)fenil]metilo, [(1R)-1-feniletil], (2-fenilfenil)metilo, benzhidrilo, 2-(4-clorofenil)propilo o (2-fenilfenil)metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es bencilo;
R^1 representa bencilo, benzhidrilo, [2-(trifluorometil)fenil]metilo, (2-piridin-3-ilfenil)metilo, (4-fenoxifenil)metilo, (2,4-difluorofenil)metilo, [4-(difluorometoxi)fenil]metilo, [3-(difluorometoxi)fenil]metilo, (3-pirrol-1-ilfenil)metilo, (3-fluorofenil)metilo, (4-cianofenil)metilo, (3,5-dimetoxifenil)metilo, (2-metoxifenil)metilo, (2-etoxifenil)metilo, [4-(trifluorometil)fenil]metilo, (3,4-difluorofenil)metilo, (2,5-dimetilfenil)metilo, [3,5-bis(trifluorometil)fenil]metilo, (2-metilfenil)metilo, (2,3-

difluorofenil)metilo, (2-bromofenil)metilo, [(4-fluorofenil)-piridina-3-il-metilo], [(4-clorofenil)-piridin-4-il-metilo], (fenil-piridin-2-il-metilo), (1-metil-5-fenil-pirazol-3-il)metilo, (5-metil-2-fenil-1,3-oxazol-4-il)metilo, (5-metil-3-fenil-1,2-oxazol-4-il)metilo, (3-fenil 1,2-oxazol-5-il)metilo, 2-(4-clorofenil)etilo, 2-(4-fluorofenil)etilo, 2-[4-(trifluorometil)fenil]etilo, 2-(5-bromo-2-metoxifenil)etilo, 2-(3-bromo-4-metoxifenil)etilo, 2-(4-fluorofenil)propilo, 2-(4-clorofenil)propilo, 4-fenilbutan-2-ilo, [2-(4-cloro-2-metil-fenil)-2,2-difluoro-etilo], 2-naftalen-1-ilpropilo, (2-metil-2-fenilpropilo), 2-fenoxipropilo, 2-(4-fluorofenoxi)propilo, 2-fenilpropan-2-ilo, cicloheptilo, 2-(2-metoxifenil)etilo, 1-naftalen-1-iletilo, 2-[3-(trifluorometil)fenil]etilo, 2-(6-cloro-1H-indol-3-il)etilo, 2-(4-clorofenil)propilo, [(1R)-1-(4-metoxifenil)etilo], [(1R)-1-(3-metoxifenil)etilo], 4-fenilbutan-2-ilo, 1-feniletilo, 2-feniletilo, 1-naftalen-2-iletilo, 2-(1-ciclohexenil)etilo, 1-(4-fluorofenil)etilo, 2-(4-fluorofenil)propan-2-ilo, 2-fenilpropan-2-ilo, 1-fenilpropilo o (2-fenilfenil)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5- R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro, -OH, metilo o metoxi;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es n-butilo;

R^1 es (2-fenilfenil)metilo, (2-fenoxifenil)metilo, [2-(4-fluorofenoxi)fenil]metilo, 2-(3-fluorofenil)etilo, 2-(4-fluorofenil)etilo, 2-(4-clorofenil)etilo, 2-[4-(trifluorometil)fenil]etilo, 2-(4-clorofenil)propilo, 2-(4-fluorofenil)propilo, (2-fenilfenil)metilo, 2-(4-fenilfenil)etilo, 2-naftalen-1-ilpropilo, 2-(2-etoxifenil)etilo, 2-(2-fenoxifenil)etilo, 2-(4-fenoxifenil)etilo, 2-[2-(trifluorometoxi)fenil]etilo, 2-(3,5-dimetoxifenil)etilo, 2-benzo[1,3]dioxol-5-iletilo, (1-fluoro-3-fenil-propan-2-ilo), 2-(4-clorofenil)propilo, naftalen-1-ilmetilo, 1-naftalen-2-iletilo, (2-fenilfenil)metilo, [2-(4-clorofenil)-2-metilpropilo];

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, -OH, metilo, metoxi;

o uno de sus enantiómeros.

En una realización de esta invención R^2 es etilo;
R^1 es benzhidrilo, (2-fenilfenil)metilo o 2-(4-clorofenil)propilo
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, -OH, metilo, metoxi;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es 2-feniletilo;
R^1 es (2-fenilfenil)metilo, 2-(4-metoxifenil)etilo, (4-clorofenil)metilo, 2-(4-clorofenil)etilo, 2-(3,4-diclorofenil)etilo, (3,4-difluorofenil)metilo, 2-(4-clorofenil)propilo, (2-cloro-4-fluorofenil)metilo o 4-fenilbutan-2-ilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, -OH, metilo, metoxi;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es propilo;
R^1 es (2-fenilfenil)metilo, benzhidrilo o 2-(4-clorofenil)propilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, -OH, metilo, metoxi;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es piridin-3-ilmetilo o piridin-4-ilmetilo;
R^1 es (2-fenilfenil)metilo, 2-(4-clorofenil)propilo, (3,4-difluorofenil)metilo, (2-cloro-4-fluorofenil)metilo o 1-(4-fluorofenil)etilo;
R^3 es hidrógeno;
R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, cloro, -OH;
o uno de sus enantiómeros.

En una realización de esta invención R^2 es terc-butilo;
R^1 es (2-fenilfenil)metilo, [2-(trifluorometil)fenil]metilo, [4-(difluorometoxi)fenil]metilo, (2-clorofenil)metilo, (2-metoxifenil)metilo, (3,4-difluorofenil)metilo, (3,4-difluorofenil) metilo, (4-fenoxifenil)metilo, [3,5-bis(trifluorometil)fenil]metilo, (4-fluoro-2-fenilfenil) metilo, (5-fluoro-2-fenilfenil)metilo, 1-feniletilo, 2-(4-clorofenil)etilo, 2-(2-fenoxifenil) etilo, 2-[2-(trifluorometoxi)fenil]etilo, 2,2-difeniletilo, 2-(4-fluorofenil)propilo, 2-(4-clorofenil)propilo, (2-fenilfenil)metilo, 2-(4-fenilfenil)etilo, [2-(3-fluorofenil)fenil]metilo, [2-(4-fluorofenil)fenil]metilo, [2-(3,4-difluorofenil)fenil]metilo, [2-(2,4-difluorofenil) fenil]metilo, [2-(2,5-difluorofenil)fenil]metilo, [2-(2,4-diclorofenil)fenil]metilo, [2-(3,4-diclorofenil)fenil]metilo, [2-(2-clorofenil)fenil]metilo, [2-(4-clorofenil)fenil]metilo, [2-(4-metilfenil)fenil]metilo, [2-(4-fluoro-2-metilfenil)fenil]metilo, [2-(4-metoxifenil)fenil]metilo, [4-fluoro-2-(4-fluorofenil)fenil]metilo, [2-(3-cloro-4-fluorofenil)fenil]metilo, [2-(4-fluoro-2-metilfenil)fenil]metilo, [5-fluoro-2-(4-fluorofenil)fenil]metilo, benzhidrilo, [(1R)-2-(4-clorofenil)-1-(4,4,4-trifluorobutilcarbamoil)etilo], [3,5-bis(trifluorometil)fenil]metilo, 9H-fluoren-9-ilo, [2-[4-(trifluorometil)fenoxi]fenil]metilo, 2-naftalen-1-ilpropilo, [(1R)-2-(4-clorofenil)-1-metoxicarbonil-etilo], (1-metil-5-fenil-pirazol-3-il)metilo o [2-(4-cloro-2-metilfenil)-2,2-difluoroetilo], (3-fenilfenil)metilo, (4-fluorofenil)metilo, (4-fenilfenil)metilo, [(4-clorofenil)-piridin-4-ilmetilo], 2-(4-fluorofenil)propilo, 2-(4-fenoxifenil)etilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 son independientemente –OH, bromo, cloro, fluoro, metilo, metoximetilsulfonilamino, trimetilsililo, ciano, $-OCHF_2$, $-OCH_2F$, $-OSO_2CF_3$,
o uno de sus enantiómeros.

En una realización de esta invención R^2 es trimetilsililmetilo;
R^1 es [3-(difluorometoxi)fenil]metilo, [4-(difluorometoxi)fenil]metilo, naftalen-1-ilmetilo, 1-naftalen-1-iletilo, 2-(4-bromofenil)etilo, (2-cloro-6-fenoxifenil)metilo o (3,4-diclorofenil)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno:

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro;

o uno de sus enantiómeros.

En una realización de la invención el compuesto de la invención está de acuerdo con la fórmula I según se definió antes pero también incluido el requisito d), además de los requisitos a), b) y c), que cuando R^2 representa $-(CH_2)_kN(R^{19a})(R^{19b})$,donde k representa 2; y R^{19a} y R^{19b} representan metilo;

o R^2 representa Het^4 seleccionado entre tiazolilo o piridilo;

o R^2 representa fenilo sustituido con dimetilamino;

y R^5-R^7 se seleccionan entre C_1-C_3 alquilo, $-OR^{36}$, donde R^{36} se selecciona entre C_1-C_3 alquilo:

entonces R^1 no representa fenilo, bencilo, piridilo, piridilmetilo, pirimidinilo, ciclohexilo, metilpiperazinilo, indanilo o naftilo, opcionalmente sustituidos con uno a tres sustituyentes seleccionados entre halógeno como fluoro, cloro, bromo y yodo, hidroxi, C_1-C_4 alquilo como metilo, etilo, propilo, isopropilo y butilo, C_1-C_4 alcoxi como metoxi, etoxi, propoxi, isopropoxi y butoxi, trifluorometilo, C_1-C_3 alquilo sustituido con al menos 1 átomo de flúor, como trifluorometoxi, trifluoroetoxi y trifluoropropoxi, amida, carboxi, ciano, C_1-C_4 alquiltio como metiltio, etiltio, propiltio y butiltio, nitro, amino, metilamino, dimetilamino, dimetilaminometilo, dipropilaminometilo, metilenodioxi, fenoxi, benciloxi, C_2-C_5 alcanoiloxi como acetoxi, propioniloxi y butiriloxi, C_1-C_3 ω-hidroxialquilo como hidroximetilo, hidroxietilo, C_2-C_5 alcanoiloxi- C_1-C_3 alquilo como acetiloximetilo, acetiloxiletilo y propioniloximetilo,

C_2-C_5 alcanoilamino como acetilamino y propionilamino; alcoxicarbonilo como metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, isopropoxicarbonilo y butoxicarbonilo, fenoxicarbonilo y benciloxicarbonilo.

A menos que se especifique lo contrario, los grupos alquilo y alcoxi según se les definió aquí pueden ser de cadena lineal o, cuando hay un número suficiente de átomos de carbono (es decir un mínimo de tres) pueden ser de cadena ramificada o cíclicos. Además, cuando hay un número suficiente de átomos de carbono (es decir un mínimo de cuatro), dichos

grupos alquilo y alcoxi también pueden ser en parte cíclicos y en parte acíclicos. A menos que se especifique lo contrario, los grupos alquilo y alcoxi también pueden estar sustituidos con uno o más átomos de halógeno, y especialmente átomos de flúor. A menos que se especifique lo contrario los alquilos cíclicos, por ejemplo C_3-C_8 cicloalquilo pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, oxo, halo, ciano, nitro, amino, alquilamino, C_{1-6} alquilo, C_{1-6} alcoxi, arilo, ariloxi o un grupo Het.

Los grupos alquileno según se los definió aquí son divalentes y pueden ser de cadena lineal o, cuando hay un número suficiente de átomos de carbono (es decir un mínimo de tres), de cadena ramificada. A menos que se especifique lo contrario, los grupos alquileno también pueden estar sustituidos con uno o más átomos de halógeno, y especialmente átomos de flúor.

El término "arilo", cuando se usa aquí, incluye grupos C_{6-10} arilo como fenilo, naftilo y similares. El término "ariloxi", cuando se usa aquí, incluye grupos C_{6-10} ariloxi como fenoxi, naftoxi y similares. Para evitar dudas, los grupos ariloxi a los que se hace referencia aquí están unidos al resto de la molécula a través del átomo de O del grupo oxi. A menos que se especifique lo contrario, los grupos arilo y ariloxi pueden estar sustituido con uno o más sustituyentes que incluyen –OH, halo, ciano, nitro, C_{1-6} alquilo, C_{1-6} alcoxi, sulfamoilo, metilsulfonilo, arilo, anilino y metilsulfinilo. Cuando están sustituidos, los grupos arilo y ariloxi están preferentemente sustituidos con uno a tres sustituyentes.

Los términos "halo" y "halógeno", cuando se usan aquí, incluyen flúor, cloro, bromo y yodo.

Los grupos Het (Het^1- Het^{76}) que pueden ser mencionados incluyen los que contienen 1 a 4 heteroátomos (seleccionados entre del grupo de oxígeno nitrógeno y/o azufre) y en los cuales el número total de átomos en el sistema de anillo puede ser entre 5 y 12. Los grupos Het pueden estar totalmente saturados, pueden tener carácter completamente aromático, parcialmente aromático y/o bicíclico. Los grupos heterocíclico que pueden ser mencionados incluyen benzodioxanilo, benzodioxepanilo, benzodioxolilo, benzofuranilo, bencimidazolilo, benzomorfolinilo, benzotriazol, benzoxazinolilo, benzotiofenilo, cromanilo, cinolinilo, dioxanilo, dioxotiolanilo, furanilo, imidazolilo, imidazo[1,2-

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α]piridinilo, indolilo, isoquinolinilo, isoxazolilo, morfolinilo, oxopirrolidinilo, oxopiperidinilo, oxazolilo, ftalazinilo, piperazinilo, piperidinilo, purinilo, piranilo, pirazinilo, pirazolilo, piridinilo, pirimidindinilo, pirrolidinonilo, pirrolidinilo, pirrolinilo, pirrolilo, quinazolinilo, quinolinilo, tetrahidropiranilo, tetrahidrofuranilo, tetrazol, tiazolilo, tienilo, tiocromanilo, triazolilo y similares. Los sustituyentes en los grupos Het pueden, cuando corresponda, estar ubicados en cualquier átomo del anillo incluso un heteroátomo. El punto de unión de los grupos Het puede ser a través de cualquier átomo del sistema de anillo incluso (cuando corresponda) un heteroátomo, o un átomo de cualquier anillo carbocíclico fusionado que pueda estar presente como parte del sistema de anillo. Los grupos Het también pueden estar en la forma N- o S-oxidada.

A menos que se especifique lo contrario, los grupos Het, pueden estar opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, oxo, halo, ciano, nitro, C_{1-6} alquilo, C_{1-6} alcoxi, arilo, ariloxi u otro grupo Het.

Además, el término "hidrocarburo" se refiere a cualquier estructura que comprenda sólo átomos de carbono e hidrógeno.

El término "radical hidrocarburo" o "hidrocarbilo" se refiere a cualquier estructura que resulte de la eliminación de uno o más hidrógenos de un hidrocarburo.

El término "alquenilo" se refiere a un grupo alquilo monovalente de cadena lineal o ramificada que tenga al menos un doble enlace carbono-carbono. El doble enlace de un alquenilo puede estar conjugado o no conjugado con otro grupo insaturado. A menos que se especifique lo contrario, los grupos alquenilo según se les definió aquí pueden ser de cadena lineal o, cuando hay un número suficiente de átomos de carbono (es decir un mínimo de tres) pueden ser de cadena ramificada o cíclicos. Además, cuando hay un número suficiente de átomos de carbono (es decir un mínimo de cuatro), dicho grupo alquenilo también puede ser en parte cíclico y en parte acíclico. A menos que se especifique lo contrario, los grupos alquenilo también pueden estar sustituidos con uno o más átomos de halógeno, y especialmente átomos de flúor.

El término "heteroalquilo" se refiere a un radical formado como resultado de reemplazar uno o más átomos de carbono de un alquilo con uno o más heteroátomos seleccionados entre N, O y S.

Los compuestos de la invención pueden presentar tautomerismo. Todas las formas tautoméricas y sus mezclas están comprendidas por el alcance de la invención.

Los compuestos de la invención también pueden contener uno o más átomos de carbono asimétricos y por consiguiente pueden presentar isomería óptica o diastereoisomería. Los diastereoisómeros se pueden separar usando técnicas convencionales, por ejemplo cromatografía o cristalización fraccionada. Los diversos estereoisómeros se pueden aislar mediante separación de una mezcla racémica u otra mezcla de los compuestos usando técnicas convencionales, por ejemplo cristalización fraccionada o HPLC. Alternativamente, los isómeros ópticos deseados se pueden preparar por reacción de los materials de partida ópticamente activos adecuados en condiciones que no causen racemización ni epimerización, o mediante derivatización, por ejemplo con un ácido homoquiral seguida de separación de los ésteres diastereoisoméricos por medios convencionales (por ejemplo, HPLC o cromatografía en sílice). Todos los estereoisómeros están comprendidos por el alcance de la invención. Todos los enantiómeros y sus mezclas están comprendidos por el alcance de la invención.

Las abreviaturas se listan al final de esta especificación.

Los ejemplos ilustrativos de cualquier sustituyente, grupo R o cualquier parte de tales grupos incluyen, pero no exclusivamente, a:

C_1-C_6 alquilo: metilo, etilo, propilo, isopropilo, 2-metil-1-propilo, 2-metil-2-propilo, 2-metil-1-butilo, 3-metil-1-butilo, 2-metil-3-butilo, 2,2-dimetil-1-propilo, 2-metil-1-pentilo, 3-metil-1-pentilo, 4-metil-1-pentilo, 2- metil-2-pentilo, 3-metil-2-pentilo, 4-metil-2-pentilo, 2,2-dimetil-1-butilo, 3,3- dimetil-1-butilo, 2-etil-1-butilo, butilo, isobutilo, t-butilo, pentilo, isopentilo, neopentilo y hexilo.

C_2-C_6 alquenilo: vinilo, alilo, butenilo, pentenilo, hexenilo, ciclohexenilo, butadienilo, pentadienilo y hexadienilo;

C_3-C_8 cicloalquilo: ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y ciclooctilo;

Los ejemplos ilustrativos de sustituyentes Het son benzodioxanilo, benzotriazol, furanilo, imidazolilo, indolilo, oxazolilo, piperazinilo, pirazinilo, pirazolilo, piridinilo, pirimidindinilo, pirrolidinilo, pirrolilo y tienilo.

Los compuestos de la invención que pueden ser mencionados son aquellos en los que R1 representa (2-fenilfenil)metilo, (4-fenoxifenil)metilo, (2-fenoxifenil)metilo, 2-(4-clorofenil)propilo, 2-(trifluorometil)fenilmetilo, 2,2-dimetilpropilo, benzhidrilo, 1-feniletilo o 2,2-dimetilpropilo, [2-(3,4)-difluorofenil)fenil]-metilo, [2-(4-clorofenil)-2-metilpropilo], [4-fluoro-2-(4-fluorofenil)fenil]metilo, (4-fluoro-2-fenilfenil)metilo, [5-fluoro-2-(4-fluorofenil)fenil]metilo, (5-fluoro-2-fenilfenil)metilo, 1-(4-fluorofenil)etilo, 2-(4-clorofenil)propan-2-ilo, 2-(4-fluorofenil)propan-2-ilo o 1-(4-clorofenil)etilo.

Los compuestos de la invención que pueden ser mencionados son aquellos en los que R^2 representa
etilo, propilo, butilo, terc-butilo, 4,4-difluorobutilo, 4,4,4-trifluorobutilo, metoxicarbonilmetilo, bencilo, 3,4-diclorofenilmetilo, (4-fluorofenil)metilo, [3-(difluorometoxi)fenil]metilo, (5-oxo-1-propan-2-il-pirrolidin-3-il)metilo, propan-2-ilcarbamoilmetilo, (2-fluorofenil)metilo, (3-fluorofenil)metilo, 1-feniletilo, 2-fenilpropan-2-ilo o 5-cianopentilo.

Los compuestos de la invención que pueden ser mencionados incluyen aquellos en los que arilo es fenilo, opcionalmente sustituido con uno o más de los siguientes: fluoro, cloro, hidroxi, metoxi, ciano, carbamoil, dialquilamino, metilsulfonilo, trifluorometilo, aminoalquilo o difluorometoxi.

Los compuestos de la invención que pueden ser mencionados son aquellos en los que al menos uno de los sustituyentes de R^1 y R^2 es un arilo.

Los compuestos de la invención que pueden ser mencionados son aquellos en los que R^1 se selecciona entre cadenas laterales voluminosas y ramificadas, por ejemplo bifenilos, benzhidrilos (difenilmetilo), fenetilos ramificados y grupos butilo terciarios; y R^2 se

selecciona entre bencilo y grupos lipófilos. Los grupos lipófilos se seleccionan entre, por ejemplo, butilo terciario, 4,4-difluorobutilo, 4,4,4-trifluorobutilo y n-butilo.

En una realización el compuesto de la invención está de acuerdo con la fórmula I

donde

R^1 representa C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, ciano, oxo, $-OR^8$, $-SR^{10}$, $-COXR^{11}$, $-N(R^{12a})(R^{12b})$, $-N(R^{13a})C(O)OR^{13b}$, $-OC(O)N(R^{14a})(R^{14b})$, $-SO_2R^{15}$, arilo o Het^1); además R^1 representa arilo o Het^2;

R^8, R^{10}, R^{11}, R^{13a}, R^{13b}, R^{15} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^9 (donde los grupos C_1-C_6 alquilo, arilo y Het^9 están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{10});

R^{12a} y R^{12b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{11} (donde los grupos C_1-C_6 alquilo, arilo y Het^{11} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{12});

R^{14a} y R^{14b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{13} (donde los grupos C_1-C_6 alquilo, arilo y Het^{13} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{14});

R^2 representa C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, trialquilsililo, $–COXR^{18}$, arilo o Het^3);

además R^2 representa $-(CH_2)_kN(R^{19a})(R^{19b})$, $-(CH_2)_kNR^{20a}C(O)N(R^{20b})(R^{20c})$, $-(CH_2)_nNR^{21a}SO_2R^{21b}$, $-(CH_2)_nSO_2R^{22}$, $-OC(O)N(R^{24a})(R^{24b})$, arilo o Het^4;

R^{18}, R^{21}, R^{22} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{15} (donde los grupos C_1-C_6 alquilo, arilo y Het^{15} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{16});

R^{19a} y R^{19b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{19} (donde los grupos C_1-C_6 alquilo, arilo y Het^{19} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{20});

R^{20a}, R^{20b} y R^{20c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{21} (donde los grupos C_1-C_6 alquilo, arilo y Het^{21} están opcionalmente sustituidos con uno o más sustituyentes selecionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{22});

R^3 representa hidrogeno, C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6alquenilo, trialquilsililo, –$COXR^{27}$, arilo o Het^5); además R^3 representa -$(CH_2)_kN(R^{28a})(R^{28b})$, -$(CH_2)_kN(R^{29a})C(O)N(R^{29b})(R^{29c})$, -$(CH_2)_nNR^{30a}SO_2R^{30b}$, -$(CH_2)_nSO_2R^{31}$, -$OC(O)N(R^{33a})(R^{33b})$, arilo o Het^6;

R^{27}, R^{30a}, R^{30b}, R^{31} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{23} (donde los grupos C_1-C_6 alquilo, arilo y Het^{23} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{24});

R^{28a} y R^{28b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{25} (donde los grupos C_1-C_6 alquilo, arilo y Het^{25} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{26});

R^{33a} y R^{33b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{27} (donde los grupos C_1-C_6 alquilo, arilo y Het^{27} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{28});

R^{29a}, R^{29b} y R^{29c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{29} (donde los grupos C_1-C_6 alquilo, arilo y Het^{29} están opcionalmente sustituidos con uno o más sustituyentes selecionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{30});

R^4 representa hidrógeno, –OH, arilo, C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, hidroxi, C_2-C_4 alquenilo, trialquilsililo), $-OR^{34}$, $-(CH_2)_mR^{35}$;

R^{34} representa independientemente, cada vez que aparece, hidrógeno, C_1-C_6 alquilo, arilo o Het^{31} (donde los grupos C_1-C_6 alquilo, arilo y Het^{31} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{32});

R^{35} representa independientemente arilo o Het^{33}(donde los grupos arilo y Het^{33} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{34});

R^5 a R^7 representan independientemente, cada vez que aparecen, hidrógeno, -OH, halógeno, ciano, nitro, C_{1-6} alquilo, $-OR^{36}$, $-N(R^{37a})(R^{37b})$, $-C(O)R^{38}$, $-C(O)OR^{39}$, $-C(O)N(R^{40a})(R^{40b})$, $-NC(O)OR^{41}$, $-OC(O)N(R^{42a})(R^{42b})$, $-N(R^{43a})C(O)R^{43b}$, $-N(R^{44a})S(O)_2R^{44b}$, $-S(O)_2R^{45}$, $-OS(O)_2R^{46}$, $-(CH_2)_nN(R^{47a})(R^{47b})$, $-(CH_2)_nNR^{48a}C(O)N(R^{48b})(R^{48c})$, $-(CH_2)_nNR^{49a}SO_2R^{49b}$, trialquilsililo, alilo o Het^7;

R^{36}, R^{38}, R^{39}, R^{41}, R^{43}, R^{44a}, R^{44b}, R^{45}, R^{46}, R^{49a} y R^{49b} representa independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{35} (donde los grupos C_1-C_6 alquilo,

arilo y Het^{35} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{36});

R^{37a} y R^{37b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{37} (donde los grupos C_1-C_6 alquilo, arilo y Het^{37} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{38});

R^{40a} y R^{40b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{39} (donde los grupos C_1-C_6 alquilo, arilo y Het^{39} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{40});

R^{42a} y R^{42b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{41} (donde los grupos C_1-C_6 alquilo, arilo y Het^{41} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{42});

R^{47a} y R^{47b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{43} (donde los grupos C_1-C_6 alquilo, arilo y Het^{43} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{44});

R^{48a}, R^{48b} y R^{48c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{45} (donde los grupos C_1-C_6 alquilo, arilo y Het^{45} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{46});

arilo está, cada vez que aparece, opcionalmente sustituido con –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, C_3-C_8 cicloalquilo, C_2-C_6 alquenilo, arilo, Het^8, $-OR^{50}$, $-(CH_2)_mR^{51}$, $-SR^{52}$, $-C(O)R^{53}$, $-COXR^{54}$, $-N(R^{55a})(R^{55b})$, $-SO_2R^{56}$, $-OS(O)_2R^{57}$, $-(CH_2)_mN(R^{58a})(R^{58b})$, $-(CH_2)_mNR^{59a}C(O)N(R^{59b})(R^{59c})$, $-C(O)OR^{60}$, $-C(O)N(R^{61a})(R^{61b})$, $-N(R^{62a}C(O)R^{62b}$,

$-N(R^{63a})C(O)OR^{63b}$, $-OC(O)N(R^{64a})(R^{64b})$, $-N(R^{65a})S(O)_2R^{65b}$ y $OC(O)R^{66}$;

R^{50} a R^{54}, R^{56}, R^{57}, R^{60}, R^{62a}, R^{62b}, R^{63a}, R^{63b}, R^{65a}, R^{65b} y R^{66} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{47} (donde los grupos C_1-C_6 alquilo, arilo y Het^{47} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{48});

R^{51} representa independientemente arilo o Het^{49} (donde los grupos arilo y Het^{49} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{50});

R^{55a} y R^{55b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{51} (donde los grupos C_1-C_6 alquilo, arilo y Het^{51} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{52});

R^{58a} y R^{58b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{53} (donde los grupos C_1-C_6 alquilo, arilo y Het^{53} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{54});

R^{59a}, representa independientemente, cada vez que aparece, hidrógeno, C_1-C_6 alquilo, arilo o Het^{55} (donde los grupos C_1-C_6 alquilo, arilo y Het^{55} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{56});

R^{61a} y R^{61b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{57} (donde los grupos C_1-C_6 alquilo, arilo y Het^{57} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{58});

R^{64a} y R^{64b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{59} (donde los grupos C_1-C_6 alquilo, arilo y Het^{59} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{60});

Het^1 a Het^{60} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde los grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro, C_{1-6} alquilo, C_{2-6} alquenilo, arilo, otro Het, $-OR^{67}$, $-(CH_2)_mR^{68}$, $-SR^{69}$, $-COXR^{70}$, $-N(R^{71a})(R^{71b})$, $-SO_2R^{72}$, $-(CH_2)_mN(R^{73a})(R^{73b})$, $-(CH_2)_mNR^{74a}C(O)N(R^{74b})(R^{74c})$, $-C(O)R^{75}$, $-C(O)OR^{76}$, $-C(O)N(R^{77a})(R^{77b})$, $-N(R^{78a})C(O)R^{78b}$, $-N(R^{79a})S(O)_2R^{79b}$, $OC(O)R^{80}$, $-NC(O)OR^{81}$, $-OC(O)N(R^{82a})(R^{82b})$;

R^{67}, R^{69}, R^{70}, R^{72}, R^{75}, R^{76}, R^{78a}, R^{78b}, R^{79a}, R^{79b}, R^{80} o R^{81} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{61} (donde los grupos C_1-C_6 alquilo, arilo y Het^{61} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{62});

R^{68} representa independientemente arilo o Het^{63}(donde los grupos arilo y Het^{63} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{64});

R^{71a} y R^{71b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{65} (donde los grupos C_1-C_6 alquilo, arilo y Het^{65} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{66});

R^{73a} y R^{73b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{67} (donde los grupos C_1-C_6 alquilo, arilo y Het^{67} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{68});

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R^{74a} y R^{74b} y R^{74c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{69} (donde los grupos C_1-C_6 alquilo, arilo y Het^{69} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{70});

R^{77a} y R^{77b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{71} (donde los grupos C_1-C_6 alquilo, arilo y Het^{71} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{72});

R^{82a} y R^{82b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{73} (donde los grupos C_1-C_6 alquilo, arilo y Het^{73} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{74});

Het^{61} a Het^{74} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde los grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro y C_{1-6} alquilo:

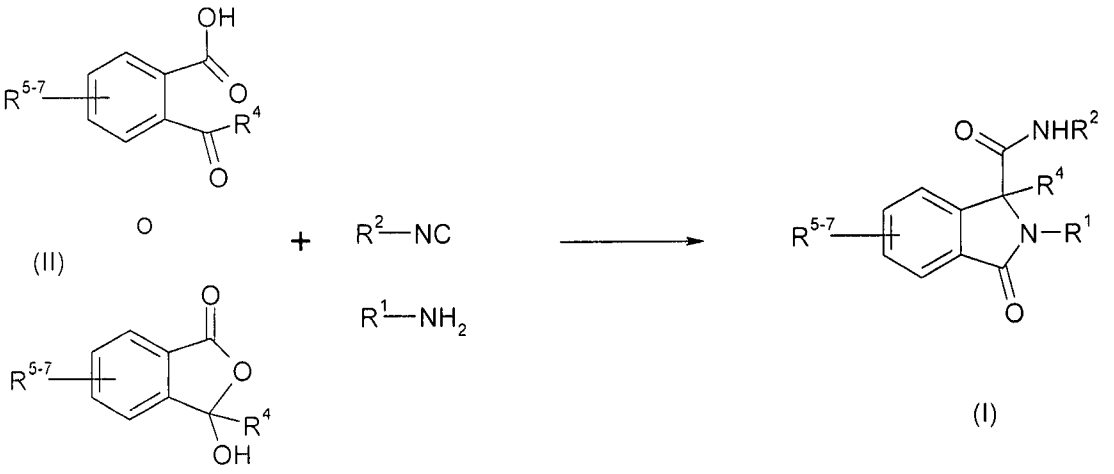
X representa un átomo de nitrógeno u oxígeno;
m es un número entero entre 0 y 10;
n es un número entero entre 0 y 4;
k es un número entero entre 1 y 5;
y con las condiciones a), b) y c) según se definieron antes.

En una realización el compuesto de la invención está de acuerdo con la fórmula I donde

R^4 representa –OH, arilo, C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, hidroxi, C_2-C_4 alquenilo, trialquilsililo), $-OR^{34}$, $-(CH_2)_mR^{35}$;

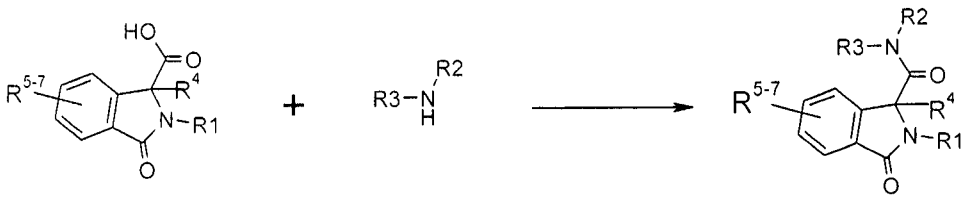
Preparación:

De acuerdo con la invención también se estipula un proceso para la preparación de compuestos de fórmula I que comprende:
la reacción de un compuesto de fórmula II,



donde R^3 a R^5 son los definidos antes, con una amina R^1-NH_2 y un isonitrilo R^2-NC en condiciones estándar de reacción de Ugi para dar compuestos de fórmula I donde R^1 a R^5 son los definidos antes.

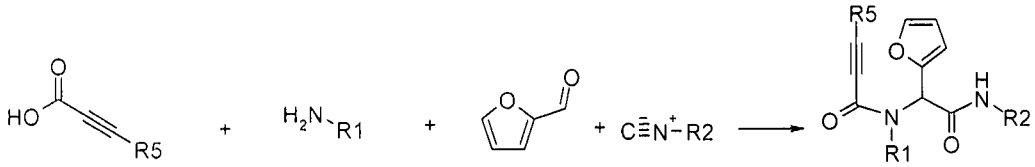
De acuerdo con la invención también se estipula un proceso para la preparación de compuestos de fórmula I que comprende la reacción que un compuesto de fórmula III con una amina en condiciones estándar de reacción de acoplamiento de amida.



(III)

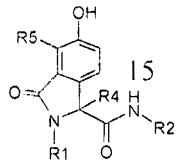
donde R^1 a R^7 son los definidos antes.

De acuerdo con la invención también se estipula un proceso para la preparación de un compuesto de fórmula I que comprende una reacción de UGI de cuatro componentes con una amina, un ácido, un aldehído e isonitrilo para el compuesto intermedio (IV)



(IV)

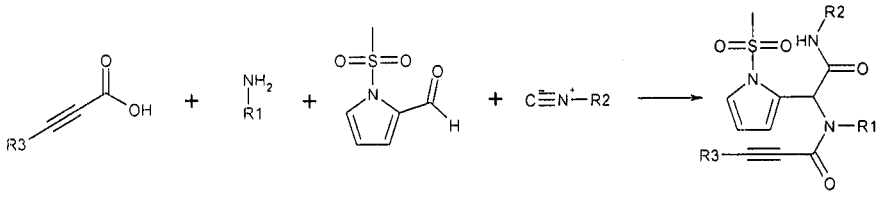
Después el compuesto (IV) se somete a una reacción intramolecular de Diels-Alder de acuerdo con los métodos bibliográficos para dar compuestos de fórmula I.



R4=H (I)

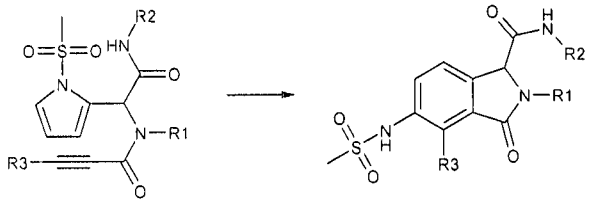
La secuencia de síntesis se originó en un procedimiento publicado. D. L. Wright, C. V. Robotham y K. Aboud, *Tetrahedron Lett.* 2002, *43*, 943–946.

De acuerdo con la invención también se estipula un proceso para la preparación de un compuesto de fórmula I que comprende una reacción de UGI de cuatro componentes con una amina, un ácido, un aldehído e isonitrilo para el compuesto intermedio (V)



(V)

Después el compuesto (V) se somete a una reacción intramolecular de Diels-Alder de acuerdo con métodos bibliográficos para dar compuestos de fórmula I.



Una reacción similar se describe en J. Org. Chem. 2004, *69*, 1.207-1.214.

Para evitar dudas se debe comprender que cuando en esta especificación un grupo se califica como "precedentemente definido" "definido precedentemente" o "definido antes" dicho grupo abarca la primera definición que se produzca y la más amplia así como todas las otras definiciones particulares para ese grupo.

Los prefijos *n*-, *s*-, *i*- *t*-, *terc*- tienen sus significados usuales: normal, secundario, *iso* y terciario.

Los técnicos con experiencia también apreciarán que diversas interconversiones y transformaciones de sustituyentes o de grupos funcionales corrientes con ciertos compuestos de fórmula I proporcionarán otros compuestos de fórmula I. Por ejemplo, el carbonilo se puede reducir a hidroxi o alquileno, e hidroxi se puede convertir en halógeno, y yodo, bromo y cloro se pueden convertir en ciano.

Los compuestos de la invención también se pueden aislar de sus mezclas de reacción usando técnicas convencionales.

Los técnicos con experiencia en el área apreciarán que, en el proceso descrito antes, los grupos funcionales de compuestos intermedios pueden estar, o puede ser necesario que estén, protegidos por grupos protectores.

Los grupos funcionales que es deseable proteger incluyen hidroxi, amino y ácido carboxílico. Los grupos protectors adecuados para hidroxi incluyen grupos trialquilsililo y diarilalquilsililo (por ejemplo, *terc*-butildimetilsililo, *terc*-butildifenilsililo o trimetilsililo), grupos tetrahidropiranilo y alquilcarbonilo (por ejemplo, grupos metil- y etilcarbonilo). Los grupos protectores adecuados para amino incluyen bencilo, sulfonamido (por ejemplo bencenosulfonamido), *terc*-butiloxicarbonilo, 9-fluoroenil-metoxicarbonilo o benciloxicarbonilo. Los grupos protectores adecuados para amidino y guanidino incluyen benciloxicarbonilo. Los grupos protectores adecuados para ácido carboxílico incluyen C_{1-6} alquilo o ésteres de bencilo.

La protección y desprotección de grupos funcionales puede tener lugar antes o después de cualquiera de los pasos de reacción descritos precedentemente.

Los grupos protectores se pueden eliminar siguiendo técnicas bien conocidas por los técnicos con experiencia en el área como se describió antes.

El uso de grupos protectores se describe en detalle en "Protective Groups in Organic Chemistry", editado por J.W.F. McOmie, Plenum Press (1973) y "Protective Groups in Organic Synthesis" 3ª edición, T.W. Greene y P.G.M. Wuts, Wiley-Interscience (1999).

Los técnicos con experiencia en el área apreciarán que, para obtener compuestos de la invención de manera alternativa, y en algunas ocasiones, más conveniente, los pasos individuales del proceso mencionado aquí se pueden realizar en un orden diferente, y/o las reacciones individuales se pueden realizar en una etapa diferente de la ruta general (es decir se pueden agregar sustituyentes y/o realizar transformaciones químicas a productos intermedios diferentes a los asociados precedentemente con una reacción particular). Esto dependerá entre otras cosas de factores como la naturaleza de los otros grupos funcionales presentes en un sustrato particular, la disponibilidad de productos intermedios clave y la estrategia de

grupos protectores que se va a adoptar (si es que se va adoptar alguna). Claramente, el tipo de reacción química involucrada influirá en la elección del reactivo que se usa en dichos pasos de la síntesis, la necesidad y el tipo de grupos protectors que se emplean, y la secuencia para llevar a cabo la síntesis.

Los técnicos con experiencia en el área también apreciarán que, aunque ciertos derivados protegidos de los compuestos de formula I, que pueden ser preparados antes de una etapa final de desprotección, pueda no poseer actividad farmacológica en sí mismos, pueden ser administrados parenteralmente u oralmente y después ser metabolizados en el organismo para formar compuestos de la invención que son farmacológicamente activos. Por consiguiente, dichos derivados pueden ser descritos como "profármacos". Además, ciertos compuestos de fórmula I pueden actuar como profármacos de otros compuestos de fórmula I.

Todos los profármacos de los compuestos de fórmula I están comprendidos por el alcance de la invención.

Uso médico y farmacéutico

Los compuestos de la invención son útiles porque poseen la actividad farmacológica. Por consiguiente se indican como productos farmacéuticos.

Por lo tanto, de acuerdo con otro aspecto de la invención se estipulan los compuestos de la invención para usar como productos farmacéuticos.

En particular, los compuestos de la invención presentan actividad inhibitoria del canal de potasio, especialmente actividad bloqueante de Kv1.5, por ejemplo como se demostró en la prueba que describe a continuación.

Por lo tanto, se espera que los compuestos de la invención sean útiles tanto en la profilaxis como en el tratamiento de una afección el cual es efectuado o facilitado por la inhibición de Kv1.5, en particular las arritmias cardíacas, por ejemplo la fibrilación auricular, el aleteo auricular, la arritmia auricular y la taquicardia auricular.

Por lo tanto, los compuestos de la invención se indican en el tratamiento o la profilaxis de las enfermedades cardíacas, o en indicaciones relacionadas con enfermedades cardíacas, en las cuales las arritmias, por ejemplo, la fibrilación auricular, el aleteo auricular, la arritmia auricular y la taquicardia auricular, se cree que desempeñan un papel principal, entre ellas la cardiopatía isquémica, el ataque cardíaco súbito, el infarto miocárdico, la insuficiencia cardíaca, la cirugía cardíaca y los sucesos tromboembólicos.

De acuerdo con otro aspecto de la invención, se estipula un método de tratamiento de una arritmia que comprende la administración de una cantidad terapéuticamente eficaz de un compuesto de la invención a una persona que sufre de, o esta predispuesta a sufrir, dicha afección.

Preparaciones farmacéuticas

Los compuestos de la invención se administrarán generalmente por vía oral, subcutánea, intravenosa, intraarterial, transdérmica, intranasal, por inhalación, o por cualquier otra ruta parenteral, en forma de preparaciones farmacéuticas que comprenden el principio activo. En una forma farmacéutica aceptable desde el punto de vista farmacéutico. Dependiendo del trastorno y del paciente a ser tratado, así como de la vía de administración, las composiciones se pueden administrar a diferentes dosis.

Los compuestos de la invención también se pueden combinar con cualquier otro fármaco útil en el tratamiento de las arritmias y/o otros trastornos cardiovasculares.

De acuerdo con otro aspecto de la invención se estipula por lo tanto una formulación farmacéutica que incluye un compuesto de la invención mezclado con un adyuvante, diluyente o portador farmacéuticamente aceptable.

Las dosis diarias adecuadas de los compuestos de la invención en el tratamiento terapéutico de los seres humanos son entre aproximadamente 0,005 y 25,0 mg/kg peso corporal en la administración oral y entre aproximadamente 0,005 y 10,0 mg/kg peso corporal en la

administración parenteral. Los ejemplos de dosis diarias de los compuestos de la invención en el tratamiento terapéutico de los seres humanos son entre aproximadamente 0,005 y 10,0 mg/kg peso corporal en la administración oral y entre aproximadamente 0,005 y 5,0 mg/kg peso corporal en la administración parenteral.

Los compuestos de la invención tienen la ventaja de que son eficaces contra las arritmias cardíacas.

Los compuestos de la invención también se pueden combinar con cualquier otro fármaco útil en el tratamiento de las arritmias y/o otros trastornos cardiovasculares.

Los compuestos de la presente invención se pueden emplear solos o combinados entre sí y/o con otros agentes terapéuticos adecuados útiles en el tratamiento de los trastornos mencionados antes u otros trastornos, incluidos: otros antiarrítmicos como los agentes clase I (por ejemplo, propafenona), los agentes clase II (por ejemplo, carvadiol y propranolol), los agentes clase III (por ejemplo, sotalol, dofetilida, amiodarona, azimilida e ibutilida), los agentes clase IV (por ejemplo, diltiazem y verapamilo), los antagonistas de 5 HT (por ejemplo, sulamserol, serralina y trosetron), dronedarona, compuestos selectivos auriculares como RSD1235, glucósidos cardíacos incluidos digitalis y ouabaína, bloqueantes de los canales de calcio (tanto tipo L como tipo T) como diltiazem, verapamilo, nifedipina, amlodipina y mibefradil.

En otro aspecto de la invención, el compuesto de fórmula (I), o una de sus sales o solvatos, o un solvato de dicha sal, farmacéuticamente aceptable, se puede administrar en asociación con antitrombóticos por ejemplo clorhidrato de anagrelida, bivalirudina, cilostazol, dalteparina sódica, danaparoid sódico, clorhidrato de dazoxibeno, sulfato de efegatrán, enoxaparina sódica, fluretofeno, ifetrobán, ifetrobán sódico, lamifibán, clorhidrato de lotrafibán, napsagatrán, acetato de orbofibán, acetato de roxifibán, sibrafibán, tinzaparina sódica, trifenagrel, abciximab y zolimomab aritox o sus derivados farmacéuticamente aceptables.

En otro aspecto de la invención, el compuesto de fórmula (I), o una de sus sales o solvatos o un solvato de dicha sal, farmacéuticamente aceptable, se puede administrar en asociación con otros agentes que actúan como o liberan un agonista del Factor IIa por ejemplo 3DP-4815, AZD-0837, melagatrán, ximelagatrán, ART-123, lepirudina, AVE-5026, bivaluridina, etexilato de dabigatrán, E-4444, odiparcil, ardeparina sódica, pegmusirudina, LB-30870, sulfato de dermatán, argatrobán, MCC-977, desirudina, deligoparina sódica, PGX-100, idraparinux sódico, SR-123781, SSR-182289A, SCH-530348, TRIB50, TGN-167, TGN-255 y los compuestos descritos en WO94/29336, WO97/23499 y WO02/44145, que se incorporan aquí por referencia.

En otro aspecto de la invención, el compuesto de fórmula (I), o una de sus sales o solvatos, o un solvato de dicha sal, farmacéuticamente aceptable, se puede administrar en asociación con antagonistas del receptor de fibrinógeno por ejemplo acetato de roxifibán, fradafibán, orbofibán, clorhidrato de lotrafibán, tirofibán, xemilofibán, anticuerpo monoclonal 7E3 y sibrafibán, o sus derivados farmacéuticamente aceptables.

En otro aspecto de la invención, el compuesto de fórmula (I), o una de sus sales o solvatos, o un solvato de dicha sal, farmacéuticamente aceptable, se puede administrar en asociación con inhibidores plaquetarios por ejemplo cilostezol, bisulfato de clopidogrel, epoprostenol, epoprostenol sódico, clorhidrato de ticlopidina, aspirina, ibuprofeno, naproxeno, sulindae, indometacina, mefenamato, droxicam, diclofenac, sulfinpirazona y piroxicam, dipiridamol, o sus derivados farmacéuticamente aceptables.

En otro aspecto de la invención, el compuesto de fórmula (I), o una de sus sales o solvatos, o un solvatos de dicha sal, farmacéuticamente aceptable, se puede administrar en asociación con inhibidores de la agregación plaquetaria por ejemplo acadesina, beraprost, beraprost sódico, ciprosteno cálcico, itezigrel, lifarizina, clorhidrato de lotrafibán, acetato de orbofibán, oxagrelato, fradafibán, orbofibán, tirofibán y xemilofibán o sus derivados farmacéuticamente aceptables.

En otro aspecto de la invención, el compuesto de fórmula (I), o uno de sus derivados farmacéuticamente aceptables, se puede administrar en asociación con agentes hemorreológicos por ejemplo pentoxifilina o sus derivados farmacéuticamente aceptables.

En otro aspecto de la invención, el compuesto de fórmula (I), o uno de sus derivados farmacéuticamente aceptables, se puede administrar en asociación con inhibidores de la coagulación asociada a lipoproteínas; o sus derivados farmacéuticamente aceptables.

En otro aspecto de la invención, el compuesto de fórmula (I), o una de sus sales o solvatos, o un solvato de dicha sal, farmacéuticamente aceptable, se puede administrar en asociación con un inhibidor del Factor VIIa o un derivado farmacéuticamente aceptable. Inhibidores de la ciclooxigenasa (es decir, inhibidores de COX-1 y/o COX-2) como aspirina, indometacina, ibuprofeno, piroxicam, Naproxen®, Celebrex® y los AINE; diuréticos como clorotiazida, hidroclorotiazida, flumetiazida, hidroflumetiazida, bendroflumetiazida, metilclorotiazida, triclorometiazida, politiazida, benztiazida, ácido etacrínico y tricrinafén, clortalidona, furosemida, musolimina, bumetanida, triamtereno, amilorida, y espironolactona; antihipertensivos como bloqueadores alfa adrenérgicos, bloqueadores beta adrenérgicos, bloqueantes de los canales de calcio, diuréticos, inhibidores de la renina, inhibidores de ACE, (por ejemplo, captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), antagonistas de AII (por ejemplo, losartán, irbesartán, valsartán), antagonistas ET (por ejemplo, sitaxsentán, atrsentán y compuestos divulgados en las patentes U.S. Patent N°. 5, 612, 359 y 6,043, 265), antagonistas duales de ET/AII (por ejemplo los compuestos divulgados en WO 00/01389), inhibidores de la endopeptidasa neutra (NEP), inhibidores de la vasopepsidasa (inhibidores duales de NEP-ACE) (por ejemplo, omapatrilat y gemopatrilat), nitratos y combinaciones de dichos antihipertensivos; inhibidores de la HMG-CoA reductasa como pravastatina, lovastatina, atorvastatina, simvastatina, NK-104 (por otro nombre itavastatina, o nisvastatina o nisbastatina) y ZD-4522 (por otro nombre rosuvastatina, o atavastatina o visastatina); otros hipocolesterolemiantes o hipolipidemiantes como reductores de las LDL como torcetrapid (Pfizer), exetimibe, una combinación de atorvastatina y torcetrapid, una combinación de

simvastatina y ezetimibe, inhibidores de la escualeno sintasa, fibratos, secuestrantes del ácido biliar (por ejemplo, questran).

En otro aspecto de la invención, el compuesto de fórmula (I), o una de sus sales o solvatos, o un solvatos de dicha sal, farmacéuticamente aceptable, se puede administrar en asociación con un compuesto antiobesidad, o uno de sus derivados farmacéuticamente aceptables, por ejemplo un inhibidor de la lipasa pancreática, por ejemplo, orlistat (EP 129,748), ATL-962, GT-389255 una sustancia para controlar el apetito (saciedad) por ejemplo sibutramina (Meridia®, Reductil®, GB 2,184,122 y US 4,929,629), PYY 3-36 (amilina), APD-356, 1426, Axokina, T-71, un antagonista o un agonista inverso del canabinoide 1 (CB1), o sus sales, solvatos, solvatos de dichas sales o profármacos farmacéuticamente aceptables, por ejemplo rimonabant (EP 656354), AVE-1625, CP945598, SR-147778, SLV-319, y según se describe en WO01/70700, o un inhibidor de la síntesis de ácidos grasos (FAS), o sus sales, solvatos o solvatos de dicha sales o profármacos farmacéuticamente aceptables, o un antagonista de la hormona concentradora de melanina (MCH), o sus sales, solvatos, solvatos de dichas sales o profármacos farmacéuticamente aceptables, por ejemplo 856464 y según se describe en WO 04/004726, antidiabéticos como biguanidas (por ejemplo, metformina), inhibidores de la glucosidasa (por ejemplo, acarbosa), insulinas, meglitinidas (por ejemplo, repaglinida), sulfonilureas (por ejemplo, glimepridia, gliburida y glipizida), combinaciones de biguanida/gliburida (es decir, glucovance), tiozolidinadionas (por ejemplo, troglitazona, rosiglitazona y pioflitazona), agonistas de PPAR-gamma, inhibidores de aP2, e inhibidores de DP4; miméticos tiroideos (incluidos antagonistas del receptor tiroideo) (por ejemplo, tirotropina, politiroid, KB-130015, y dronedarona).

Los compuestos de la invención también se pueden administrar como el único principio activo o en combinación con un marcapasos o un dispositivo desfibrilador.

En otro aspecto de la invención, el compuesto de fórmula (I), o una de sus sales o solvatos, un solvatos de dicha sal, farmacéuticamente aceptable, se puede administrar en asociación con anticoagulantes seleccionados entre argatrobán, bivalirudina, dalteparina sódica,

desirudina, dicumarol, liapolato sódico, mesilato de nafamostat, fenprocumón, tinzaparina sódica y warfarina sódica o un derivado farmacéuticamente aceptable.

De acuerdo con otro aspecto de la invención, se estipula una combinación de productos que comprende:

(A) un compuesto de la invención, como los definidos precedentemente, o un derivado farmacéuticamente aceptable; y

(B) un anticoagulante,

donde cada uno de los componentes (A) y (B) se formula mezclado con un adyuvante, diluyente o portador farmacéuticamente aceptable. El componente B también puede ser cualquiera de los agentes terapéuticos mencionados previamente.

Dichos productos de combinación prevén la administración de los compuestos de la invención junto con el otro agente terapéutico y de este modo se pueden presentar como formulaciones separadas, en las que al menos una de esas formulaciones comprende un compuesto de la invención y al menos una comprende el otro agente terapéutico, o se pueden presentar (es decir formular) como una preparación combinada (es decir presentada como una única formulación que incluye un compuesto de la invención y el otro agente terapéutico).

Por lo tanto, se estipula además:

(1) una formulación farmacéutica que incluye un compuesto de la invención, como el definido precedentemente, o uno de sus derivados farmacéuticamente aceptables, un anticoagulante y un adyuvante, diluyente o portador farmacéuticamente aceptable; y

(2) un conjunto de piezas que comprende los componentes:

(a) una formulación farmacéutica que incluye un compuesto de la invención, como el definido precedentemente, o uno de sus derivados farmacéuticamente aceptables, mezclado con un adyuvante, diluyente o portador farmacéuticamente aceptable; y

(b) una formulación farmacéutica que incluye un anticoagulante con un adyuvante, diluyente o portador farmacéuticamente aceptable,

donde cada uno de los componentes (a) y (b) se proporciona en una forma que es adecuada para la administración conjunta con el otro.

Cuando se usa aquí, el término " un anticoagulante" incluye referencias a una sustancia seleccionada del grupo que consiste en aspirina, warfarina, enoxaparina, heparina, heparina de bajo peso molecular, cilostazol, clopidogrel, ticlopidina, tirofibán, abciximab, dipiridamol, fracción de proteína plasmática, albúmina humana, dextrano de bajo peso molecular, hetaalmidón, reteplasa, alteplasa, estreptocinasa, urocinasa, dalteparina, filgrastina, inmunoglogulina, ginkolide B, hirudinas, foropafant, rocepafant, bivalirudina, sulfato de dermatán mediolanum, eptilibatida, tirofibán, trombomodulina, abcxmab, sulfato de dermatán de bajo peso molecular-opocrina, eptacog alfa, argatrobán, fondaparinux sódico, tifacogina, lepirudina, desirudina, OP2000, roxifibán, parnaparina sódica, hemoglobina humana (Hemosol), hemoglobina bovina (Biopure), hemoglobina humana (Northfield), antitrombina III, RSR 13, heparina-oral (Emisphere) antitrombina transgénica III, H37695, enoxaparina sódica, mesoglicán, CTC 111, bivalirudina, y todos sus derivados y/o combinaciones.

Los anticoagulantes particulares que se pueden mencionar incluyen aspirina y warfarina.

El término "un anticoagulante" también incluye referencias a los inhibidores de trombina. Los inhibidores de trombina que se pueden mencionar incluyen inhibidores de trombina de bajo peso molecular. La expresión "inhibidores de trombina de bajo peso molecular" será comprendida por los técnicos con experiencia en el área, e incluye referencias a cualquier composición del tema (por ejemplo, compuesto químico) que inhiba trombina a un grado experimentalmente determinable (según se determina por pruebas *in vivo* y/o *in vitro*), y

que posee un peso molecular por debajo de aproximadamente 2.000, preferentemente por debajo de aproximadamente 1.000.

Los inhibidores de trombina de bajo peso molecular preferidos incluyen inhibidores de trombina a base de péptidos, a base de aminoácidos, y/o a base de análogos peptídicos de bajo peso molecular, así como sus derivados.

La expresión "inhibidores de trombina a base de péptidos, a base de aminoácidos, y/o a base de análogos peptídicos de bajo peso molecular" sera comprendida por los técnicos con experiencia en el área e incluye referencias a los inhibidores de trombina de bajo peso molecular con una a cuatro uniones a péptidos, e incluye los descritos en el artículo de revisión de Claesson in *Blood Coagul. Fibrin.* 5, 411 (1994), así como los divulgados en la patente de los Estados Unidos
US Patent N° 4,346,078, las solicitudes de patente internacional WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704 y WO 00/08014; y las solicitudes de patente europea 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 y 623 596, cuyas divulgaciones se incorporan aquí por referencia en su totalidad.

En la presente solicitud, los derivados de los inhibidores de trombina incluyen modificaciones químicas, como ésteres, profármacos y metabolitos, ya sea activos o inactivos y las sales y solvatos farmacéuticamente aceptables, como los hidratos, de cualquiera de ellos, y solvatos de cualquiera de dichas sales.

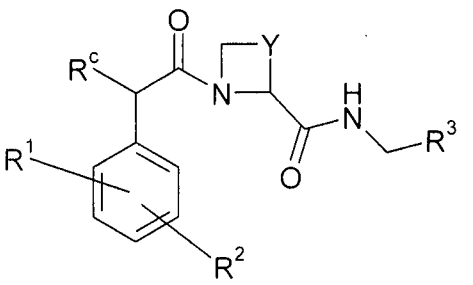
Los inhibidores de trombina a base de péptidos de bajo peso molecular preferidos incluyen los que se conocen colectivamente como "gatranes". Los gatranes particulares que se pueden mencionar incluyen HOOC-CH_2-(R)Cha-Pic-Nag-H (conocido como inogatrán) y HOOC-CH_2-(R)Cgl-Aze-Pab-H (conocido como melagatrán) (consulte las solicitudes de patente internacional WO 93/11152 y WO 94/29336, respectivamente, y las listas de abreviaturas contenidas en ellas).

La solicitud de patente internacional WO 97/23499 divulga una cantidad de compuestos que se encontró que son útiles como profármacos de los inhibidores de trombina. Dichos profármacos tienen la fórmula general

$R^aOOC\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}R^b$

donde R^a representa H, bencilo o C_{1-10} alquilo, R^b (que reemplaza uno de los átomos de hidrógeno en la unidad amidino de Pab-H) representa OH, $OC(O)R^c$ o $C(O)OR^d$, R^c representa C_{1-17} alquilo, fenilo o 2-naftilo y R^d representa C_{1-12} alquilo, fenilo, C_{1-3} alquilfenilo, o 2-naftilo. Los compuestos preferidos incluyen R^aOOC-CH_2-(R)Cgl-Aze-Pab-OH, donde R^a representa bencilo o C_{1-10} alquilo, por ejemplo, etilo o isopropilo, especialmente EtOOC-CH_2-(R)Cgl-Aze-Pab-OH. Los inhibidores de trombina activos en sí mismos se divulgan en WO 94/29336.

Otros inhibidores de trombina de bajo peso molecular que pueden ser mencionados incluyen los divulgados en WO 02/44145, como los compuestos de la fórmula general siguiente.



donde

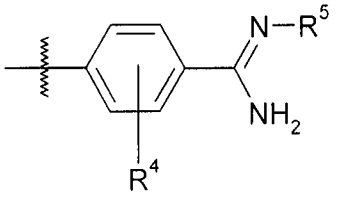
R^c representa -OH o -CH_2OH;

R^1 representa al menos un sustituyente halo opcional;

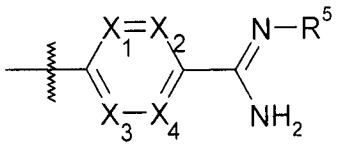
R^2 representa uno o dos sustituyentes C_{1-3} alcoxi, cuyas partes alquilo están ellas mismas sustituidas con uno o más sustituyentes fluoro (es decir, R^2 representa uno o dos grupos fluoroalcoxi(C_{1-3}));

Y representa $-CH_2-$ o $-(CH_2)_2-$; y

R^3 representa un fragmento structural de fórmula I(i) o I(ii):



I(i)



I(ii)

donde

R^4 representa H o uno o más sustituyentes fluoro;

R^5 representa H, OR^6 o $C(O)OR^7$;

R^6 representa H, C_{1-10} alquilo, C_{1-3} alquilarilo o C_{1-3} alquiloxiarilo (donde la partes alquilo de los dos últimos grupos están opcionalmente interrumpidas por uno o más átomos de oxígeno, y las partes arilo de los dos últimos grupos están opcionalmente sustituidas con uno o más sustituyentes seleccionados entre halo, fenilo, metilo o metoxi, donde los tres últimos grupos también están opcionalmente sustituidos con uno o más sustituyentes halo);

R^7 representa C_{1-10} alquilo (donde el último grupo está opcionalmente interrumpido por uno o más átomos de oxígeno), o C_{1-3} alquilarilo o C_{1-3} alquiloxiarilo (donde las partes alquilos de los últimos dos grupos están opcionalmente interrumpidas por uno o más átomos de oxígeno, y las partes arilo de los últimos dos grupos están opcionalmente sustituidas con uno o más sustituyentes seleccionados entre halo, fenilo, metilo o metoxi, donde los últimos tres grupos también están opcionalmente sustituidos con uno o más sustituyentes halo); y

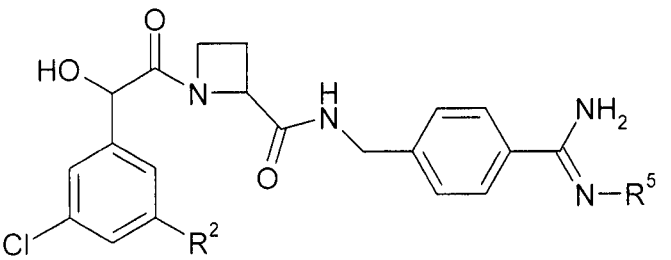
uno o dos de X_1, X_2, X_3 y X_4 representa -N- y los otros representan -CH-;

o uno de sus derivados farmacéuticamente aceptables.

Se encontró que los compuestos de la fórmula general anterior en los que R^5 es diferente de H son útiles como profármacos de inhibidores de trombina (donde los inhibidores de

trombina incluyen los compuestos correspondientes de la fórmula general anterior en los que R^5 es H).

Los compuestos particulares divulgados en WO 02/44145 que pueden ser mencionados incluyen los de la fórmula general siguiente:



donde

R^2 representa $-OCHF_2$, $-OCF_3$, $-OCH_2CH_2F$ o $-OCH_2CHF_2$;

R^5 representa H o OR^6; y

R^6 representa metilo, etilo, *n*-propilo, *i*-propilo o ciclobutilo.

A este respecto, compuestos más particulares divulgados en WO 02/44145 que pueden ser mencionados incluyen el inhibidor de trombina

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-Aze-Pab

y su profármaco metoxiamidino

Ph(3-Cl)(5-$OCHF_2$)-(*R*)CH(OH)C(O)-Aze-Pab(OMe).

Los compuestos de la invención tienen la ventaja de que son eficaces contra las arritmias cardíacas.

Los compuestos de la invención tienen propiedades ventajosas en comparación con los compuestos de la técnica anterior, en particular mayor potencia, mayor selectividad y/o reducción de la depuración total. Estas ventajas pueden prevér las correspondientes propiedades útiles en la práctica. Por ejemplo, cuando se usan como agentes farmacéuticos, los compuestos de la presente invención pueden tener una dosis clínica diaria menor, una duración de la acción más prolongada y/o un mejor perfil de efectos colaterales.

Los compuestos de la invención también pueden tener la ventaja de que pueden ser más eficaces que, menos tóxicos que, tener un rango de actividad más amplio que, ser más potentes que, tener una acción más prolongada que, producir menos efectos colaterales (incluso una menor incidencia de proarritmias como *torsades de pointes*) que, ser más fácilmente absorbidos que, o tener otras propiedades farmacológicas útiles que los compuestos conocidos en la técnica anterior.

Pruebas biológicas

Prueba A

Ensayo de salida de Rb^+

Este ensayo identifica los compuestos que bloquean el canal de potasio humano Kv1.5, canal expresado heterólogamente en células de ovario de hámster chino (CHO) por medio por medio de la salida del ion Rb+ usando Espectroscopia de Absorción Atómica de Llama. Para los estudios experimentales, las celulas CHO transfectadas establemente con ADNc para Kv1.5 humano se cultivaron como capas confluentes en placas Falcon, de 384 pocillos, tratadas para cultivo tisular, de paredes negras y fondo transparente que se incubaron durante toda la noche a 37 °C en una estufa de incubación para cultivo celular. Después de la incubación durante toda la noche, se lavaron las placas de células y se agregó un amortiguador que contenía iones de Rb+ a las placas de células. Después las placas se incubaron durante otras 3-4 horas en una estufa de incubación con CO_2 (37°C). A continuación de este período de incubación las placas se lavaron, se agregaron los compuestos y posteriormente se agregó una solución amortiguadora que contenía concentraciones elevadas de K+ para activar el canal Kv1.5. Después de un breve período de incubación, se transfirieron alícuotas de los sobrenadantes a las placas de sobrenadante para la determinación posterior del contenido de Rb+ usando Espectrometría de Absorción Atómica (instrumento ICR8000, Aurora Biomed Inc.). La salida basal de Rb+ (conc. mg/L en pocillos que recibieron sólo solución amortiguadora de lavado) se definió como 100% de inhibición y la salida estimulada de Rb+ (conc. mg/L en los pocillos que recibieron sólo soluciión amortiguadora que contenía concentraciones elevadas de iones K^+) se definió como el 0% de inhibición.

Prueba B

Los registros electrofisiológicos de las corrientes de potasio en las células que expresan establemente el canal de potasio Kv1.5 humano confirman la actividad y proporcionan una medida funcional de la potencia de los compuestos que afectan específicamente a los canales Kv1.5. Los estudios electrofisiológicos se realizaron usando el ensayo de pinzamiento zonal planar de membrana para elevada capacidad (Schroeder et al, J Biomol. Screen (2003)8(1):50-64,; Willumsen, Am Biotech Lab (2006) 24 (4);20-21) o la configuración estándar de célula entera de la técnica de pinzamiento zonal (Hamill et al, Pflugers Archiv (1981) 391:85). Después las células CHO, transfectadas establemente con ADNc para Kv1.5 humano, se expusieron a los fármacos y se activaron los canales Kv1.5

4 1.7 N-bencil-2-(1-metil-1-feniletil)-3-oxoisoindolina-1-carboxamida

por un protocolo de prueba adaptado de Pelsson et al (Cardiavasc Pharmacol (2005)46:7-17). El análisis de datos se realizó fuera de línea, se usaron comparaciones por pares entre antes del fármaco y después del fármaco para determinar el efecto inhibitorio de cada compuesto.

El compuesto del título de los ejemplos anteriores se evaluaron en la prueba A y la prueba B. La mayoría de los compuestos de la invención tiene una actividad cuando se evalúa en la prueba A, y se encontró que la mayoría de ellos tenían un CI_{50} de <30 μM, preferentemente una CI_{50} de <10 μM, o una inhibición de >20% a una concentración de 30 μM, o

Actividad de CI_{50} <10 μM en la prueba A:

El compuesto de la invención	**CI_{50} Prueba A**	**ejemplo**
N-bencil-2-(1-metil-1-feniletil)-3-oxoisoindolina-1-carboxamida	1,7	
N-bencil-3-oxo-2-(1-fenilpropil)isoindolina-1-carboxamida	0,4	
N-[3-(difluorometoxi)bencil]-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida	2,4	
N,2-dibencil-6-bromo-3-oxoisoindolina-1-carboxamida	0,84	
(1R o 1S)-N-bencil-3-oxo-2-[(1S o 1R)-1-	1,5	25

feniletil]isoindolina-1-carboxamida (E4)		
6-bromo-2-(2-ciclopentilbencil)-N-metil-3-oxoisoindolina-1-carboxamida	2,7	
6-cloro-2-(2-ciclopentilbencil)-N-(4,4-difluorobutil)-3-oxoisoindolina-1-carboxamida	1,3	
N-bencil-6-cloro-3-oxo-2-[(1S)-1-feniletil]isoindolina-1-carboxamida	2,2	
N-bencil-5-bromo-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida	2,1	
N-bencil-6-bromo-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida	0,21	
N-[3-(difluorometoxi)bencil]-6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida	1,4	
N-(3-clorobencil)-6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida	0,34	
6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida	1,7	
6-cloro-N-[3-(difluorometoxi)bencil]-2-(3- hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida	0,41	
6-cloro-N-(3-clorobencil)-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida	2,1	
N-(terc-butil)-3-oxo-2-[2-(trifluorometil)bencil] isoindolina-1-carboxamida	1,9	
N-(terc-butil)-6-cloro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida	1,1	
6-cloro-3-oxo-N-(4,4,4-trifluorobutil)-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida	2,5	
6-cloro-3-oxo-2-[(1R)-1-feniletil]-N-(4,4,4-trifluorobutilo)isoindolina-1-carboxamida	2	
2-(bifenil-2-ilmetil)-N-(terc-butil)-6-ciano-3-oxoisoindolina-1-carboxamida	2,4	36

2-[(4-clorofenil)(piridin-4-il)metil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida	2,1	
2-(bifenil-2-ilmetil)-6-cloro-N-etil-3-oxoisoindolina-1-carboxamida	1	
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-propilisoindolina-1-carboxamida	1,1	
2-(bifenil-2-ilmetil)-6-fluoro-3-oxo-N-propilisoindolina-1-carboxamida	2,8	
6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida	0,68	
6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida	0,42	
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida	1,5	
2-[2-(4-clorofenil)propil]-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida	0,78	
2-(bifenil-2-ilmetil)-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida	0,94	
N-bencil-6-cloro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida	0,55	9
N-bencil-6-fluoro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida	1,3	
N-bencil-6-fluoro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida	1,4	
2-[2-(4-clorofenil)propil]-6-fluoro-3-oxo-N-propilisoindolina-1-carboxamida	2,3	
2-[2-(4-clorofenil)propil]-3-oxo-N-propilisoindolina-1-carboxamida	1,3	
2-[2-(4-clorofenil)propil]-3-oxo-N-(4,4,4-	1,8	

trifluorobutil)isoindolina-1-carboxamida		
2-(bifenil-2-ilmetil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida	1,5	
N-(terc-butil)-2-[(1-metil-5-fenil-1H-pirazol-3-il)metil]-3-oxoisoindolina-1-carboxamida	2,5	28
2-(bifenil-2-ilmetil)-6-bromo-N-(terc-butil)-3-oxoisoindolina-1-carboxamida	2,4	29
N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida	2	
N-(terc-butil)-2-[(3',4'-diclorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida	0,72	
N-[3-(difluorometoxi)bencil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida	1,8	
N-[3-(difluorometoxi)bencil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida	1,3	
N-(terc-butil)-6-cloro-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida	2,8	
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida	0,61	
N-bencil-2-(bifenil-2-ilmetil)-6-cloro-3-oxoisoindolina-1-carboxamida	0,42	
2-(bifenil-2-ilmetil)-N-(terc-butil)-6-cloro-3-oxoisoindolina-1-carboxamida	1,6	
6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida	0,46	
6-cloro-2-[2-(4-clorofenil)propil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida	2,8	
N-(terc-butil)-6-cloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida	0,91	
N-bencil-6-cloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida	0,15	

N-(4,4-difluorobutil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida	8	22
2-[2-(4-clorofenil)propil]-N-[(2,2-difluoro-1,3-benzodioxol-5-il)metil]-3-oxoisoindolina-1-carboxamida	0,58	
N-(3,4-diclorobencil)-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida	2,5	
(R o S) 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (E1)	1,1	3
(S o R) 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (E2)	17	3
2-(bifenil-2-ilmetil)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida	2,7	19
2-(bifenil-2-ilmetil)-N-(terc-butil)-6-fluoro-3-oxoisoindolina-1-carboxamida	6,7	
N-bencil-2-(bifenil-2-ilmetil)-6-fluoro-3-oxoisoindolina-1-carboxamida	1	
2-(bifenil-2-ilmetil)-N-(terc-butil)-5-(fluorometoxi)-4-metil-3-oxoisoindolina-1-carboxamida	1,7	14
2-(bifenil-2-ilmetil)-N-(terc-butil)-5-metoxi-4-metil-3-oxoisoindolina-1-carboxamida	2,2	
N-(3-clorobencil)-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida	2,9	
N-bencil-2-[2-(4-clorofenil)etil]-N-etil-3-oxoisoindolina-1-carboxamida	0,93	
N-bencil-2-[2-(4-clorofenil)etil]-N-metil-3-oxoisoindolina-1-carboxamida	0,89	
N-(terc-butil)-5-hidroxi-4-metil-3-oxo-2-{2-[4-(trifluorometil)fenoxi]bencil}isoindolina-1-carboxamida	2	
N-bencil-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida	0,56	

2-(difenilmetil)-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida	2,5	
N-bencil-2-[2-(4-clorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida	0,71	
N-bencil-2-[2-(4-clorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida	0,74	
N-bencil-N-butil-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida	0,34	
N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida	2,2	46
N-(terc-butil)-2-[(4'-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida	7,3	
2-[2-(4-clorofenil)propil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida	0,62	
2-(bifenil-2-ilmetil)-N-(terc-butil)-7-hidroxi-3-oxoisoindolina-1-carboxamida	3	42
2-(bifenil-2-ilmetil)-N-(4-{[(difluoroacetil)-amino]metil}bencil)-3-oxoisoindolina -1-carboxamida	2,4	17
2-(3-clorobencil)-N-(3-cianobencil)-3-oxoisoindolina-1-carboxamida	2	
2-[2-(4-clorofenil)propil]-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida	1,2	
2-(bifenil-2-ilmetil)-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida	2,8	7
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-(fluorometoxi)-4-metil-3-oxoisoindolina-1-carboxamida	3	
2-[3,5-bis(trifluorometil)bencil]-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida	1,8	
2-[2-(4-clorofenil)propil]-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida	1,8	
N-(1,3-benzodioxol-5-ilmetil)-2-[2-(4-	0,62	

clorofenil)propil]-3-oxoisoindolina-1-carboxamida		
(1S o 1R)-N-butil-2-[(2R o 2S)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida (E2)	0,73	13
(1R o 1S)-N-butil-2-[(2S o 2R)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida (E4)	1,7	13
(1R o 1S)-N-butil-2-[(2R o 2S)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida (E3)	0,5	13
(1S o 1R)-N-butil-2-[(2S o 2R)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida (E1)	15	13
N-bencil-3-oxo-2-[(3-fenilisoxazol-5-il)metil]isoindolina-1-carboxamida	1	
N-butil-2-[2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida	1,3	12
N-(terc-butil)-5,6-dicloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida	1,8	
2-[2-(4-clorofenil)propil]-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida	0,7	
N-(2-clorobencil)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida	0,75	
(R o S) 2-(bifenil-2-ilmetil)-N-(terc-butil)-3-oxoisoindolina-1-carboxamida	3,4	34
2-[2-(4-clorofenil)propil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida	1,9	
N-bencil-2-[2-(4-clorofenil)propil]-4,5-dimetoxi-3-oxoisoindolina-1-carboxamida	0,61	
N-bencil-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida	0,51	
N-bencil-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida	6	24
N-bencil-2-(2-bromobencil)-3-oxoisoindolina-1-carboxamida	2,5	

2-(bifenil-2-ilmetil)-N-(terc-butil)-3-oxoisoindolina-1-carboxamida	3,3	33
N-bencil-2-(2-ciclohex-1-en-1-iletil)-3-oxoisoindolina-1-carboxamida	1,8	
N-bencil-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida	1	
N-butil-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida	0,73	
N-butil-2-[2-(4-clorofenil)-2-metilpropil]-3-oxoisoindolina-1-carboxamida	0,53	49
N-(terc-butil)-2-[(4',5-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida	9,3	
N-(terc-butil)-2-[(5-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida	13	
N-(terc-butil)-2-[(4,4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida	5,6	48
N-(terc-butil)-2-[(4-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida	5,2	
(1R o 1S)-N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida	13	47
(1S o 1R)-N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida	5,5	47

La invención se ilustra mediante los ejemplos siguientes.

EJEMPLOS

La denominación de los compuestos en esta solicitud de patente se hizo utilizando un programa de ACD Labs (versión 9.0, Name Batch o labs).

Ejemplos

Abreviaturas:

AIBN	2,2'-Azobis(2-metilpropionitrilo)
C	Celsius
Anhídrido BOC	dicarbonato de di-terc-butilo
Reactivo de Dess-Martin	1,1,1-triacetoxi-1,1-dihidro-1,2-benziodoxol-3(1H)-ona
DCM	diclorometano
DMF	*N, N'*-dimetilformamida
DME	dimetoxietano
DMAP	dimetilaminopiridina
DMSO	dimetilsulfóxido
ES	electronebulización
ESI	ionización por electronebulización
EtOAc	acetato de etilo
EtOH	etanol
DME	dimetoxietano
HPLC	cromatografía líquida de alta resolución
HRMS	espectrometría de masas de alta resolución
LAH	hidruro de litio y aluminio
MeCN	acetonitrilo
MeOH	metanol
MTBE	éter metil terc-butílico
K_2CO_3	carbonato de potasio
MS	espectroscopía de masas
NMR	resonancia magnética nuclear
TEA	trietilamina
TFA	ácido trifluoroacético
THF	tetrahidrofurano
UV	ultravioleta
atm	atmósfera
rt	temperatura ambiente
h	hora(s)
min	minutos

br	ancho
br s	singulete ancho
s	singulete
d	doblete
t	triplete
q	cuartete
m	multiplete
sep	septete
dd	doblete doble
dm	multiplete doble
td	doblete triple

Procedimientos experimentales generales

La cromatografía en columna instantánea se realizó utilizando gel de sílice de fase normal 60 (0,040-0,063 mm, Merck) o el sistema de purificación SP1™ de Biotage™ usando cartuchos de sílice FLASH+™ a menos que se indique lo contrario.

Las mediciones de ^{1}H NMR y ^{13}C NMR se realizaron en un espectrómetro BRUKER ACP 300 o en un Varian Unity Plus 400, 500 ó 600, operando frecuencias de ^{1}H de 300, 400, 500 ó 600 MHz, respectivamente, y frecuencias de ^{13}C de 75, 100, 125 y 150 MHz. Alternativamente, se realizaron mediciones de ^{13}C NMR en un espectrómetro BRUKER ACE 200 a una frecuencia de 50,3 MHz.

Los rotámeros pueden, o no. estar indicados en los espectros dependiendo de la facilidad de interpretación del espectro.

Los desplazamientos químicos se informan en valores δ (ppm) con los solventes usados como estándar interno, a menos que se indique lo contrario.

*Las soluciones se toman de una muestra concentrada disuelta en $(CH_3)_2SO$ y se diluyen con $(CD_3)_2SO$. Dado que hay una cantidad importante de $(CH_3)_2SO$ presente en la muestra, primero se realiza y se analiza un escaneado previo para suprimir automáticamente los picos de $(CH_3)_2SO$ (2,54 ppm) y H_2O (3,3 ppm). Esto significa que en el experimento denominado wet1D la intensidad de los picos que se encuentran en las áreas alrededor de

3,3 ppm y 2,54 ppm está reducida. Además se ven impurezas en el espectro que originan un triplete a 1,12 ppm, un singulete a 2,96 y dos multipletes entre 2,76-2,70 ppm y 2,61-2,55 ppm. Muy probablemente esas impurezas sean dimetilsulfona y dietilsulfóxido.

El calentamiento en microondas se realizó usando calentamiento monomodal en un Smith Creador o Emrys Optimizer de Personal Chemistry, Uppsala, Suecia.

Los datos de espectro de masas (MS) se obtuvieron usando un instrumento ZQ, cuadrupolar de Waters y, cuando correspondió, se obtuvieron datos de ión positivo o datos de ión negativo.

Los datos de espectros de masas exactas (HRMS) se obtuvieron usando TOF-MS en un sistema LCT, Q-TOF micro o LCTP, todos de Waters.

Se usó un filtro de jeringa de Advantec MFS Inc. con un tamaño de poro de 0,5 µm.

Se usaron columnas de intercambio catiónico de Isolute®.

Síntesis de productos intermedios

Preparación A

2-(4-fluorofenil)-propilamina

(i) 1-fluoro-4-isopropenil-benceno

Se agregó terc-butoxido de potasio (52,9 g, 0,47 mol) a la suspensión de yoduro de metil trifenilfosfonio (190 g, 0,47 mol) en THF(400 ml) en condición de enfriamiento con hielo. Después de 1 h de agitación en condición de enfriamiento con hielo, se agregó gota a gota una solución de 4-fluoroacetofenona (30 g, 0,199 mol) en THF (100 ml). Después la mezcla de reacción se agitó a temperatura ambiente durante 2 h y la reacción se detuvo con solución saturada de cloruro de amonio. El THF se eliminó a presión reducida y la mezcla de reacción se extrajo con pet éter, se lavó con agua, solución saturada de cloruro de sodio y se secó sobre sulfato de sodio anhidro. Se obtuvo el compuesto del subtítulo (30 g, 100%) como un líquido amarillo pálido por concentración de la capa de éter de petróleo.

(ii) 2-(4-fluorofenil)-propilamina

Se agregó gota a gota borano en THF (96 ml, 0,096 mol, solution 1 M) a la solución de 1-fluoro-4-isopropenilbenceno del paso (i) anterior (30 g, 0,24 mol) en THF (350 ml) a 0 °C

y la mezcla de reacción se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se enfrió a 0 °C y se agregó ácido hidroxilamina-O-sulfónico (27,72 g, 0,24 mol) en porciones. La mezcla de reacción se agitó a reflujo durante toda la noche. Después la mezcla de reacción se enfrió rápidamente con agua, se concentró y se acidificó con ácido clorhídrico 1,5 N. La mezcla de reacción se extrajo con acetato de etilo, la capa acuosa se neutralizó con solución de hidróxido de sodio al 10% y se extrajo con diclorometano. La capa de diclorometano se lavó con agua, solución saturada de cloruro de sodio y se evaporó para dar el compuesto del título (8,5 g, 23%).

Preparación B

[2-(4-clorofenil)propil]amina

(i) 1-cloro-4-isopropenilbenceno

Se agregó terc-butoxido de potasio (72,4 g, 0,646 mol) a la suspensión de yoduro de metil trifenilfosfonio (261 g, 0,646 mol) en THF (500 ml) en condición de enfriamiento con hielo. Después de 1 h de agitación en condición de enfriamiento con hielo, se agregó gota a gota una solución de 4-cloroacetofenona (50 g, 0,323 mol) en THF (100 ml). Después la mezcla de reacción se agitó temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con pet éter y se filtró, se concentró el filtrado. Se obtuvo el compuesto del subtítulo como un líquido de color amarillo pálido por purificación cromatográfica en columna del producto crudo usando acetato de etilo al 6% en pet éter como eluyente. Rendimiento (42 g, 86%).

(ii) [2-(4-clorofenil)propil]amina

Se agregó gota a gota borano en THF (124 ml, solución 1 M) a la solución de 1-cloro-4-isopropenilbenceno del paso (i) anterior (41,5 g, 0,272 mol) en THF (500 ml) a 0 °Cy la mezcla de reacción se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se enfrió a 0 °C y se agregó ácido hidroxilamina-O-sulfónico (30,76 g, 0,272 mol) en porciones. La mezcla de reacción se agitó a reflujo durante toda la noche. La mezcla de reacción se enfrió rápidamente con agua y se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con agua, solución saturada de cloruro de sodio, se secó sobre sulfato de sodio y se concentró. La masa concentrada se disolvió en éter dietílico seco (20

ml) y se agitó con HCl saturado en éter dietílico durante ½ h. La sal sólida se aisló por filtración, se neutralizó con solución de bicarbonato de sodio y la amina libre se extrajo con éter dietílico. La capa de éter dietílico se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró para dar el compuesto del título (18 g, 39%).

Preparación C

1-(4'-fluorobifenil-2-il)metanamina

(i) N-[[2-(4-fluorofenil)fenil]metil]carbamato de terc-butilo

Se disolvieron N-(terc-butoxicarbonil)-2-bromobencilamina (1,74 mmol, 0,5 g) y, tetrakis(trifenilfosfina)paladio (0,087 mmol, 0,101 g) y ácido 4-fluorobencenoborónico (2,096 mmol, 0,293 g) en (DME ,10 ml) en un vial adecuado para usar en un horno de microondas. Se disolvió carbonato de cesio (3,49 mmol, 1,14 g) en 2 ml de agua y después se agregó a la mezcla. Se hizo burbujear Ar (g) a través de la mezcla durante 5 minutos. La reacción se realizó en un horno de microondas (10 min, 130°). El crudo (0,5 g, 1,65 mmol) del compuesto del subtítulo se tomó para el paso siguiente sin más purificación.

(ii) [2-(4-fluorofenil)fenil]metanoamina

Se disolvió el N-[[2-(4-fluorofenil)fenil]metil]carbamato de terc butilo (1,6591 mmol, 0,5 g) del paso (i) anterior en HCl saturado en EtOAc y se agitó a rt durante 2 h. El solvente se eliminó por evaporación y la sal de HCl se purificó por cromatografía instantánea (se comenzó con isocrática heptano/DCM 50/50 y después se aumentó la concentración de DCM hasta 100% después el producto se eluyó con MeOH al10% (saturado con NH3), (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación, para dar 320 mg (1,59 mmol) del compuesto del título.

Preparación D

Las aminas siguientes se prepararon de acuerdo con la preparación C anterior:

1-(4'-metilbifenil-2-il)metanamina

1-(4'-metoxibifenil-2-il)metanamina

1-(4'-fluoro-2'-metilbifenil-2-il)metanamina

Preparación E

sal del ácido clorhídrico de (2-ciclopentilbencil)amina

(i) trifluoroacetato de 2-ciclopentilfenilo

A una solución de 2-ciclopentilfenol (10 g, 0,09 mol) en DCM seco (150 ml) se le agregó piridina (8 ml, 0,14 mol) y se enfrió a 0 °C seguido de la adición gota a gota de anhídrido del ácido trifluoroacético (15,6 ml, 0,14 mmol). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se enfrió rápidamente con agua y se extrajo con DCM (200 ml). La capa orgánica se lavó con agua (2 x 50 ml) y solución saturada de cloruro de sodio (1 x 50 ml) y se concentró para obtener el producto del paso 1 (18 g, 99,4%) como un líquido marrón. El producto crudo se tomó tal cual para el paso siguiente

(ii) 2-ciclopentilbenzonitrilo

A una solución de trifluoroacetato de 2-ciclopentilfenilo (18 g, 0,06 mol) en DMF seco (150 ml) se le agregó $Zn(CN)_2$ (7,2 g; 0,06 mol) seguido de $Pd(PPh_3)_4$ (5,6 g; 0,005 mol) y se calentó a reflujo a 130 °C durante toda la noche en atmósfera de nitrógeno. Después la mezcla de reacción se enfrió a temperatura ambiente, la reacción se detuvo con agua (200 ml) y se diluyó con EtOAc (200 ml) y se filtró. El filtrado se lavó bien con agua (3 x 50 ml) y solución saturada de cloruro de sodio (1 x 50 ml). La capa orgánica se concentró y el producto crudo se purificó por cromatografía en columna de gel de sílice usando EtOAc al 5% en pet éter para obtener el producto del paso 2 (10,4 g, 99,3%) como un sólido amarillo pálido.

(iii) (2-ciclopentilbencil)amina

A una suspension de hidruro de litio y aluminio (5,7 g, 0,15 mmol) en THF seco (50 ml) a 0 °C se le agregó gota a gota 2-ciclopentilbenzonitrilo (10,4 g, 0,06 mol) disuelto en THF seco (100 ml). La reacción se agitó a temperatura ambiente durante toda la noche. La masa de reacción se enfrió a 0 °C y la reacción se detuvo con KOH 6 M y se diluyó con THF.

Después se filtró a través de celite y se concentró el filtrado. A una solución del producto crudo en éter dietílico (100 ml) se le agregó HCl saturado en éter dietílico (50 ml) y se agitó durante 10 minutos. Después se filtró y el precipitado se lavó con éter de petróleo para obtener el compuesto del título (10,3 g, 98,1%) como un sólido blanco.

Preparación F

sal del ácido clorhídrico de (2-ciclohexilbencil)amina

(i) 2-ciclohexilbenzonitrilo

A una solución de 2-ciclohexilbromobenceno (12 g, 0,05 mol) en DMF seco (100 ml) se le agregó $Zn(CN)_2$ (5,9 g, 0,05 mol) seguido de $Pd(PPh_3)_4$ (5,8 g, 0,005 mol) y se calentó a reflujo a 130 °C durante toda la noche. Después la masa de reacción se enfrió a temperatura ambiente, la reacción se detuvo con agua (200 ml) y se diluyó con EtOAc (200 ml) y se filtró. El filtrado se lavó bien con agua (3 x 50 ml) y solución saturada de cloruro de sodio (1 x 50 ml). La capa orgánica se concentró para obtener el producto del paso 1 (10 g) como un líquido gomoso amarillo. El producto crudo se usó en el paso siguiente.

(ii) (2-ciclohexilbencil)amina

A una suspensión de hidruro de litio y aluminio (5,1 g, 0,13 mmol) en THF seco (60 ml) a 0 °C se le agregó gota a gota 2-ciclohexilbenzonitrilo del paso (i) anterior (10 g, 0,054 mol) disuelto en THF seco (140 ml). Después de agitar la mezcla de reacción durante toda la noche a RT, se enfrió a 0 °C y la reacción se detuvo con KOH 6 M. Después se diluyó con THF y se filtró a través de celite. El filtrado se concentró al vacío. A una solución del producto crudo en éter dietílico (100 ml) se le agregó HCl saturado en éter dietílico (20 ml) y se agitó durante 10 minutos. Después se filtró y el precipitado se lavó con éter de petróleo para obtener el compuesto del título (8 g, 78,4%) como un sólido blanco.

Preparación G

clorhidrato de (4-fluorobutil)amina

(i) (4-{[terc-butil(dimetil)silil]oxi}butil)amina

A una solución de 4-aminobutanol (20 g, 0,224 mol) en diclorometano (200 ml) se le agregó trietilamina a 0 °C. Se agregó terc-butildimetilclorosilano (33,8 g, 0,224 mol) a la misma temperatura y se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se diluyó con agua. La capa orgánica se lavó con agua, solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. El producto crudo (42 g, 92%) se usó para el paso siguiente sin purificación.

(ii) (4-{[terc-butil(dimetil)silil]oxi}butil)carbamato de terc-butilo

A una solución de (4-{[terc-butil(dimetil)silil]oxi}butil)amina (42 g, 0,20 mol) en diclorometano (400 ml) y trietilamina (58 ml, 0,413 mol) se le agregó BOC-anhídrido (54,12 g, 0,248 mol) a 0 °C en atmósfera de nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con agua helada. La capa orgánica se lavó con agua y solución saturada de cloruro de sodio. Después la capa orgánica se secó sobre sulfato de sodio anhidro y se concentró. El residuo se purificó por cromatografía en gel de sílice usando (EtOAc/pet éter) para dar (60 g, 95%) del compuesto del subtítulo como un aceite incoloro.

(iii) (4-{[terc-butil(dimetil)silil]oxi}butil)imidodicarbonato de di-terc-butilo

A una solución de (4-{[terc-butil(dimetil)silil]oxi}butil)carbamato de terc-butilo del paso (ii) anterior (60 g, 95%) en acetonitrilo seco (600 ml) se le agregó DMAP (36,23 g, 0,29 mol). Se agregó BOC-anhídrido (64,7 g, 0,29 mol) y la mezcla de reacción se agitó a temperatura ambiente durante 24 h. Después se agregaron DMAP (36,23 g, 0,29 mol) y anhídrido BOC (64,7 g, 0,29 mol) una vez más. La mezcla de reacción se agitó a temperatura ambiente durante otros 4 días. La mezcla de reacción se concentró y el residuo se purificó por cromatografía en gel de sílice usando (EtOAc/pet éter) para dar (62 g, 77%) del compuesto del subtítulo como un aceite incoloro.

(iv) (3-hidroxipropil)imidodicarbonato de di-terc-butilo

A una solución de (4-{[terc-butil(dimetil)silil]oxi}butil)imidodicarbonato de di-terc-butilo (60 g, 0,148) del paso (iii) anterior en THF (600 ml) se le agregó fluoruro de tetrabutilamonio (150 ml, solución 1 M en THF) a 0 °C en atmósfera de nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. La mezcla de

reacción se concentró y la masa concentrada se disolvió en acetato de etilo. La capa de acetato de etilo se lavó sucesivamente con agua, ácido cítrico al 10%, bicarbonato de sodio al 10% y solución saturada de cloruro de sodio. La mezcla de reacción se concentró y el residuo se purificó por cromatografía en gel de sílice usando (EtOAc/pet éter) para dar (37 g, 86%) del compuesto del subtítulo como un líquido amarillo pálido.

(v) (3-fluoropropil)imidodicarbonato de di-terc-butilo

A una solución de (3-hidroxipropil)imidodicarbonato de di-terc-butilo (35 g, 0,121 mol) del paso (iv) anterior en THF seco (400 ml) se le agregó trietilamina (84,9 mol, 0,60 ml) y (dimetilamino)-trifluoruro de azufre (102 g, 0,60 mol) a –40 °C en atmósfera de nitrógeno. Se dejó que la mezcla de reacción se calentara lentamente hasta temperatura ambiente y se agitó a temperatura ambiente durante 3 días. La reacción se detuvo por adición de metanol a 0 °C. La mezcla de reacción se concentró y el residuo se purificó por cromatografía en gel de sílice usando (EtOAc/pet éter) para dar (11,8 g, 33%) del compuesto del subtítulo como un líquido amarillo pálido.

(vi) clorhidrato de (4-fluorobutil)amina

A una solución de (3-fluoropropil)imidodicarbonato de di-terc-butilo (11,8 g, 0,040 mol) del paso (v) anterior en éter dietílico seco (30 ml) se le agregó HCl saturado en éter (200 ml) a 0 °C. La mezcla de reacción se agitó a temperatura ambiente durante 24 h. La mezcla de reacción se concentró y se obtuvo el compuesto del título (4,1 g, 80%) como un sólido amarillo pálido por recristalización de acetona/éter dietílico.

Preparación H

clorhidrato de (4,4-difluorobutil)amina

(i) (3-oxopropil)imidodicarbonato de di-terc-butilo

A una solución del reactivo de Dess-Martin (66 g, 0,155 mol) en diclorometano (300 ml) se le agregó (3-hidroxipropil)imidodicarbonato de di-terc-butilo (30 g, 0,103 mol) en diclorometano a –78 °C en atmósfera de nitrógeno. Después se dejó que la mezcla de reacción se calentara hasta temperatura ambiente y se agitó a la misma temperatura durante toda la noche. La mezcla de reacción se filtró sobre celite y se concentró el filtrado. La

masa concentrada se agitó con éter dietílico y la capa etérea se separó y se concentró. El crudo concentrado se purificó por cromatografía en columna usando (EtOAc/pet éter) para dar (23 g, 77%) del producto intermedio deseado como un líquido amarillo pálido.

(ii) (4,4-difluorobutil)imidodicarbonato de di-terc-butilo

A una solución del producto intermedio del paso (i) (23 g, 0,080 mmol) en diclorometano seco (200 ml) se le agregó (dimetilamino)-trifluoruro de azufre (38,7 g, 0,24 mol) a –40 °C en atmósfera de nitrógeno. Se dejó que la mezcla de reacción se calentara lentamente hasta temperatura ambiente y se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se vertió lentamente en agua fría. La capa orgánica separada se lavó con agua y solución saturada de cloruro de sodio, y se concentró. El residuo se purificó por cromatografía en gel de sílice usando (EtOAc/pet éter) para dar (11,12 g, 45%) del compuesto del subtítulo como un líquido amarillo pálido.

(iii) clorhidrato de (4,4-difluorobutil)amina

A una solución del producto intermedio del paso (ii) (11,2 g, 0,035 mol) en éter dietílico seco (30 ml) se le agregó HCl saturado en éter (150 ml) a 0 °C. La mezcla de reacción se agitó a temperatura ambiente durante 24 h. La mezcla de reacción se concentró y se obtuvo el compuesto del título (4,5 g, 86%) como un sólido amarillo pálido por recristalización de la masa cruda con acetona/éter dietílico.

Preparación I

(4,4-difluorobutil)formamida

Se calentaron a reflujo (4,4-difluorobutil)amina (Prep. H anterior) (6 g, 0,041 mol) y trietilamina (14,46 ml, 0,103 mol) en formiato de etilo (150 ml) durante toda la noche. La mezcla de reacción se enfrió a temperatura ambiente y se filtró. El filtrado se concentró y el producto crudo se purificó por cromatografía en columna usando (EtOAc/ pet éter) para dar el compuesto del título (4,2 g, 74%) como un líquido amarillo pálido.

Preparación J

(4,4,4-trifluorobutil)formamida

(i) clorhidrato de (4,4,4-trifluorobutil)amina

Una solución de diazodicarboxilato de dietilo (31,1 ml, 0,195 mol) en tolueno (150 ml) se agregó lentamente a la solución de 4,4,4-trifluorobutanol (25 g, 0,195 ml), trifenilfosfina (51 g, 0,195 mol) y butiliminodicarboxilato de di-terc-butilo (38 g, 0,175 mol) en tolueno (300 ml) a temperatura ambiente. La mezcla de reacción se agitó a la misma temperatura durante 24 h. Se agregó ácido trifluoroacético (20 ml) a la mezcla de reacción a condición de enfriamiento con hielo y después se agitó a temperatura ambiente durante otras 24 h. La mezcla de reacción se diluyó con agua (500 ml). La capa acuosa separada se lavó con éter dietílico y después se hizo alcalina con solución de hidróxido de sodio 5 N. La solución alcalina se extrajo con éter dietílico. La capa de éter dietílico se secó sobre sulfato magnesio anhidro. Después se agregó ácido clorhídrico saturado en éter a la solución etérea anterior y se agitó durante toda la noche. El éter se eliminó a presión reducida y la masa resultante se hizo azeótropa con tolueno para dar el compuesto del título (11,8 g, 37%).

(ii) (4,4,4-trifluorobutil)formamida

Una mezcla de (4,4,4-trifluorobutil)amina (8,7 g) del paso (i) anterior y trietilamina (14,6 ml, 0,14 mol) se calentó a reflujo en formiato de etilo (250 ml) durante 24 h. La mezcla de reacción se calentó a temperatura ambiente y se filtró. El filtrado se concentró y el producto crudo se purificó por cromatografía en columna usando acetato de etilo al 50% en pet éter como eluyente para dar el compuesto del título (5,5 g, 67%, 3,84 g como un líquido incoloro.

Preparación K

(4-fluorobutil)formamida

Se calentaron a reflujo clorhidrato de (4-fluorobutil)amina (Prep. G anterior) (4,12 g, 0,032 mmol) y trietilamina (14,6 ml, 0,14 mol) en formiato de etilo (13,6 ml, 0,097 mol) durante 24 h. Después la mezcla de reacción se enfrió a temperatura ambiente y se filtró. El filtrado se concentró y el producto crudo se purificó por cromatografía en columna usando acetato de etilo al 50% en pet éter como eluyente para dar el compuesto del título (3,12 g, 80%) como un líquido amarillo pálido.

Preparación L

3-isocianometil-5-metil-isoxazol

(i) N-(5-metil-isoxazol-3-ilmetil)-formamida

Se cargó en un vial adecuado para usar en un horno de microondas con una solución de (5-metil-isoxazol-3-il)-metilamina (1 g, 8,9 mmol) y formiato de etilo (17 ml, 212 mmol). La mezcla se calentó en atmósfera de nitrógeno a 150 °C durante 15 min. Después de la irradiación la mezcla se enfrió a temperatura ambiente y se evaporó. Se obtuvieron 1,378 g del producto crudo, N-(5-metil-isoxazol-3-ilmetil)formamida (rendimiento del 99%) que se usó sin más purificación.

[M+1] (ES) 141,0

^{1}H NMR (500 MHz, $CDCl_3$) δ 8,57 (br s, 1H); 8,12 (s, 1H); 6,11 (s, 1H); 4,29 (d, 2H); 2,37 (s, 3H)

(ii) 3-isocianometil-5-metil-isoxazol

Se agregó sal interna hidróxido de (metoxicarbonilsulfamoil)trietilamonio (4,2 g, 17,7 mmol) a una solución de N-(5-metil-isoxazol-3-ilmetil)formamida (1,378 g; 8,8 mmol del paso (i) anterior) en acetonitrilo (15 ml). La mezcla se agitó a 50 °C durante 3 h en atmósfera de nitrógeno y después se enfrió a temperatura ambiente.

La solución de 3-isocianometil-5-metil-isoxazol se usó para preparar compuestos de los ejemplos sin más purificación.

Preparación M

(isocianometil)benceno

(i) *N*-bencilformamida

Se disolvió bencilamina (2,07 ml, 19 mmol) en formiato de etilo (24 ml) y la reacción se dejó en agitación a 45 °C durante 20 h. El solvente se evaporó y el producto se concentró a presión reducida para dar el compuesto del título (2,44 g, 95,2%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8,36-8,25 (s, 1 H); 7,5-7,2 (m, 5 H); 6,02-5,57 (s, 1H); 4,56-4,46 (d, 2 H).

(ii) (isocianometil)benceno

Se agregaron *N*-bencilformamida del paso (i) anterior (2,44 g, 18,1 mmol) y sal interna hidróxido de (metoxicarbonilsulfamoil)trietilamonio (reactivo de Burgess) (4,31 g, 18,1mmol) a un matraz y se agregó MeCN (25 mL) seco. La mezcla de reacción se dejó en agitación durante 3 h a 50 °C y el compuesto del título crudo se usó sin más purificación en el paso siguiente.

Preparación N

1-cloro-3-(isocianometil)benceno

(i) *N*-(3-clorobencil)formamida

Se disolvió 1-(3-clorofenil)metanamina (0,283 g, 2,0 mmol) en formiato de etilo (8 mL) y la reacción se dejó en agitación a 45 °C durante 16 h. El solvente se evaporó y el producto se concentró a presión reducida para dar el compuesto del título (0,350 g, 103%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8,23-8,09 (m, 1H); 7,38-7,18 (m, 3H); 4,8-4,34 (s, 2H).

(ii) 1-cloro-3-(isocianometil)benceno

Se agregaron *N*-(3-clorobencil)formamida (0,128 g, 0,755 mmol) y sal interna hidróxido de (metoxicarbonilsulfamoil)trietilamonio (reactivo de Burgess) (0,182 g, 0,764 mmol) a un matraz y se agregó MeCN (6 mL). La mezcla de reacción se dejó en agitación durante 3 h a 50 °Cy el crudo se usó sin más purificación en el paso siguiente.

Preparación O

4-(isocianometil)-5-metil-2-fenil-1,3-oxazol

(i) *N*-[(5-metil-2-fenil-1,3-oxazol-4-il)metil]formamida

Se disolvió 1-(5-metil-2-fenil-1,3-oxazol-4-il)metanamina (0,512 g, 2,72 mmol) en formiato de etilo (8 mL) y la reacción se dejó en agitación a 45 °C durante 22 h. El solvente se evaporó y el producto se concentró a presión reducida para dar el compuesto del subtítulo (0,559 g, 95%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8,3-8,18 (m, 1H); 8,07-7,99 (m, 2H); 7,62-7,34 (m, 3H); 6,51-5,91 (m, 1H); 4,46-4,32 (d, 2H); 2,62-2,38 (m, 2H); MS (ESI) m/z 217 ($[M+H]^+$).

(ii) 4-(isocianometil)-5-metil-2-fenil-1,3-oxazol

Se agregaron *N*-[(5-metil-2-fenil-1,3-oxazol-4-il)metil]formamida del paso (i) anterior (0,259 g, 1,20 mmol) y sal interna hidróxido de (metoxicarbonilsulfamoil)trietilamonio (reactivo de Burgess) (0,288 g, 1,21 mmol) a un matraz y se agregó MeCN (6 mL). La mezcla de reacción se dejó en agitación durante 3 h a 50 °Cy el crudo se usó sin más purificación en el paso siguiente.

Preparación P

1,1-difluoro-4-isocianobutano

Se agregaron *N*-(4,4-difluorobutil)formamida (de la prep. I anterior) (0,076 g, 0,554 mmol) y sal interna hidróxido de (metoxicarbonilsulfamoil)trietilamonio (reactivo de Burgess) (0,132 g, 0,554 mmol) a un matraz y se agregó MeCN (2 mL). La mezcla de reacción se dejó en agitación durante 3 h a 50 °Cy el crudo se usó sin más purificación para preparar compuestos de los ejemplos siguientes.

Preparación Q

clorhidrato de [(2,2-difluoro-1,3-benzodioxol-5-il)metil]amina

(i) oxima de 2,2-difluoro-1,3-benzodioxol-5-carbaldehído

Una solución de 2,2-difluoro-1,3-benzodioxol-5-carbaldehído (8 g, 0,0429 mol) en metanol (50 ml) se agregó gota a gota a una solución bien agitada de clorhidrato de hidroxilamina (4,18 g, 0,060 mol) y acetato de sodio (4,9 g, 0,060 mol) en metanol (100 ml) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 6 h. Después la mezcla de reacción se concentró a presión de reducida, la masa concentrada se diluyó con agua y se extrajo con diclorometano. La capa de diclorometano se lavó con agua, solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró para dar el producto intermedio crudo. Se obtuvo el compuesto del título (6,2 g, 72%) por cristalización del producto intermedio crudo de solvente diclorometano/hexano.

(ii) clorhidrato de 1-(2,2-difluoro-1,3-benzodioxol-5-il)metanamina

Una solución de 2,2-difluoro-1,3-benzodioxol-5-carbaldehído oxima (6,2 g, 0,030 mol) del paso (i) anterior en THF (25 ml) se agregó lentamente la suspensión de LAH (2,9 g, 0,077 mol) en THF (100 ml) a 0 °C en atmósfera de nitrógeno. Después la mezcla de reacción se dejó en agitación a temperatura ambiente durante 8 h. La mezcla de reacción se enfrió a 0 °C y la reacción se detuvo con solución de KOH 6 M (3 ml). La mezcla de reacción se filtró a través de celite y el residuo sólido se lavó varias veces con acetato de etilo. El filtrado combinado se concentró para dar el producto crudo. El producto crudo se disolvió en éter y se agitó con HCl insaturado en éter (2 0 ml) durante 2 h. Después la solución se filtró y el residuo se secó para dar el compuesto del título (4,8 g, 83,3%) como un polvo blanco.

Preparación R

isocianuro de (2,2-difluoro-1,3-benzodioxol-5-il)metilo

(i) 1-(2,2-difluoro-1,3-benzodioxol-5-il)metanamina

Se agregó clorhidrato de 1-(2,2-difluoro-1,3-benzodioxol-5-il)metanamina (2,0 g, 8,94 mmol) a un matraz, y se agregó una solución de K_2CO_3 2 M (30 mL) y DCM (30 mL). La mezcla de reacción se dejó en agitación a rt 2 h. Se separaron las dos fases y la fase acuosa se extrajo una vez más con DCM (20 ml). Las fases orgánicas se recogieran y se secaron con $MgSO_4$ y se filtró la sal. La fase orgánica se evaporó y el producto se concentró a presión reducida para dar el compuesto del título (1,53 g, 91,4%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7,15-6,95 (m, 3H); 4,07-3,78 (s, 2H); MS (ESI) m/z 188 ($[M+H]^+$);

(ii) *N*-[(2,2-difluoro-1,3-benzodioxol-5-il)metil]formamida

Se disolvió 1-(2,2-difluoro-1,3-benzodioxol-5-il)metanamina (del paso (i) anterior (1,53 g, 8,18 mmol) en formiato de etilo (40 mL) y la reacción se dejó en agitación a 45 °C durante 20 h. Se evaporó el solvente y el producto se concentró a presión reducida para dar el compuesto del título (1,72 g, 97,6%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8,35-8,25, 7,09-6,95 (m, 3H); 6,01-5,61 (m 1H);4,53-4,45 (d, 2H); MS (ESI) m/z 214 ($[M+H]^+$).

(iii) isocianuro de (2,2-difluoro-1,3-benzodioxol-5-il)metilo

Se agregaron *N*-[(2,2-difluoro-1,3-benzodioxol-5-il)metil]formamida del paso (ii) anterior (0,320 g, 1,49 mmol) y sal interna hidróxido de (metoxicarbonilsulfamoil)trietilamonio (reactivo de Burgess) (0,359 g, 1,51 mmol) a un matraz y se agregó MeCN seco (8 mL). La mezcla de reacción se dejó en agitación durante 3 h a 50 °C y el crudo se usó sin más purificación en el paso siguiente (AZ12609901).

Preparación S

1,2-dicloro-4-(isocianometil)benceno

(i) *N*-(3,4-diclorobencil)formamida

A 1-(3,4-diclorofenil)metanamina (352 mg, 2,00 mmol) se le agregó formiato de etilo (8,0 mL, 99,4 mmol). La mezcla se agitó a 45° durante toda la noche (16 h) y después se concentró al vacío para dar 433 mg del producto crudo. El producto crudo se usó en el paso siguiente sin más purificación.

^{1}H-NMR (500 MHz, CD_3OD) δ 8,18 (s, 1H); 7,51-7,47 (m, 2H); 7,27-7,23 (m, 1H); 4,40 (s, 2H).

(ii) 1,2-dicloro-4-(isocianometil)benceno

A *N*-(3,4-el clorobencil)formamida (del paso (i) anterior) (245 mg, 1,20 mmol) disuelta en MeCN (6 mL) se le agregó sal interna hidróxido de (metoxicarbonilsulfamoil)trietilamonio (reactivo de Burgess) (286 mg, 1,20 mmol). La mezcla se agitó a 50 °C durante 3 h. Después de enfriar a rt, la mezcla se transfirió directamente al paso de reacción siguiente sin ningún tratamiento.

Preparación T

No se prepararon isonitrilos que estuvieran comercialmente disponibles a partir de las correspondientes aminas, a través de las formamidas, en analogía con la preparación L, M, N, O, P, Q, R anterior, ni se usaron para preparar los compuestos de los ejemplos siguientes

Preparación U

4-fluoro-3-hidroxi-2-benzofuran-1(3H)-ona

(i) 3-fluoro-N-(2-hidroxi-1,1-dimetiletil)benzamida

A una solución de ácido 3-fluorobenzoico (20 g, 0,142 mol) en diclorometano (200 ml) se le agregó cloruro de oxalilo (14,6 ml, 0,171 mol) seguido de una gota de DMF a 0 °C en atmósfera de nitrógeno. La mezcla de reacción se agitó durante 2 h a temperatura ambiente. Después la mezcla de reacción se concentró y se agregó gota a gota a la solución de 2-amino-2-metil propanol (28 g, 0,314 mol) en diclorometano (100 ml) a 0 °C en atmósfera de nitrógeno. La solución resultante se agitó a temperatura ambiente durante otras 2 h. La mezcla de reacción se filtró y el filtrado se concentró. El sólido blanco concentrado (30 g) se usó para el paso siguiente sin purificación.

(ii) 2-(3-fluorofenil)-4,4-dimetil-4,5-dihidro-1,3-oxazol

Se agregó gota a gota cloruro de tionilo (60 g) a la 3-fluoro-N-(2-hidroxi-1,1-dimetiletil) benzamida (del paso (i) anterior) (30 g) en agitación a temperatura ambiente y se agitó durante otros 15 minutos. La solución amarilla se vertió en éter dietílico seco (200 ml) y la mezcla de reacción se neutralizó con solución de hidróxido de sodio al 20% fría.

La capa de éter dietílico se lavó con agua, solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. El residuo se purificó por cromatografía en gel de sílice usando (EtOAc/pet éter) para dar el compuesto del subtítulo (18,5 g, 67,3%) como un líquido marrón.

(iii) 4-fluoro-3-hidroxi-2-benzofuran-1(3H)-ona

A una solución de 2-(3-fluorofenil)-4,4-dimetil-4,5-dihidro-1,3-oxazol (18,5 g, 0,958 mol) (del paso (ii) anterior) en éter dietílico (200 ml) se le agregó gota gota *sec*-BuLi (103 ml, 1,4 M en ciclohexano) a –78 °C en atmósfera de nitrógeno y se agitó durante otros 30 minutos a la misma temperatura. Después se agregó DMF seco (20 ml) y la mezcla de reacción se dejó en agitación a temperatura ambiente durante otras 2 h. La reacción se detuvo con HCl 6 N y se concentró. La masa concentrada se calentó a reflujo con HCl 6 N (400 ml) durante toda la noche. Después la mezcla de reacción se enfrió a temperatura ambiente y se agitó con éter dietílico (200 ml). La capa orgánica se separó y se lavó con

agua, solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró para dar el producto cíclico crudo. La masa cruda se purificó por recristalización (éter dietílico/pet éter) para dar el compuesto del título (8 g, 49,6%) como un sólido blanco

Preparación V

5-cloro-3-hidroxi-2-benzofuran-1(3H)-ona

(i) 4-cloro-N-(2-hidroxi-1,1-dimetiletil)benzamida

A una solución de ácido 4-clorobenzoico (50 g, 0,319 mol) en diclorometano (400 ml) se le agregó cloruro de oxalilo (34 ml, 0,383 mol) seguido de una gota de DMF a 0 °C en atmósfera de nitrógeno. La mezcla de reacción se agitó durante 2 h a temperatura ambiente. Después la mezcla de reacción se concentró y se agregó gota a gota a la solución de 2-amino-2-metilpropanol (62,8 g, 0,702 mol) en diclorometano (200 ml) a 0 °C en atmósfera de nitrógeno. La solución resultante se agitó a temperatura ambiente durante otras 2 h. La mezcla de reacción se filtró y el filtrado se concentró. El residuo se purificó por cromatografía en gel de sílice usando ($MeOH/CHCl_3$) para dar el producto intermedio deseado (68 g, 93,5%) como un líquido marrón.

(ii) 2-(4-clorofenil)-4,4-dimetil-4,5-dihidro-1,3-oxazol

Se agregó gota a gota cloruro de tionilo (120,8 g, 1,05 mol) a la 4-cloro-N-(2-hidroxi-1,1-dimetiletil) benzamida (68 g, 0,30 mol) (del paso (i) anterior) en agitación a temperatura ambiente y se agitó durante otros 15 minutos. Después la solución amarilla se vertió en éter dietílico seco (500 ml) y la mezcla de reacción se neutralizó con solución de hidróxido de sodio al 20% fría. La capa de éter dietílico se lavó con agua, solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. El residuo se purificó por cromatografía en gel de sílice usando (EtOAc/pet éter) para dar el compuesto del subtítulo (53 g, 84,6%) como un líquido marrón.

(iii) 5-cloro-2-(4,4-dimetil-4,5-dihidro-1,3-oxazol-2-il)benzaldehído

A una solución de 2-(4-clorofenil)-4,4-dimetil-4,5-dihidro-1,3-oxazol (19 g, 0,906 mol) (del paso (ii) anterior) en éter dietílico (400 ml) se le agregó gota a gota *sec*-BuLi (110 ml, 1,4 M en ciclohexano) a –78°C en atmósfera de nitrógeno y se dejó que la mezcla de

reacción se calentara hasta 0 °C y se agitó a 0 °C durante 1 h más. La mezcla de reacción se enfrió nuevamente a –78°C y se agregó DMF seco (10 ml) y se calentó a temperatura ambiente durante toda la noche. La reacción se detuvo y se diluyó con agua. La capa orgánica separada se lavó con agua y solución saturada de cloruro de sodio. Después la capa orgánica se secó sobre sulfato de sodio anhidro y se concentró al vacío para dar el compuesto del subtítulo crudo (20 g) como un líquido amarillo.

(iv) 5-cloro-3-hidroxi-2-benzofuran-1(3H)-ona

Se calentó 5-cloro-2-(4,4-dimetil-4,5-dihidro-1,3-oxazol-2-il)benzaldehído del paso (iii) anterior (20 g) a 80 °C durante toda la noche con HCl en agua (300 ml agua, 150 ml HCl conc.). Después la mezcla de reacción se enfrió a temperatura ambiente y se agitó con éter dietílico (500 ml). La capa de éter dietílico se lavó con agua y solución saturada de cloruro de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró al vacío. La masa cruda se recristalizó del sistema solvente acetato de etilo/pet éter para dar el compuesto del título (4,9 g, 31,6%) como un sólido marrón claro.

Preparación W

5-bromo-3-hidroxi-2-benzofuran-1(3H)-ona

(i) ácido 4-bromo-2-(hidroxi metil)benzoico

Se calentó a reflujo 5-bromo ftalida (9 g, 0,042 mol) con hidróxido de sodio acuoso 2 N (100 ml) en metanol (150 ml) durante toda la noche. La mezcla de reacción se concentró a presión reducida. La masa concentrada se diluyó con agua y se acidificó con HCl diluido. El precipitado sólido se filtró y el residuo se lavó con agua fría y acetato de etilo frío y se secó para dar el compuesto del subtítulo (9,7 g, 100%) como un sólido blanco

(i) 5-bromo-3-hidroxi-2-benzofuran-1(3H)-ona

A una solución de ácido 4-bromo-2-(hidroximetil)benzoico del paso (i) anterior (9,7 g, 0,042 mol) en acetonitrilo (300 ml) se le agregó periodinano Dess-Martin (26,8 g, 0,0633 mol) a 0 °C en atmósfera de nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 14 h. La mezcla de reacción se filtró y los precipitados se lavaron con diclorometano. Se concentró el filtrado. La masa concentrada se calentó con 200 ml de

HCl conc. durante 6 h a 70 °C. La mezcla de reacción se diluyó con un gran volumen de agua y se extrajo con acetato de etilo. La capa orgánica se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. La masa concentrada se purificó por recristalización de acetato de etilo/pet éter para dar el compuesto del título (4,9 g, 51%) como un sólido blanco

Preparación X

5-fluoro-3-hidroxi-2-benzofuran-1(3H)-ona

(i) 4-fluoro-N-(2-hidroxi-1,1-dimetiletil)benzamida

A una solución de ácido 4-fluorobenzoico (50 g, 0,357 mol) en diclorometano (400 ml) se le agregó cloruro de oxalilo (34 ml, 0,393 mol) seguido de una gota de DMF a 0 °C en atmósfera de nitrógeno. La mezcla de reacción se agitó durante 2 h a temperatura ambiente. Después la mezcla de reacción se concentró y se agregó gota a gota a la solución de 2-amino-2-metil propanol (70 g, 0,785 mol) en diclorometano (200 ml) a 0 °C en atmósfera de nitrógeno. La solución resultante se agitó a temperatura ambiente durante otras 2 h. La mezcla de reacción se filtró y el filtrado se concentró. La masa líquida concentrada (75 g) se usó para el paso siguiente sin purificación.

(ii) 2-(4-fluorofenil)-4,4-dimetil-4,5-dihidro-1,3-oxazol

Se agregó gota a gota cloruro de tionilo (144 g) a la 4-fluoro-N-(2-hidroxi-1,1-dimetiletil) benzamida (75 g) (del paso (i) anterior) en agitación a temperatura ambiente y se agitó durante otros 15 minutos. Después la solución amarilla se vertió en éter dietílico seco (500 ml) y la mezcla de reacción se neutralizó con solución de hidróxido de sodio al 20% fría. La capa de éter dietílico se lavó con agua, solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. El residuo se purificó por cromatografía en gel de sílice usando (EtOAc/pet éter) para dar el compuesto del subtítulo (65 g, 95%) como un líquido marrón.

(iii) 2-(4,4-dimetil-4,5-dihidro-1,3-oxazol-2-il)-5-fluorobenzaldehído

A 2-(4-fluorofenil)-4,4-dimetil-4,5-dihidro-1,3-oxazol (40 g, 0,206 mol) (del paso (ii) anterior) en éter dietílico (800 ml) se le agregó gota gota *sec*-BuLi (192 ml, 1,4 M en

ciclohexano) a –78 °C en atmósfera de nitrógeno y se agitó durante otras 3 h a la misma temperatura. Después se agregó DMF seco (40 ml) y se calentó a temperatura ambiente durante toda la noche. La reacción se detuvo y se diluyó con agua. La capa orgánica separada se lavó con agua y solución saturada de cloruro de sodio. Después la capa orgánica se secó sobre sulfato de sodio anhidro y se concentró al vacío para dar el producto intermedio crudo (36 g) como un líquido amarillo.

(iv) 5-fluoro-3-hidroxi-2-benzofuran-1(3H)-ona

Se calentó 2-(4,4-dimetil-4,5-dihidro-1,3-oxazol-2-il)-5-fluorobenzaldehído (36 g) del paso (iii) anterior a 80 °C durante toda la noche con HCl en agua (400 ml agua, 200 ml HCl conc.). La mezcla de reacción se enfrió a temperatura ambiente y se agitó con éter dietílico (500 ml). La capa de éter dietílico se lavó con agua y solución saturada de cloruro de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró al vacío. La masa cruda se recristalizó del sistema solvente acetato de etilo/pet éter para dar el compuesto del título (7 g, 26%) como un sólido color hueso.

Preparación Y

ácido 2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxílico

(i) 2-(2-etoxi-2-oxoetil)benzoato de etilo

Se disolvió ácido 2-carboximetilbenzoico (25 g) en etanol absoluto (250 ml) y se agregó ácido sulfúrico conc. (1 ml). La solución resultante se calentó a reflujo en un aparato Dean & Stark durante 2 días y el solvente se reemplazó tres veces con etanol absoluto. Se eliminó el etanol a presión reducida y la masa concentrada se disolvió en acetato de etilo. La capa de acetato de etilo se lavó con solución saturada de bicarbonato de sodio, agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró para obtener el compuesto del subtítulo (30 g) como un aceite amarillo.

(ii) 2-(1-bromo-2-etoxi-2-oxoetil)benzoato de etilo

Se mezcló 2-(2-etoxi-2-oxoetil)benzoato de etilo (30 g, 0,127 mol) del paso (i) anterior con N-bromosuccinamida (22,5 g, 0,127 mol) en tetracloruro de carbono (300 ml). Se agregó AIBN y se calentó a reflujo durante 2 días. Después la mezcla de reacción se lavó con

agua, se secó sobre sulfato de sodio anhidro y se concentró. El producto intermedio crudo se purificó por cromatografía en columna usando acetato de etilo al 2% en pet. éter para dar el compuesto del subtítulo (26 g, 65%) como un líquido marrón.

(iii) 2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxilato de etilo

Se agregó gota a gota [2-(4-clorofenil)propil]amina (20 g, 0,118 mol) a la solución del producto intermedio del paso 2 (18,6 g, 0,059 mol) en acetonitrilo (150 ml) a 0 °C en atmósfera de nitrógeno. Después la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se filtró, el residuo se lavó con diclorometano y el filtrado combinado se concentró. El producto crudo se purificó usando acetato de etilo al 10% en pet éter como eluyente para dar el compuesto del subtítulo (23 g, 100%) como un sólido blanco.

(iv) ácido 2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxílico

Se agregó una solución acuosa de hidróxido de sodio (3 g, en 50 ml de agua, 0,075 mol) a una solución bien agitada de 2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxilato de etilo (13 g, 0,036 mol) en etanol (100 ml) a 0 °C. La mezcla de reacción se dejó en agitación a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida, se diluyó con agua y se extrajo con acetato de etilo. La capa acuosa se acidificó con HCl 2 M y se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró a presión reducida para dar el compuesto del título (11,5 g, 95,8%).

Preparación Z

2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxilato de etilo

Se agregó gota a gota 2-(4-clorofenil)etilamina (25 g, 0,16 mol) a la solución 2-(1-bromo-2-etoxi-2-oxoetil)benzoato de etilo (25 g, 0,0793 mol) en acetonitrilo (150 ml) a 0 °C en atmósfera de nitrógeno. Después la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se filtró, el residuo se lavó con diclorometano y el filtrado combinado se concentró. El producto crudo se purificó usando acetato de etilo

al 15% en pet éter como eluyente para dar el compuesto del título (22 g, 80,8%) como un sólido blanco

Preparación AA

ácido 2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxílico

Se agregó una solución acuosa de hidróxido de sodio (3 g, en 50 ml de agua, 0,075 mol) a una solución bien agitada de 2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxilato de etilo (preparación Z anterior) (15 g, 0,043 mol) en etanol (100 ml) a 0 °C. Después la mezcla de reacción se dejó en agitación a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida, se diluyó con agua y se extrajo con acetato de etilo. La capa acuosa se acidificó con HCl 2 N y se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró a presión reducida para dar el compuesto del título (13 g, 94,8%).

Preparación AB

clorhidrato de (2-fenoxibencil)amina

(i) 1-bromo-2-fenoxibenceno

Se agregó gota a gota una solución de nitrito de sodio (9,2 g, 0,135 mol) en agua (20 ml) a una solución de 2-fenoxianilina (25 g, 0,135 mol) en ácido bromhídrico al 40% (50 ml) a 0 °C y se agitó durante otros 10 minutos. Después la mezcla de reacción se agregó a la mezcla en ebullición de bromuro cuproso (21,3 g, 0,149 mol) en ácido bromhídrico al 40% (50 ml) y después de la adición se dejó que se calentara a reflujo durante otros 30 minutos La mezcla de reacción se enfrió, se diluyó con agua y se extrajo con éter dietílico. La capa de éter dietílico se lavó con ácido clorhídrico al 5%, hidróxido de potasio al 10%, agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio y se concentró para dar el producto intermedio crudo. Se obtuvo el compuesto del subtítulo (14,8 g, 45%) por purificación en columna del producto intermedio crudo usando pet éter como eluyente.

(ii) 2-fenoxibenzonitrilo

Una solución de 1-bromo-2-fenoxibenceno del paso (i) anterior (14,8 g, 0,0594 mol), $Zn(CN)_2$ (6,9 g, 0,0594 mol) y $Pd(PPh_3)_4$ (6,8 g, 0,00594 mol) en dimetilformamida (100 ml) se calentó a 130 °C durante toda la noche en atmósfera de nitrógeno. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con agua (200 ml). La mezcla de reacción se agitó con acetato de etilo (200 ml) durante 15 minutos y se filtró a través de celite. La capa de acetato de etilo se separó y se lavó con agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. El producto intermedio crudo se purificó por cromatografía en columna usando acetato de etilo al 4% en pet éter para dar el compuesto del subtítulo (10,1 g, 87,8%) como un líquido incoloro.

(iii) clorhidrato de (2-fenoxibencil)amina

Una solución de 2-fenoxibenzonitrilo (del paso (ii) anterior (10, 1 g, 0,0517 mol)) en THF (50 ml) se agregó gota a gota a una suspensión bien agitada de LAH (4,9 g, 0,129 mol) en THF (50 ml) a 0 °C en atmósfera de nitrógeno y después se dejó en agitación a temperatura ambiente durante toda la noche. La mezcla de reacción se enfrió rápidamente con KOH 6 N (5 ml) a 0 °C y se agitó con THF (50 ml) durante otros 30 minutos. La mezcla de reacción se filtró y el residuo se lavó con acetato de etilo. El filtrado se concentró para dar la amina cruda. Se agregó HCl saturado en éter dietílico (20 ml) a la solución de la amina cruda en éter dietílico (20 ml) y se agitó durante 2 h. Después la mezcla de reacción se filtró y el residuo se secó para dar el compuesto del título (10 g, 97,08

Preparación AC

clorhidrato de (dipiridin-3-ilmetil)amina

(i) dipiridin-3-ilmetanona

Se agregó gota a gota n-BuLi (71,3 ml, 1,6 M, 0,114 mol) a la solución de3-bromopiridina (15 g, 0,095 mol) en éter dietílico seco (200 ml) a –78 °C y se agitó durante 15 minutos. Se agregó gota a gota una solución de nicotinato de etilo (13 g, 0,095 mol) en éter dietílico seco (50 ml) a la mezcla de reacción a – 78 °C y se agitó durante otras 2 h a la misma temperatura. Después la mezcla de reacción se enfrió rápidamente con cloruro de amonio saturado y se extrajo con acetato de etilo. La capa orgánica se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. El producto

crudo se purificó en columna de alúmina neutra usando (metanol/diclorometano) para dar el compuesto del subtítulo (8,5 g, 49%) como un líquido marrón.

(ii) oxima de dipiridin-3-ilmetanona

Se agregó una solución de dipiridin-3-ilmetanona del paso (i) anterior (8,5 g, 0,046 mol) en metanol seco (50 ml) a una solución bien agitada de acetato de sodio (9,6 g, 0,117 mol) y clorhidrato de hidroxilamina (8,12 g, 0,117 mol) en metanol seco (50 ml). La mezcla de reacción se calentó reflujo en atmósfera de nitrógeno durante 2 h. Después la mezcla de reacción se concentró, se diluyó con agua y se extrajo con diclorometano. La capa orgánica se lavó con agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró para dar el compuesto del subtítulo (9,5 g, 100%).

(iii) clorhidrato de (dipiridin-3-ilmetil)amina

Se disolvieron la oxima de dipiridin-3-ilmetanona (paso (ii) anterior (9,5 g, 0,0477 mmol) y acetato de amonio (5,5 g, 0,0716 mmol) en etanol (00 ml), agua (80 ml) y NH_3 acuoso al 40% (100 ml). La mezcla se calentó a 80 °C y se agregó polvo de cinc (15,5 g, 0,23 mmol) en el transcurso de 1 h. Después la reacción se agitó a 80 °C durante toda la noche y luego se enfrió a rt, se filtró y el filtrado se concentró al vacío. La solución acuosa remanente se hizo básica con NaOH (ac.) 10 M y se extrajo con diclorometano.

Las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio (40 ml), se secaron sobre sulfato de sodio anhidro y se concentraron. La masa gomosa amarilla concentrada se disolvió en acetato de etilo y se agregó gota a gota éter dietílico (50 ml) saturado con HCl gaseoso y se agito durante 1 h. La mezcla de reacción se filtró y el residuo sólido se secó para dar el compuesto del título (9,2 g, 65%) como un sólido color hueso.

Preparación AD

sal del ácido trifluoroacético de 3-(2-aminoetil)benzonitrilo

(i) [2-(3-bromofenil)etil]carbamato de terc-butilo

Se agregó anhídrido-BOC (12 ml, 0,054 mol) a una solución helada de 3-bromofenetilámina (10 g, 0,049 mol) y trietilamina (10,4 ml, 0,10 mol) en diclorometano

(100 ml). Después de 1 h de agitación a temperatura ambiente la mezcla de reacción se enfrió rápidamente con agua y se extrajo con diclorometano. La capa orgánica se lavó con agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró para dar el compuesto del subtítulo (15 g, 100%).

(ii) [2-(3-cianofenil)etil]carbamato de terc-butilo

Una mezcla de [2-(3-bromofenil)etil]carbamato de terc-butilo (15 g, 0,05 mol), $Zn(CN)_2$ (5,87 g, 0,05 mol) y tetrakis(trifenilfosfina)paladio (0) (5,7 g, 0,005 mol) se calentó a 140 °C durante 5 h en DMF seco (150 ml) en atmósfera de nitrógeno. Después la mezcla de reacción se enfrió a temperatura ambiente, la reacción se detuvo con agua y se filtró a través de una almohadilla de celite. La mezcla de reacción se extrajo con acetato de etilo y la capa de acetato de etilo se lavó sucesivamente con agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. Después el material crudo se purificó porcromatografía en columna usando acetato de etilo al 20% en pet éter como eluyente para dar el compuesto del subtítulo deseado (7 g, 57%) como un sólido blanco.

(iii) sal del ácido trifluoroacético de 3-(2-aminoetil)benzonitrilo

Se agregó ácido trifluoroacético (5 ml) a una solución de [2-(3-cianofenil)etil]carbamato de terc-butilo (10 g) en diclorometano (20 ml) y se agitó a temperatura ambiente durante toda la noche. El solvente y el exceso de ácido trifluoroacético se eliminaron a presión reducida para dar un aceite gomoso. Al triturar el aceite gomoso con éter dietílico, apareció un sólido blanco Se decantó el éter dietílico y el sólido blanco se secó para obtener el compuesto del título (6 g).

Preparación AE

[2-fluoro-4-(metilsulfonil)bencil]amina

(i) dimetiltiocarbamato de O-(4-ciano-3-fluorofenilo)

Una mezcla de 2-fluoro-4-hidroxibenzonitrilo (10 g, 0,0729 mol), DMAP (900 mg, 0,00729 mol), trietilamina (30 ml, 0,218 mol) y cloruro de dimetiltiocarbamoilo (11 g, 0,0875 mol) en diclorometano seco (200 ml) se agitó a reflujo en atmósfera de nitrógeno durante toda la noche. La mezcla de reacción se enfrió rápidamente con agua y se extrajo

con diclorometano. La capa orgánica se lavó con agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio. El solvente se evaporó a presión reducida y el residuo se trituró con pet éter. El producto se filtró y se secó al vacío para dar el compuesto del subtítulo (14 g, 85,8%) como un sólido amarillo.

(ii) dimetiltiocarbamato de S-(4-ciano-3-fluorofenilo)

Se mezclaron dimetiltiocarbamato de O-(4-ciano-3-fluorofenilo) del paso (i) anterior (14 g) y éter difenílico (200 ml) y se agitaron a 210 °C durante 6 h. Después el éter difenílico se eliminó por destilación a presión reducida y la masa cruda se agitó con pet éter y se filtró. El residuo se lavó con pet éter varias veces y se secó el aire para dar el compuesto del subtítulo (13,4 g, 95,7%) como un sólido marrón claro.

(iii) 2-fluoro-4-mercaptobenzonitrilo

Se tomó el dimetiltiocarbamato de S-(4-ciano-3-fluorofenilo) del paso (ii) anterior (13,4 g, 0,059 mol) en THF (150 ml) al cual se agregó una solución de KOH (6,7 g, 0,11 mol) en metanol (200 L). La mezcla de reacción se agitó a RT durante 3 h y después se concentró. La masa cruda se disolvió en acetato de etilo. La capa de acetato de etilo se acidificó con HCl 3 N hasta pH = 2. La capa de acetato de etilo se lavó con agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. El producto intermedio crudo (9 g) obtenido se tomó directamente para el paso siguiente sin más

(iv) 2-fluoro-4-(metiltio)benzonitrilo

Se agregó gota a gota yoduro de metilo (12,5 g, 0,058 mol) a una solución de 2-fluoro-4-mercaptobenzonitrilo (9 g, 0,058 mol) (del paso (iii) anterior) y carbonato de potasio (12, 1 g, 0,088 mol) en acetonitrilo seco (150 ml) y se agitó a temperatura ambiente durante 3 h en atmósfera de nitrógeno. La mezcla de reacción se filtró y el filtrado se concentró para dar el compuesto del subtítulo (9,6 g, 100%).

(v) 2-fluoro-4-(metilsulfonil)benzonitrilo

Se agregó 2-fluoro-4-(metiltio)benzonitrilo (9,6 g, 0,0524 mol) del paso (iv) anterior) a una mezcla de ácido acético glacial/agua/etanol (140 ml, 2:2:3) y se agitó durante 10 min. La mezcla de reacción se enfrió 0 °C y se agregó oxona (40,4 g, 0,065 mol) en porciones. La

mezcla de reacción se agitó a RT durante 2 h y se diluyó con diclorometano. Se filtraron los productos inorgánicos el y licor madre se particionó entre agua y diclorometano. La capa orgánica se lavó con agua y solución saturada de cloruro de sodio, y se secó sobre sulfato de sodio. La evaporación del solvente a presión reducida seguida de recristalización del producto crudo usando acetato de etilo/pet éter produjo la su forma deseada (9 g, 80%).

(vi) 2-fluoro-4-(metilsulfonil)benzonitrilo

A una solución de 2-fluoro-4-(metiltio)benzonitrilo (9 g) en metanol (150 ml), se le agregó níquel Raney (2 g) y después se saturó con amoníaco (g). La mezcla de reacción se hidrogenó en un agitador parr a una presión de hidrógeno de 3 kg durante toda la noche. La mezcla de reacción se filtró y el filtrado se concentró. La masa concentrada se disolvió en acetato de etilo y se agitó con HCl saturado en éter durante toda la noche en atmósfera de nitrógeno. Los precipitados sólidos se filtraron, se lavaron con éter dietílico y se secaron para dar el compuesto del título (1,3 g, 14,3%) como un sólido amarillo pálido

Preparación AF

clorhidrato de [2-cloro-4-(metilsulfonil)bencil]amina

(i) dimetiltiocarbamato de O-(3-cloro-4-cianofenilo)

Una mezcla de 2-cloro-4-hidroxibenzonitrilo (25 g, 0,162 mol), DMAP (1,9 g, 0,162 mol), trietilamina (68 ml, 0,483 mol) y cloruro de dimetiltiocarbamoilo (24 g, 0,195 mol) en diclorometano seco (500 ml) se agitó a reflujo en atmósfera de nitrógeno durante toda la noche. La mezcla de reacción se enfrió rápidamente con agua y se extrajo con diclorometano. La capa orgánica se lavó con agua y solución saturada de cloruro de sodio, y se secó sobre sulfato de sodio. El solvente se evaporó a presión reducida y el residuo se trituró con pet éter. El producto se filtró y se secó al vacío para dar el producto intermedio deseado (38 g, 97%) como un sólido amarillo.

(ii) dimetiltiocarbamato de S-(3-cloro-4-cianofenilo)

Se mezclaron dimetiltiocarbamato de O-(3-cloro-4-cianofenilo) (38 g) y éter difenílico (500 ml) y se agitaron a 210 °C durante 6 h. Después el éter difenílico se eliminó por destilación a presión reducida, y la masa cruda se agitó con pet éter y se filtró. El residuo

se lavó con pet éter varias veces y se secó el aire para dar el producto intermedio deseado (37,8 g, 99,5%) como un sólido marrón claro.

(iii) 2-cloro-4-mercaptobenzonitrilo

Se tomó el dimetiltiocarbamato de S-(3-cloro-4-cianofenilo) (35 g, 0,145 mol) en THF (400 ml) al cual se agregó una solución de KOH (163 g, 0,30 mol) en metanol (200 L). La mezcla de reacciónse agitó a RT durante 3 h y después se concentró. La masa cruda se disolvió en acetato de etilo. La capa de acetato de etilo se acidificó con HCl 3 N hasta pH = 2. La capa de acetato de etilo se lavó con agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio anhidro y se concentró. El producto intermedio crudo (25 g) obtenido se tomó directamente para el paso siguiente sin más purificación.

(iv) 2-cloro-4-(metiltio)benzonitrilo

Se agregó gota a gota yoduro de metilo (31,4 g, 0,22 mol) a una solución de 2-cloro-4-mercaptobenzonitrilo (25 g, 0,147 mol) y carbonato de potasio (20,4 g, 0,22 mol) en acetonitrilo seco (300 ml) y se agitó a temperatura ambiente durante 3 h en atmósfera de nitrógeno. Después la mezcla de reacción se filtró y el filtrado se concentró para el producto intermedio deseado (26 g, 96,2%).

(v) 2-cloro-4-(metilsulfonil)benzonitrilo

Se agregó 2-cloro-4-(metiltio)benzonitrilo (26 g, 0,145 mol) a una mezcla de ácido acético glacial/agua/etanol (900 ml, 2:2:3) y se agitó durante 10 min. La mezcla de reacción se enfrio a 0 °C y se agregó oxona (217 g, 0,353 mol) en porciones. La mezcla de reacción se agitó a RT durante toda la noche y se diluyó con diclorometano. Se filtraron los productos inorgánicos y el licor madre se particionó entre agua y diclorometano. La capa orgánica se lavó con agua y solución saturada de cloruro de sodio, y se secó sobre sulfato de sodio. La evaporación del solvente a presión reducida seguida de recristalización del producto crudo usando acetato de etilo/pet éter produjo el compuesto del subtitulo (18 g, 59%) como un solido blanco.

(vi) clorhidrato de [2-cloro-4-(metilsulfonil)bencil]amina

A una solución del producto intermedio del paso 5 (8 g) en metanol (200 ml), se le agregó níquel Raney (2,5 g) y después se saturó con amoníaco (g). La mezcla de reacción se hidrogenó en un agitador parr a una presión de hidrógeno de 3 kg durante toda la noche. La mezcla de reacción se filtró y el filtrado se concentró. La masa concentrada se disolvió en acetato de etilo y se agitó con HCl saturado en éter durante toda la noche en atmósfera de nitrógeno. Los precipitados sólidos se filtraron, se lavaron con éter dietílico y se secaron para dar el compuesto del título (7 g, 86,4%) como un sólido.

Preparación AG

clorhidrato de 2-(4-clorofenil)-2-metil-propan-1-amina

(i) 2-(4-clorofenil)-2-metilpropanonitrilo

A una solución en agitación de 2-(4-clorofenil)acetonitrilo (10 g, 0,066 mol) en DMF, se le agregó en porciones hidruro de sodio (3,95 g, 0,1649 mol) a 0 °C. La mezcla de reacción se dejó en agitación durante 1 h a temperatura ambiente. Después se enfrió nuevamente a 0 °C y se agregó gota a gota yoduro de metilo (28,0 g, 0,198 mol). La mezcla de reacción se dejó en agitación a 40 °C durante 4 h. La mezcla de reacción se diluyó con agua fría y el producto se extrajo con EtOAc. La capa orgánica se lavó con agua y solución saturada de cloruro de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice usando (EtOAc/pet éter) para dar el compuesto del subtítulo (7,7g, 65%) como un líquido incoloro.

(ii) clorhidrato de 2-(4-clorofenil)-2-metil-propan-1-amina

A una mezcla de $LiAlH_4$ (4,06 g, 0,107 mol) en THF se le agregó gota a gota el producto intermedio del paso1 (7,7 g, 0,043 mol) en THF a 0 °C. La mezcla de reacción se dejó en agitación a temperatura ambiente durante toda la noche. La mezcla de reacción se enfrió a 0 °C y la reacción se detuvo con 10 ml de solución de KOH 6 M. La mezcla de reacción se diluyó con THF y se dejó en agitación a temperatura ambiente durante 30 min. La mezcla de reacción se filtró y el filtrado se concentró. El residuo se diluyó con éter dietílico y se le agregó HCl en éter a 0 °C. El sólido blanco se recogió por filtración, se lavó con éter dietílico seco y se secó al vacío para obtener el producto deseado (6 g, 77%) del compuesto del título.

Preparación AH

7-fluoro-3-hidroxi-2-benzofuran-1(3H)-ona

(i) 1-(dimetoximetil)-3-fluorobenceno

A una solución en agitación de 3-fluorobenzaldehído (17,5 g, 0,141 mol) en metanol (175 ml) se le agregaron ortoformiato de trimetilo (17,5 ml, 0,159 mol) y PTSA (175 mg). La mezcla de reacción se agitó a RT durante toda la noche. La mezcla de reacción se enfrió rápidamente con 30 ml de solución de KOH al 1% en metanol. La masa de reacción se concentró, después se diluyó con agua y el producto se extrajo con acetato de etilo. La capa orgánica se lavó con agua y solución saturada de cloruro de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró al vacío. El crudo se destiló fraccionadamente para obtener el producto intermedio deseado (20 g, 83,6%) como un líquido incoloro.

(ii) 7-fluoro-3-hidroxi-2-benzofuran-1(3H)-ona

A una solución de 1-(dimetoxibencil)-3-fluorobenceno (20 g, 0,11 mol) en THF (200 ml) (del paso (i) anterior) se le agregó gota a gota *sec*BuLi (220 ml, 1,4 M en ciclohexano) a –78 °C en atmósfera de nitrógeno y se agitó durante otras 3 h a la misma temperatura. Después se purgó el CO_2 hasta que la solución roja se tornó amarilla y se calentó lentamente hasta temperatura ambiente. La mezcla de reacción se agitó durante otra 1 h y después se enfrió rápidamente con 20 ml de HCl. Después la mezcla de reacción se concentró. La masa de reacción cruda así obtenida se calentó a 80 °C durante toda la noche con HCl en agua (300 ml de HCl conc., 200 ml de agua). Después la mezcla de reacción se enfrió a temperatura ambiente y se agitó con éter dietílico (100 ml). La capa de éter dietílico se lavó con agua y solución saturada de cloruro de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró al vacío. La masa cruda se sometió a HPLC preparativa para dar el compuesto del título (2,3 g, 11,7%) como un sólido blanco.

Preparación AI

1-(3',4'-difluorobifenil-2-il)metanamina

(i) [(3',4'-difluorobifenil-2-il)metil]carbamato de terc-butilo

Se disolvieron (2-bromobencil)carbamato de terc-butilo (1,74 mmol, 0,50 g), tetrakis(trifenilfosfina)paladio (0,087 mmol, 0,10 g) y ácido (3,4-difluorofenil)borónico (2,10 mmol, 0,33 g) en (DME 10 ml) en un micro vial. Se disolvió carbonato de cesio (3,49 mmol, 1,14 g) en 2 ml de agua y después se agregó a la mezcla. Se hizo burbujear Ar (g) a través de la mezcla durante 5 minutos. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 90/10 y después se aumentó la concentración de EtOAc hasta 70% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (3,00 g, 89,6%). 1H-NMR (500 MHz, $CDCl_3$): δ 7,46-7,42 (m, 1H); 7,41-7,36 (m, 1H); 7,36-7,30 (m, 1H); 7,25-7,18 (m, 2H); 7,17-7,11 (m, 1H); 7,06-7,01 (m, 1H); 4,75 (bs, 1H); 4,31-4,17 (m, 2H); 1,45 (s, 9H).

(i) 1-(3',4'-difluorobifenil-2-il)metanamina

Se disolvió [(3',4'-difluorobifenil-2-il)metil]carbamato de terc-butilo (9,39 mmol, 3,00 g) en HCl saturado en EtOAc y se agitó a rt durante 2 h. El solvente se eliminó por evaporación y la sal de HCl se purificó por cromatografía instantánea (se comenzó con isocrática heptano/DCM 50/50 y después se aumentó la concentración de DCM hasta 100% después el producto se eluyó con MeOH al 10% (saturado con NH3), (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (2,00 g, 97,1 %).
1H-NMR (500 MHz, $CDCl_3$): δ 7,55-7,50 (m, 1H); 7,42-7,35 (m, 1H); 7,32-7,15 (m, 4H); 7,14-7,06 (m, 1H); 4,82-4,79 (m, 2H); 3,78-3,73 (m, 2H).

Preparación AJ

1-(4,4'-difluorobifenil-2-il)metanamina

(i) [(4,4'-difluorobifenil-2-il)metil]carbamato de terc-butilo

Se disolvieron 1-bromo-4-fluoro benceno (11,15 mmol, 1,95 g), tetrakis(trifenilfosfina)paladio (0,41 mmol, 0,47 g) y ácido (2-{[(terc-butoxicarbonil)amino]metil}-4-fluorofenil)borónico (9,29 mmol, 2,50 g) en (DME 10 ml)

en un micro vial. Se disolvió carbonato de cesio (18,58 mmol, 6,05 g) en 2 ml de agua y después se agregó a la mezcla. Se hizo burbujear N_2 (g) a través de la mezcla durante 5 minutos. La reacción se realizó en un horno de microondas (20 min, 130°). El crudo se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 95/5 y después se aumentó la concentración de EtOAc hasta 60% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (2,54 g, 85,6 %). 1H-NMR (500 MHz, $CDCl_3$): δ 7,30-7,21 (m, 2H); 7,21-7,08 (m, 4H); 7,03-6,97 (m, 1H); 4,79 (bs, 1H); 4,29-4,13 (m, 2H); 1,45 (s, 9H).

(ii) 1-(4,4'-difluorobifenil-2-il)metanamina

Se disolvió [(4,4'-difluorobifenil-2-il)metil]carbamato de terc-butilo (7,95 mmol, 2,54 g) en HCl saturado en EtOAc y se agitó a rt durante 2 h. El solvente se eliminó por evaporación y la sal de HCl del producto se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 50/50 y después se aumentó la concentración de EtOAc hasta 100%, después el producto se eluyó con MeOH al 10% (saturado con NH_3), (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (1,64 g, 94,1 %). 1H-NMR (500 MHz, CD_3OD): δ 7,34-7,27 (m, 3H); 7,22-7,13 (m, 3H); 7,05-7,0 (m, 1H); 4,81 (s, 2H); 3,72 (s, 2H).

Preparación AK

Las aminas siguientes se prepararon de acuerdo con las preparaciones AI y AJ anteriores

[(4-fluorobifenil-2-il)metil]amina

[(5-fluorobifenil-2-il)metil]amina

[(4',5-difluorobifenil-2-il)metil]amina

Ejemplos

Ejemplo 1

2-[2-(4-clorofenil)propil]-N-[(5-metilisoxazol-3-il)metil]-3-oxoisoindolina-1-carboxamida

Una solución de ácido 2-formilbenzoico (1,23 g, 8,2 mmol) en metanol (15 ml) se trató con clorhidrato de 2-(4-clorofenil)-propilamina (1,69 g, 8,2 mmol) y trietilamina (1,14 ml). La mezcla se agitó a temperatura ambiente durante 30 min. Se agregó la solución de 3-isocianometil-5-metilisoxazol de la preparación L anterior y la mezcla se agitó temperatura ambiente durante 16 h. La mezcla se concentró, se disolvió en 50 ml de diclorometano y se lavó con 100 ml de solución saturada de $NaHCO_3$. La fase orgánica se separó, se secó sobre $MgSO_4$, y se evaporó. El aceite remanente se purificó usando HPLC preparativa para dar el compuesto del título (0,903 g, 26% de rendimiento).

[M+1] (ES) 424,10

^{1}H NMR (500 MHz, $CDCl_3$) δ 7,46-7,61 (m, 3H); 7,35–7,44 (m, 1H); 7,07–7,27 (m, 5H); 5,81 (s, 1H); 4,78 (s, 1H); 4,46–4,56 (m, 1H); 4,31–4,39 (m, 1H); 4,12-4,27 (m, 1H); 3,15-3,40 (m, 2H); 2,35 (s, 3H); 1,23 (d, 3H)

Ejemplo 2

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida

(i) N-(bifenil-2-ilmetil)-N-[2-(terc-butilamino)-1-(2-furil)-2-oxoetil]but-2-inamida

Se disolvió (bifenil-2-ilmetil)amina (23,78 mmol, 4,36 g) en MeOH y 2-furaldehído (23,78 mmol, 2,29 g) y se agregó ácido but-2-inoico (23,78 mmol, 2,00 g). La mezcla se agitó a rt durante 30 min. Se agregó isocianuro de terc-butilo (23,78 mmol, 1,98 g) y la mezcla se agitó a rt durante toda la noche. El solvente se eliminó por evaporación. El producto crudo se tomó en el paso siguiente sin más purificación.

(ii) 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida

Se disolvió N-(bifenil-2-ilmetil)-N-[2-(terc-butilamino)-1-(2-furil)-2-oxoetil]but-2-inamida (23,0 mmol, 9,87 g) (del paso (i) anterior) en xileno (200 ml), y se agregó trifluorometanosulfonato de iterbio(III) (2,30 mmol, 1,43 g). La mezcla se calentó a reflujo durante 1,5 h y después no quedó nada de material de partida. El solvente se eliminó por evaporación. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática

heptano/EtOAc 80/20 y después se aumentó la concentración de EtOAc hasta 100% (gel de sílice 60 0,004-0,063 mm). El producto precipitó en la columna y tuvo que ser eluido con MeOH al 50%. Después el producto se recristalizó de MeOH para dar el compuesto del título (4,52 g, 45,9%).

^{1}H-NMR (500 MHz, DMSO-d_6): δ 7,96 (s, 1H); 7,45-7,28 (m, 7H); 7,26-7,20 (m, 1H); 7,20-7,14 (m, 1H); 7,06-7,01 (m, 1H); 6,97-6,92 (m, 1H); 5,07 (d, 1H); 4,63 (s, 1H); 3,90 (d, 1H); 2,45 (s, 3H); 1,11 (s, 9H); HRMS calculada para ($C_{27}H_{28}N_2O_3$+H)+, 429,5436; encontrada (ES [M+H]+), 429,5454.

La secuencia de síntesis se originó en un procedimiento publicado.
D. L. Wright, C. V. Robotham y K. Aboud, *Tetrahedron Lett.* 2002, *43*, 943–946.

Ejemplo 3
(R o S) 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida

(S o R) 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida

Los enantiómeros de 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (ejemplo 2) (0,20 g, 0,47 mmol) se separaron por HPLC preparativa usando una columna quiral Reprosil 20 x 250 mm usando alcohol isopropílico al 40% en heptano como fase móvil que dio (+)-enantiómero (0,10 g) (E1) y (-)-enantiómero (0,10 g) del compuesto del título (E2).

(+)-Enantiómero:
HRMS: calculada para $(C_{27}H_{28}N_2O_3+H)^+$ 429,2178; encontrada (ES $[M+H]^+$) 429,2166.
(+)-Enantiómero:
HRMS: calculada para $(C_{27}H_{28}N_2O_3+H)^+$ 429,2178; encontrada (ES $[M+H]^+$) 429,2147.

Ejemplo 4
(2*R*)-2-{1-[(terc-butilamino)carbonil]-3-oxo-1,3-dihidro-2H-isoindol-2-il}-3-(4-clorofenil)propanoato de metilo

Se disolvieron ácido 2-formil-benzoico (0,30 g, 2 mmol), clorhidrato de 4-cloro-D-fenilalaninato de metilo (0,5 g, 2 mmol) y NEt3 (0,28 mL, 2 mmol) en MeOH (5 mL) y se agitaron a temperatura ambiente durante 30 min. Se agregó isocianuro de terc-butilo (0,23 mL, 2 mmol) y la mezcla resultante se agitó durante 3 días a temperatura ambiente.
La mezcla se concentró a presión reducida y el residuo se purificó por HPLC preparativa usando un sistema Waters HPLC, equipado con una columna Kromasil C8 50,8 x 300 mm usando un sistema amortiguador de MeCN/NH_4OAc 0,1 M con un gradiente de 100% de A (5% MeCN + 95% NH_4OAc 0,1 M) a 100% de B (100% NH_4OAc 0,1 M) como fase móvil. La fracción del producto se concentró a presión reducida y se liofilizó para dar el compuesto del título (0,22 g, 25%).
1H-NMR (500 MHz, CDCl3) δ 7,87-7,83 (m, 1H); 7,60-7,49 (m, 3H); 7,17-7,13 (m, 2H); 7,02-6,98 (m, 2H); 4,17-4,12 (m, 1H); 3,96 (s, 1H); 3,94 (s, 3H); 3,80-3,40 (m, 2H); 1,22 (s, 9H)
13C-NMR (125MHz, CDCl3) δ 170,9, 169,5; 166,7; 142,1; 135,6; 133,4; 133,0; 130,5; 130,0; 129,4; 129,1; 123,8; 123,3; 67,4; 59,5; 53,6; 51,8; 34,0; 28.6
HRMS: calculada para (C23H25ClN2O4+H)+ 429,1581; encontrada (ES [M+H]+) 429,1583

Ejemplo 5

N-(terc-butil)-2-{(1*R*)-1-(4-clorobencil)-2-oxo-2-[(4,4,4-trifluorobutil)amino]etil}-3-oxoisoindolina-1-carboxamida

Se mezcló 4,4,4-trifluorobutan-1-amina (0,087 g, 0,53 mmol) con diclorometano (2 ml) en atmósfera de nitrógeno y se agregó Me_3Al (2 M en heptano). La mezcla resultante se agitó durante 1,5 h a temperatura ambiente y se agregó (2*R*)-2-{1-[(terc-butilamino)carbonil]-3-oxo-1,3-dihidro-2H-isoindol-2-il}-3-(4-clorofenil)propanoato de metilo (ejemplo 4 anterior) (0,11 g, 0,26 mmol). La mezcla resultante se agitó a temperatura ambiente durante 20 h. La reacción se detuvo por adición de metanol y las sales formadas se separaron por filtración. El filtrado se purificó por cromatografía instantánea en sílice usando un aparato Biotage Horizon con acetato de etilo/heptano como fase móvil. La

fracción del producto se concentró a presión reducida para dar el compuesto del título (0,075 g, 54%).

HRMS: calculada para $(C_{26}H_{29}ClF_3N_3O_3+H)^+$ 524,1927; encontrada (ES $[M+H]^+$) 524,1893.

Ejemplo 6

N-butil-2-[2-(4-clorofenil)etil]-N-metil-3-oxoisoindolina-1-carboxamida

Se disolvió ácido 2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxílico (0,4 mmol) (preparación AA) en DCM (2 mL) y se agregó clorhidrato de (3-dimetilaminopropil)-etil-carbodiimida (0,4 mmol) como un sólido. Después de 15 minutos se agregó N-metilbutan-1-amina (0,4 mmol) y después se dejó que la reacción continuara a 30 grados durante 2 días. La mezcla de reacción se purificó por cromatografía instantánea en sílice usando un aparato Biotage Horizon con acetato de etilo/heptano como fase móvil. La fracción del producto se concentró a presión reducida para dar el compuesto del título (0,007 g, 5%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7,91-7,87 (m, 1H); 7,58-7,48 (m, 2H); 7,40-7,32 (m, 1H); 7,30-7,24 (m, 3H); 7,21-7,13 (m, 2H); 5,26-5,15 (m, 1H); 4,40-4,24 (m, 1H); 3,45-3,21 (m, 3H); 3,10-2,89 (m, 4H); 1,57-1,45 (m, 2H); 1,35-1,26 (m, 2H); 0,94 (t, 3H)

HRMS calculada para $(C_{22}H_{25}ClN_2O_2+H)^+$ 385,1683; encontrada para (ES $[M+H]^+$) 385,1670.

Ejemplo 7

2-(bifenil-2-ilmetil)-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida

Se disolvió ácido 2-formilbenzoico (9,09 mmol, 1,36 g) en metanol (20 ml) y se agregó 1-bifenil-2-ilmetanamina (9,09 mmol, 1,66 g) y la mezcla se agitó a rt durante 30 minutos. Después se agregó 4-(isocianometil)benzonitrilo (9,09 mmol, 1,29 g) disuelto en acetonitrilo (5 ml) a la mezcla. La reacción se agitó a rt durante toda la noche. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática tolueno/EtOAc 100/0 y después se aumentó la concentración de EtOAc hasta 50% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (2,32 g, 55,8 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7,63-7,56 (m, 3H); 7,50-7,45 (m, 2H); 7,45-7,39 (m, 3H); 7,37-7,24 (m, 4H); 7,22-7,16 (m, 3H); 7,00 (d, 2H); 6,59-6,54 (m,1H); 5,24 (d, 1H); 4,77 (s, 1H); 4,31 (d, 1H); 4,29-4,18 (m, 2H).

Ejemplo 8

N-[4-(aminometil)bencil]-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida

A una solución de 2-(bifenil-2-ilmetil)-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida (ejemplo 7) (0,43 mmol, 200 mg) en 100 mL de MeOH (2 M en NH_3) se le agregó níquel Raney (prelavado con EtOH (abs). La mezcla resultante se hidrogenó a 1,3 bar durante 16 h. El solvente se eliminó por evaporación. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática tolueno/MeOH 90/10 y después se aumentó la concentración de MeOH hasta 50% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (0,172 g, 85,2 %).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7,69 (d, 1H); 7,55-7,35 (m, 3H); 7,35-7,13 (m, 11H); 7,08 (d, 2H); 4,72 (s, 1H); 4,19 (s, 2H); 3,74 (s, 2H).

Ejemplo 9

N-bencil-6-cloro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida

Se disolvió 5-cloro-3-hidroxi-2-benzofuran-1(3H)-ona (preparación V) (3,25 mmol, 0,6 g) en metanol (10 ml), se agregó [(1R)-1-feniletil]amina (3,25 mmol, 0,38 g) y se agitó durante 20 min. Después se agregó (isocianometil)benceno (3,25 mmol, 0,39 g) a la mezcla. La reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 90/10 y después se aumentó la concentración de EtOAc hasta 50% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación. La sustancia no era suficientemente pura así que se purificó por HPLC preparativa (se comenzó con isocrática acetonitrilo/amortiguador 20/80 y después se aumentó la concentración de acetonitrilo hasta 95%, el amortiguador fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0,1 M, columna KR-100-7-C8, 50

mm x 250 mm, flujo 40 ml/min). Se mezclaron las fracciones que contenían el producto y el acetonitrilo se eliminó por evaporación. El producto se liofilizó durante toda la noche para dar el compuesto del título (mezcla de diastereoisómeros) (0,345 g, 26,2%). ^{1}H-NMR (500 MHz, CDCl3): δ 7,59-6,9 (m, 12H); 6,88-6,8 (m, 1H); 5,68-5,44 (m, 1H); 5,16-4,33 (t, 2H); 4,22-3,46 (m, 1H); 1,78-159 (m, 3H); HRMS calculada para $(C_{24}H_{21}ClN_2O_2+H)^+$, 405,1368; encontrada (ES $[M+H]^+$), 405,1370.

Ejemplo 10

N-butil-2-[2-(4-fluorofenoxi)bencil]-3-oxoisoindolina-1-carboxamida

Se disolvió ácido 2-formilbenzoico (0,33 mmol, 50 mg) en metanol (1 ml) y se agregaron clorhidrato de [2-(4-fluorofenoxi)bencil]amina (0,33 mmol, 84 mg) y TEA (0,66 mmol, 64 mg). Después se agregó 1-isocianobutano (0,33 mmol, 28 mg) disuelto en acetonitrilo a la mezcla. La reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 90/10 y después se aumentó la concentración de EtOAc hasta 100% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el EtOAC se eliminó por evaporación para dar el compuesto del título (47 mg, 32,6 %).
^{1}H-NMR (500 MHz, CDCl3): δ 7,68-7,64 (d, 1H); 7,62-7,56 (d, 1H); 7,56-7,5 (t, 1H); 7,42-7,36 (t, 1H); 7,36-7,31 (d, 1H); 7,27-7,20 (t, 1H); 7,10-6,93 (m, 5h); 6,85-6,80 (d, 1h); 6,77-6,71 (m, 1H); 5,33-5,21 (d, 1H); 4,98 (s, 1H); 4,59-4,51 (d, 1H); 3,33-3,22 (m, 1H); 3,16-3,05 (m, 1H); 1,44-1,14 (m, 5H); 0,94-0,75, (m, 3H); HRMS calculada para $(C_{26}H_{25}FN_2O_3+H)+$, 433,5069; encontrada (ES [M+H]+), 433,5061

Ejemplo 11

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-(difluorometoxi)-4-metil-3-oxoisoindolina-1-carboxamida

Se disolvió 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (ejemplo 2) (0,252 mmol, 108 mg) en DCM (2 ml) en un micro vial de 2 ml, se agregaron sulfato ácido de tetrabutilamonio (0,262 mmol, 89 mg) e hidróxido de sodio (0,831 mmol, 33 mg) y el tubo se selló. Se hizo burbujear N_2 (g) a través de la mezcla

durante 5 min. Se hizo burbujear clorodifluorometano (g) a través de la mezcla durante 30 s. La mezcla se agitó a rt durante 2 h. El solvente se eliminó por evaporación y la mezcla de reacción se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 95/5 y después se aumentó la concentración de EtOAc hasta 50% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (44 mg, 36,5 %).

^{1}H-NMR (500 MHz, CDCl3): δ 7,45-7,32 (m, 7H); 7,32-7,25 (m, 4H); 6,53 (t, 1H,); 5,42 (s, 1H); 5,17 (d, 1H); 4,47 (s, 1H); 4,44 (d, 1H); 2,64 (s, 3H); 1,09 (s, 9H); HRMS calculada para ($C_{28}H_{28}F_2N_2O_3$+H)+, 479,5515; encontrada (ES [M+H]+), 479,5485.

Ejemplo 12

N-butil-2-[2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida

Se disolvió 4-fluoro-3-hidroxi-2-benzofuran-1(3H)-ona (preparación U)(11,89 mmol, 2,0 g) en metanol (10 ml) y se agregaron clorhidrato de [2-(4-clorofenil)propil]amina (11,89 mmol, 2,452 g) y TEA (13,08 mmol, 1,324 g) y se agitó durante 20 min. Después se agregó 1-isocianobutano (11,89 mmol, 0,98 g) a la mezcla. La reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 90/10 y después se aumentó la concentración de EtOAc hasta 50% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación. Al evaporar el producto precipitó y el sólido se filtró y se secó para dar el compuesto del título (1,05 g, 21,9%).

^{1}H-NMR (500 MHz, CDCl3): δ 7,42-6,90 (m, 7H); 4,95-4,43 (d, 1H, 230,16 Hz); 4,28-4,14 (m, 1H,); 3,38-3,11 (m, 4H); 1,45-1,34 (m, 2H); 1,34-1,18 (m, 5H); 0,92-0,82 (m, 3H) ; MS calculada para ($C_{22}H_{24}ClFN_2O_2$+H)+, 403,90; encontrada (ES [M+H]+); 403,12

Ejemplo 13

(1S o 1R)-N-butil-2-[(2S o 2R)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida, isómero E1

(1S o 1R)-N-butil-2-[(2R o 2S)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida, isómero E2

(1R o 1S)-N-butil-2-[(2R o 2S)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida, isómero E3
(1R o 1S)-N-butil-2-[(2S o 2R)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida, isómero E4

Los cuatro estereoisómeros de N-butil-2-[2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida (ejemplo 12 anterior) (2,60 mmol, 1,05 g) se separaron mediante un sistema de HPLC preparativa, equipado con una columna Chiralpak IA, 5 µ, 250 mm x 20 mm, usando MTBE/MeOH (95/5) como fase móvil, que dio fracción 1 que contenía el isómero E1, fracción 2 que contenía el isómero E2 y fracción 3 contenía el isómero E3 y el isómero E4.
La fracción 1 se concentró al vacío para dar (0,219 g, 20,9%) del isómero E1: [ ]D . (c 1,0; MeCN),(ee = 98,5 %).
La fracción 2 se concentró al vacío para dar (0,232 g, 22,1 %) del isómero E2: [ ]D . (c 1,0; MeCN),(ee = 99,3 %).
La fracción 3 se concentró y el isómero E3 y el isómero E4 se separaron mediante un sistema de HPLC preparativa, equipado con una columna (R,R) Whelk-O1, 5 µ, 250 mm x 20 mm, usando heptano/IPA (50/50) como fase móvil que dio fracción 3 que contenía el isómero E3 y fracción 4 que contenía el isómero E4.
La fracción 3 se concentró al vacío para dar (0,204 g, 19,4 %) del isómero E3: [ ]D . (c 1,0; MeCN), (ee = 97,7 %).
La fracción 4 se concentró al vacío para dar (0,160 g, 15,2 %) del isómero E4: [ ]D . (c 1,0; MeCN), (ee = 96,0 %).

Ejemplo 14
2-(bifenil-2-ilmetil)-N-(terc-butil)-5-(fluorometoxi)-4-metil-3-oxoisoindolina-1-carboxamida

Se disolvió 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (ejemplo 2) (0,233 mmol, 100 mg) en acetonitrilo (2 ml) en un micro vial de 2 ml, se agregó K_2CO_3 (0,256 mmol, 0,25 mg) y el tubo se selló. Se hizo burbujear N_2 (g) a través de la mezcla durante 5 min. Se hizo burbujear bromofluorometano (g) a través de la

mezcla durante 30 s. La reacción se llevó a cabo en un horno de microondas (20 min, 140 °C). El solvente se eliminó por evaporación y la mezcla de reacción se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 95/5 y después se aumentó la concentración de EtOAc hasta 50% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (68 mg, 63,3 %).

^{1}H-NMR (500 MHz, CDCl3): δ 7,45-7,25 (m, 11H); 5,82-5,79 (m, 1H); 5,71-5,69 (m, 1H); 5,47 (s, 1H); 5,16 (d, 1H); 4,47 (s, 1H); 4,43 (d, 1H); 2,59 (s, 3H); 1,08 (s, 9H); HRMS calculada para ($C_{28}H_{29}FN_2O_3$+H)+, 461,5611; encontrada (ES [M+H]+), 461,5596.

Ejemplo 15

metanosulfonato de 2-(bifenil-2-ilmetil)-1-[(terc-butilamino)carbonil]-4-metil-3-oxo-2,3-dihidro-1H-isoindol-5-ilo

Se disolvió 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (ejemplo 2) (0,24 mmol, 104 mg) en DCM y se agregó cloruro de mesilo (0,36 mmol, 42 mg), la mezcla se enfrió a 0 °C y se agregó TEA gota a gota. La solución se calentó a rt y se agitó durante 2 h hasta que no hubo material de partida remanente (LCMS). El solvente se eliminó por evaporación y la mezcla de reacción se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 95/5 y después se aumentó la concentración de EtOAc hasta 50% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (62 mg, 50,4 %).

^{1}H-NMR (500 MHz, CDCl3): δ 7,47-7,42 (m, 8H); 7,30-7,25 (m, 3H); 5,39 (s, 1H); 5,16 (d, 1H); 4,47 (s, 1H); 4,43 (d, 1H); 2,36 (s, 3H); 2,70 (s, 3H); 1,08 (s, 9H); HRMS calculada para ($C_{28}H_{30}N_2O_5S$ +H)+, 507,6335; encontrada (ES [M+H]+), 507,6326.

Ejemplo 16

N-{4-[(acetilamino)metil]bencil}-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida

Se mezclaron ácido acético (0,19 mmol, 12 mg) y tetrafluoroborato de o-(benzotriazol-1-il)-n,n,n',n'-tetrametiluronio (0,26 mmol, 0,83 mg) a rt y se agitaron durante 20 min. Se

agregaron n-metilmorfolina (0,26 mmol, 0,26 mg) y N-[4-(aminometil)bencil]-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida (ejemplo 8) (0,13 mmol, 60 mg) y la reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación y el crudo se purificó por HPLC preparativa (se comenzó con isocrática acetonitrilo/amortiguador 20/80 y después se aumentó la concentración de acetonitrilo hasta 95%, el amortiguador fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0,1 M, columna KR-100-7-C8, 50 mm x 250 mm, flujo 40 ml/min). Se mezclaron las fracciones que contenían el producto y el producto se liofilizó durante toda la noche para dar el compuesto del título (10 mg, 15,3 %). ^{1}H-NMR (500 MHz, CDCl3): δ 7,75-7,71 (m, 1H); 7,64-7,65 (m, 2H); 7,52-7,47 (m, 1H); 7,46-7,37 (m, 6H); 7,37-7,22 (m, 3H); 7,13 (d, 2H); 6,86 (d, 2H); 6,04-5,99 (m, 1H); 5,67 (brs, 1H); 5,27 (d, 1H); 4,74 (s, 1H); 4,39 (d, 2H); 4,31 (d, 1H); 4,22-4,09 (m, 2H); 2,03 (s, 3H); HRMS calculada para ($C_{32}H_{29}N_3O_3$+H)+, 504,6140; encontrada (ES [M+H]+), 504,6145.

Ejemplo 17

2-(bifenil-2-ilmetil)-N-(4-{[(difluoroacetil)-amino]metil}bencil)-3-oxoisoindolina-1-carboxamida

Se mezclaron ácido difluoroacético (0,19 mmol, 19 mg) y tetrafluoroborato de o-(benzotriazol-1-il)-n,n,n',n'-tetrametiluronio (0,26 mmol, 0,83 mg) a rt y se agitaron durante 20 min. Se agregaron n-metilmorfolina (0,26 mmol, 0,26 mg) y N-[4-(aminometil)bencil]-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida (ejemplo 8) (0,13 mmol, 60 mg) y la reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación y el crudo se purificó por HPLC preparativa (se comenzó con isocrática acetonitrilo/amortiguador 20/80 y después se aumentó la concentración de acetonitrilo hasta 95%, el amortiguador fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0,1 M, columna KR-100-7-C8, 50 mm x 250 mm, flujo 40 ml/min). Se mezclaron las fracciones que contenían el producto y el producto se liofilizó durante toda la noche para dar el compuesto del título (12 mg, 17,0 %). ^{1}H-NMR (500 MHz, CDCl3): δ 7,61-7,47 (m, 3H); 7,45-7,18 (m, 10H); 7,18-7,12 (m, 1H); 7,07 (d, 2H); 6,85 (d, 2H); 6,49 (brs, 1H); 6,27 (m, 1H); 5,90 (t, 1H); 5,20 (d, 1H); 4,69 (s, 1H); 4,41 (d, 2H); 4,29-4,21 (d, 1H); 4,21-

4,05 (m, 2H); HRMS calculada para ($C_{32}H_{27}F_2N_3O_3$+H)+, 540,5948; encontrada (ES [M+H]+), 540,5895.

Ejemplo 18:

2-(bifenil-2-ilmetil)-N-(terc-butil)-4,7-difluoro-1-metil-3-oxoisoindolina-1-carboxamida

Se disolvió ácido 2-acetil-3,6-difluorobenzoico (0,24 mmol, 50 mg) en metanol (1 ml) y se agregó (bifenil-2-ilmetil)amina (0,24 mmol, 46 mg). La mezcla se agitó a 50 °C durante toda la noche para formar la imina. Después se agregó isocianuro de terc-butilo (0,24 mmol, 21 mg) disuelto en acetonitrilo a la mezcla. La reacción se agitó a 50 °C durante 170 h. El producto precipitó y se filtró, y el sólido se lavó con EtOAc para dar el compuesto del título (23 mg, 20,5%)

^{1}H-NMR (500 MHz, CDCl3): δ 7,64-7,56 (m, 1H); 7,52-7,43 (m, 2H); 7,42-7,08 (m, 8H); 5,08 (s, 1H); 4,65 (dd, 2H); 1,37 (s, 3H); 0,94 (s, 9H); HRMS calculada para ($C_{27}H_{26}F_2N_2O_2$+H)+, 449,5250; encontrada (ES [M+H]+), 449,5248

Ejemplo 19

2-(bifenil-2-ilmetil)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida

Se disolvió 4-fluoro-3-hidroxi-2-benzofuran-1(3H)-ona (preparación X) (0,87 mmol, 147 mg) en metanol (10 ml) y se agregó (bifenil-2-ilmetil)amina (0,87 mmol, 160 mg) y se agitó durante 20 min. Después se agregó 1,1,1-trifluoro-4-isocianobutano (0,87 mmol, 120 mg) a la mezcla. La reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática heptano/acetona 90/10 y después se aumentó la concentración de acetona hasta 50% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (66 mg, 16 %).

^{1}H-NMR (500 MHz, CDCl3): δ 7,50-7,02 (m, 12H); 7,02-6,92 (m, 1H); 5,18-5,08 (D, 1H); 4,62 (s, 1H); 4,28 (d, 1H); 3,25-2,93 (m, 2H); 2,00-1,82 (m, 2H); 1,62-1,44 (m, 2H); HRMS calculada para : ($C_{26}H_{22}F_4N_2O_2$+H)+, 471,4788; encontrada (ES [M+H]+), 471,4789.

Ejemplo 20

trifluorometanosulfonato de 2-(bifenil-2-ilmetil)-1-[(terc-butilamino)carbonil]-4-metil-3-oxo-2,3-dihidro-1H-isoindol-5-ilo

Se disolvió 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (ejemplo 2) (1,40 mmol, 0,6 g) en THF (10 ml), se agregaron K_2CO_3 (4,20 mmol, 0,58 g) y n-feniltrifluorometanosulfonimida (1,54 mmo, 0,55 g). La reacción se realizó en un horno de microondas (10 min, 120 °C).

El solvente se eliminó por evaporación y el crudo se purificó por cromatografía instantánea (se comenzó con isocrática heptano/DCM 50/50 y después se aumentó la concentración de DCM hasta 100%, después se agregó EtOAc como eluyente y la concentración de EtOAc se aumentó hasta 30% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación para dar el compuesto del título (0,655 g, 83,4 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7,521 (d, 1H); 7,42-7,31 (m, 7H); 7,30-7,24 (m, 2H); 6,08 (s, 1H); 5,26 (d, 1H); 4,53 (s, 1H); 4,44 (d, 1H); 2,52 (s, 3H); 1,16 (s, 9H); HRMS calculada para $(C_{28}H_{27}F_3N_2O_5S+H)+$, 561,6048; encontrada (ES [M+H]+), 561,6019.

Ejemplo 21

2-(bifenil-2-ilmetil)-N-(4-{[(fluoroacetil)amino]metil}bencil)-3-oxoisoindolina-1-carboxamida

Se mezclaron ácido fluoroacético (0,19 mmol, 15 mg) y tetrafluoroborato de o-(benzotriazol-1-il)-n,n,n',n'-tetrametiluronio (0,26 mmol, 83 mg) a rt y se agitaron durante 20 min. Se agregaron n-metilmorfolina (0,26 mmol, 26 mg) y N-[4-(aminometil)bencil]-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida (ejemplo 8) (0,13 mmol, 60 mg) y la reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación y el crudo se purificó por HPLC preparativa (se comenzó con isocrática acetonitrilo/amortiguador 20/80 y después se aumentó la concentración de acetonitrilo hasta 95%, el amortiguador fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0,1 M, columna KR-100-7-C8, 50 mm x 250 mm, flujo 40 ml/min). Se mezclaron las fracciones que contenían el producto y el producto se liofilizó durante toda la noche para

dar el compuesto del título (35 mg, 51,6 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7,63-7,58 (m, 1H), 7,57-7,48 (m, 2H), 7,44-7,35 (m, 4H), 7,35-7,21 (m, 6H), 7,19-7,15 (m, 1H), 7,11 (d, 2H), 6,91 (d, 2H), 6,63-6,58 (m, 1H), 6,55 (bs, 1H), 5,22 (d, 1H), 4,88 (s, 1H), 4,79 (s, 1H), 4,73 (s, 1H), 4,44 (d, 2H), 4,28 (d, 1H), 4,25-4,13 (m, 2H); HRMS calculada para $(C_{32}H_{28}FN_3O_3+H)^+$, 522,6044; encontrada (ES [M+H]+), 522,6043.

Ejemplo 22

N-(4,4-difluorobutil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida

Se disolvió ácido 2-formilbenzoico (6,66 mmol, 1,00 g) en metanol (10 ml), se agregó (difenilmetil) amina (6,66 mmol, 1,22 g) y se agitó durante 20 min. Después se agregó 1,1-difluoro-4-isocianobutano (6,66 mmol, 0,79 g) a la mezcla. La reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 90/10 y después se aumentó la concentración de EtOAc hasta 50% (gel de sílice 60 0,004-0,063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación. La sustancia no era suficientemente pura así que se purificó por HPLC preparativa (se comenzó con isocrática acetonitrilo/amortiguador 20/80 y después se aumentó la concentración de acetonitrilo hasta 95%, el amortiguador fue una mezcla de acetonitrilo/agua 10/90 y acetato de amonio (0,1 M, columna KR-100-7-C8, 50 mm x 250 mm, flujo 40 ml/min). Se mezclaron las fracciones que contenían el producto y el acetonitrilo se eliminó por evaporación. El producto se liofilizó durante toda la noche para dar el compuesto del título (140 mg, 32,3 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7,68-7,49 (m, 3H); 7,49-7,18 (m, 9H); 7,06-6,93 (m, 2H); 6,78 (s, 1H); 6,25-6,12 (m, 1H); 7,78-5,30 (m, 1H); 5,24 (s, 1H); 2,89-2,70 (m, 1H); 2,63-2,43 (m, 1H); 1,54-1,30 (m, 2H); 1,25-1,05 (m, 2H); HRMS calculada para $(C_{26}H_{24}F_2N_2O_2+H)^+$, 435,1884; encontrada (ES $[M+H]^+$), 435,1882.

Ejemplo 23

(1S o 1R)-N-(4,4-difluorobutil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida; isómero E1

(1R o 1S)-N-(4,4-difluorobutil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida ; isómero E2

Se separaron N-(4,4-difluorobutilo)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (ejemplo 22) (1,63 mmol, 0,71 g) mediante un sistema de HPLC preparativa, equipado con una columna ReproSil, 10 µ, 250 mm x 20 mm, usando heptano/IPA (30/70) como fase móvil, que dio fracción 1 que contenía el isómero E1, fracción 2 que contenía el isómero E2.

La fracción 1 se concentró al vacío para dar (0,316 g, 44,5%) del isómero E1, ee = 100%.

La fracción 2 se concentró al vacío para dar (0,308 g, 43,4%) del isómero E2, ee = 99,6%.

Ejemplo 24

N-bencil-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida

Se agregaron ácido 2-formilbenzoico (2,72 g, 18,1 mmol) y 1-feniletanamina (2,30 mL, 18,1 mmol) a un matraz, después se agregó MeOH (15 ml) y la mezcla se dejó en agitación a rt durante 2 h. Se agregó (isocianometil)benceno (2,12 g, 18,1 mmol) disuelto en MeCN (25 ml) a la mezcla y la reacción se dejó en agitación a rt durante toda la noche. La reacción se finalizó a la mañana siguiente y se evaporó el solvente. El crudo se disolvió en DCM (20 ml) y se extrajo con agua (10 ml), se recogió la fase orgánica y la mayor parte del solvente se evaporó, después se agregó EtOAc y se evaporó el solvente. El crudo se purificó por cromatografía instantánea (sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando heptano y EtOAc como eluyente, seguido de la concentración al vacío para obtener el compuesto del título (4,16 g, 62%).

^{13}C-NMR (500 MHz, $CDCl_3$) δ 170,73; 170,47; 169,09; 168,26; 142,14; 142,02; 140,45; 140,37; 137,34; 137,14; 132,79; 132,75; 131,09; 130,99; 129,38; 129,35; 129,21; 129,10; 128,96; 128,71; 128,50; 128,27; 128,15; 128,02; 127,96; 127,68; 127,58; 127,49; 124,32; 124,26; 122,93; 122,78; 63,75; 63,31; 52,56; 52,12; 43,89; 43,39; 18,19; 17,58; HRMS calculada para (C24 H22 N2 O2+H)$^+$, 371,1760 encontrada (ES [M+H]$^+$), 371,1768 y 371,1771 para los diastereoisómeros, respectivamente.

Ejemplo 25

(1S o 1R)-N-bencil-3-oxo-2-[(1R o 1S)-1-feniletil]isoindolina-1-carboxamida (E1)

(1S o 1R)-N-bencil-3-oxo-2-[(1S o 1R)-1-feniletil]isoindolina-1-carboxamida (E2)

(1R o 1S)-N-bencil-3-oxo-2-[(1R o 1S)-1-feniletil]isoindolina-1-carboxamida (E3)

(1R o 1S)-N-bencil-3-oxo-2-[(1S o 1R)-1-feniletil]isoindolina-1-carboxamida (E4)

Los cuatro estereoisómeros de N-bencil-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida (ejemplo 24) se separaron mediante un sistema de HPLC preparativa, equipado con una columna Chiralpak AD-H 5 µ 250 mm x 20 mm, usando heptano/EtOH (85/15) como fase móvil, que dio fracción 1 que contenía el isómero 1, fracción 2 que contenía el isómero 2 y el isómero 3, y fracción 3 que contenía el isómero 4. La fracción 1 se concentró al vacío para dar (E1) (0,602 g, 22,8%) del isómero 1: [ ]$_D$ (c 1,0si,MeCN); HRMS calculada para (C24 H22 N2 O2+H)$^+$, 371,1759 encontrada (ES [M+H]$^+$), 371,1760

La fracción 3 se concentró al vacío para dar (E4) (0,516 g, 19,5%) del isómero 4: [ ]$_D$ (c 1,0; MeCN); HRMS calculada para (C24 H22 N2 O2+H)$^+$, 371,1759 encontrada (ES [M+H]$^+$), 371,1779

La fracción 2 se concentró y el isómero 2 y el isómero 3 se separaron por un sistema de HPLC preparativa, equipado con una columna Chiralpak IA 5 µ, 250 mm x 20 mm, usando heptano/EtOH (80/20) como fase móvil que dio fracción 1 que contenía el isómero 2 y fracción 2 que contenía el isómero 3.

La fracción 1 se concentró al vacío para dar (E2) (0,571 g, 21,6%) del isómero 2: [ ]$_D$ (c 1,0; MeCN); HRMS calculada para (C24 H22 N2 O2+H)$^+$, 371,1759 encontrada (ES [M+H]$^+$), 371,1761

La fracción 2 se concentró al vacío para dar (E3) (0,718 g, 27,1%) del isómero 3: [ ]$_D$ (c 1,0; MeCN); HRMS calculada para (C24 H22 N2 O2+H)$^+$, 371,1759 encontrada (ES [M+H]$^+$), 371,1758

Ejemplo 26

N-(3-clorobencil)-2-(3-hidroxi-2,2-dimetilpropoxi)-3-oxoisoindolina-1-carboxamida

El 3-amino-2,2-dimetilpropan-1-ol (0,276 mmol) se disolvió en MeCN (1 mL) y se agregó a ácido 2-formilbenzoico (0,276 mmol) disuelto en MeOH (1 mL), esto se agitó durante 30 min a r.t. Se agregó 1-cloro-3-(isocianometil)benceno (0,248 mmol) disuelto en MeCN (2 mL) a la mezcla y la reacción se dejó en agitación a r.t. durante toda la noche. La reacción se finalizó a la mañana siguiente y se evaporó el solvente. El crudo se disolvió en DCM (4 ml) y se extrajo con agua (3 ml), la fase orgánica se recogió y se evaporó el solvente. El crudo se disolvió en DMSO (1 ml), se filtró y se purificó por HPLC preparativa usando un sistema Waters FractionLynx III HPLC con un colector de fracción accionado por masa, equipado con una columna Xbridge Prep C18 150 x 19 mm usando un sistema amortiguador MeCN/NH_3 al 0,2% con un gradiente desde 100% de A (5% MeCN + 95% NH_3 al 0,2%) hasta 100% de B (95% MeCN + 5% NH_3 al 0,2%) como fase móvil, seguido de la concentración al vacío para obtener el compuesto del título (0,025 g, 23%).
^{1}H-NMR* (600 MHz, DMSO-d_6, DMSO*) δ 9,29-9,17 (m, 1H); 7,77-7,46 (m, 4H); 7,4-7,15 (m, 4H); 5,48-5,4 (s, 1H); 4,74-4,63 (m, 1H); 4,4-4 26 (m, 2H); 3,79-3,71 (d, 1H); 3,19-3,05 (m); 2,76-2,64 (d); 0,88-0,75 (s, 6H); HRMS calculada para (C21 H23 Cl N2 O3+H)$^+$, 387,1475 encontrada (ES [M+H]$^+$), 387,1475

Ejemplo 27

2-[2-(4-clorofenil)propil]-N-[(5-metil-2-fenil-1,3-oxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida

Se agregaron ácido 2-formilbenzoico (0,060 g, 0,44 mmol), clorhidrato de 2-(4-clorofenil)propan-1-amina (0,068 g, 0,40 mmol) y TEA (0,062 mL, 0,44 mmol) a un matraz y se disolvieron en MeOH (2 mL), esto se agitó durante 2 h a r.t. Se agregó 4-(isocianometil)-5-metil-2-fenil-1,3-oxazol (0,079 g, 0,40 mmol) disuelto en MeCN (2 mL) a la mezcla y la reacción se dejó en agitación a r.t. durante dos días. Se evaporó el solvente, el crudo se disolvió en DCM (4 ml) y se extrajo con agua (3 ml), la fase orgánica se recogió y se evaporó el solvente. El crudo se purificó por cromatografía instantánea (sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando heptano y EtOAc como eluyente, seguido de la concentración al vacío para obtener el compuesto del título (0,017 g, 8,5%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8,22-7,34 (m, 9H); 7,21-7,01 (m, 4H);

6,56-6,34 (m, 1H); 4,64-3,98 (m, 3H); 3,42-3,12 (m, 2 H); 2,53-2,16 (m, 3H); 1,4-1,08 (m, 3H);

Ejemplo 28

N-(terc-butil)-2-[(1-metil-5-fenil-1H-pirazol-3-il)metil]-3-oxoisoindolina-1-carboxamida

Se disolvió 1-(1-metil-5-fenil-1*H*-pirazol-3-il)metanamina (0,400 mmol) en MeCN (1 mL) y se agregó a ácido 2-formilbenzoico (0,400 mmol) disuelto en MeOH (1 mL), esto se agitó durante 1 h a r.t. Se agregó isocianuro de *terc*-butilo (0,400 mmol) a la mezcla y la reacción se dejó en agitación a r.t. durante dos días. Se evaporó el solvente, el crudo se disolvió en DCM (4 ml) y se extrajo con agua (3 ml), la fase orgánica se recogió y se evaporó el solvente. El crudo se purificó por cromatografía instantánea (sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando heptano y EtOAc como eluyente, seguido de la concentración al vacío para obtener el compuesto del título (0,078 g, 48,4%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7,94-7,36 (m, 9H); 6,39-6,28 (m, 1H); 5,28-5,07 (m, 2H); 4,39-4,23 (d, 1H); 3,92-3,79 (s, 3H); 1,44-1,2 (s, 9H); HRMS calculada para (C24 H26 N4 O2+H)$^+$, 403,2134 encontrada (ES $[M+H]^+$), 403,2156

Ejemplo 29

2-(bifenil-2-ilmetil)-6-bromo-N-(terc-butil)-3-oxoisoindolina-1-carboxamida

Se agregaron 1-bifenil-2-ilmetanamina (0,225 g, 1,23 mmol) y 5-bromo-3-hidroxi-2-benzofuran-1(3H)-ona (preparación W) (0,283 g, 1,24 mmol) a un matraz, se agregó MeOH (1 mL) y la mezcla se dejó en agitación a r.t. durante 3 h. Se agregó isocianuro de *terc*-butilo (0,139 mL, 1,23 mmol) a la mezcla y la reacción se dejó en agitación a r.t. durante toda la noche. Se evaporó el solvente, el crudo se disolvió en DCM (4 ml) y se extrajo con agua (3 ml), la fase orgánica se recogió y se evaporó el solvente. El crudo se purificó por cromatografía instantánea (sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando heptano y EtOAc como eluyente, seguido de la concentración al vacío para obtener el compuesto del título (0,191 g, 32,4%). ^{13}C-NMR (500 MHz, $CDCl_3$) δ 168,58; 166,16; 143,65; 142,49; 140,52; 133,37; 132,34; 130,62; 130,46; 129,15; 128,62; 128,35; 128,15; 127,99; 127,87; 127,28; 126,31; 125,21; 124,92; 62,87; 51,61; 42,93;

31,88; 28,99; 27,52; 27,24; 22,58; 13,28; HRMS calculada para (C26 H25 Br N2 O2+H)$^+$, 477,1178 encontrada (ES [M+H]$^+$), 477,1173

Ejemplo 30

2-(bifenil-2-ilmetil)-5-bromo-N-(terc-butil)-3-oxoisoindolina-1-carboxamida

Se agregaron 1-bifenil-2-ilmetanamina (0,106 g, 0,578 mmol) y ácido 5-bromo-2-formilbenzoico (disponible en el mercado) (0,132 g, 0,578 mmol) a un matraz, se agregó MeOH (1 mL) y la mezcla se dejó en agitación a r.t. durante 30 min. Se agregó isocianuro de *terc*-butilo (0,065 mL, 0,578 mmol) a la mezcla y la reacción se dejó en agitación a r.t. durante 16 h. Se evaporó el solvente, el crudo se disolvió en DCM (4 mL) y se extrajo con agua (3 mL), se recogió la fase orgánica y se evaporó el solvente. El crudo se purificó por cromatografía instantánea (sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando heptano y EtOAc como eluyente, seguido de la concentración al vacío para obtener el compuesto del título (0,143 g, 51,8%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7,89-7,82 (m, 1H); 7,78-7,71 (m, 1H); 7,56-7,24 (m, 10H); 5,47-5,33 (d, 1H); 4,72-4,63 (s, 1H); 4,23-4,07 (d, 1H); 1,39-1,13 (s, 9H); HRMS calculada para (C26 H25 Br N2 O2+H)$^+$, 477,1178 encontrada (ES [M+H]$^+$), 477,1184

Ejemplo 31

2-(bifenil-2-ilmetil)-*N*-(4,4-difluorobutil)-3-oxoisoindolina-1-carboxamida

Se disolvió 1-bifenil-2-ilmetanamina (0,400 mmol) en MeCN (1 mL) y se agregó a ácido 2-formilbenzoico (0,400 mmol) disuelto en MeOH (1 mL), esto se agitó durante 30 min a r.t. Se agregó 1,1-difluoro-4-isocianobutano (preparación P) (0,400 mmol) disuelto en MeCN (2 mL) a la mezcla y la reacción se dejó en agitación a r.t. durante toda la noche. La reacción se finalizó a la mañana siguiente y el solvente se evaporó. El crudo se disolvió en DCM (4 ml) y se extrajo con agua (3 ml), la fase orgánica se recogió y se evaporó el solvente. El crudo se disolvió en DMSO (1 ml), se filtró y se purificó por HPLC preparativa usando un sistema Waters FractionLynx I HPLC con un colector de fracción accionado por masa, equipado con una columna Xbridge Prep C18 150 x 19 mm usando un sistema amortiguador MeCN/NH_3 al 0,2% con un gradiente desde 100% de A (5% MeCN

+ 95% NH_3 al 0,2%) hasta 100% de B (95% MeCN + 5% NH_3 al 0,2%) como fase móvil, seguido de la concentración al vacío para obtener el compuesto del título (0,057 g, 33%). ^{1}H-NMR* (600 MHz, DMSO-d_6, DMSO*) δ 8,526-8,3 (m, 1H); 7,75-7,03 (m, 13H); 6,2-5,85 (m, 1H); 5,27-5,07 (d, 1H); 4,83-4,66 (s, 1H); 4,13-3,85 (d, 1H); 3,1-2,83 (m); 1,81-1,55 (m, 2H); 1,5-1,27 (m, 2H); HRMS calculada para (C26 H24 F N2 O2+H)$^+$, 435,1884 encontrada (ES [M+H]$^+$), 435,1865

Ejemplo 32

2-(bifenil-2-ilmetil)-N-[(2,2-difluoro-1,3-benzodioxol-5-il)metil]-6-fluoro-3-oxoisoindolina-1-carboxamida

Se disolvió 1-bifenil-2-ilmetanamina (0,370 mmol) en MeCN (1 mL) y se agregó a 5-fluoro-3-hidroxi-2-benzofuran-1(3H)-ona (preparación X) (0,370 mmol) disuelta en MeOH (1 mL), esto se agitó durante 30 min a r.t. Se agregó isocianuro de (2,2-difluoro-1,3-benzodioxol-5-il)metilo (preparación R) (0,370 mmol) disuelto en MeCN (2 mL) a la mezcla y la reacción se dejó en agitación a r.t. durante 3 días. Se evaporó el solvente, el crudo se disolvió en DCM (4 ml) y se extrajo con agua (3 ml), la fase orgánica se recogió y se evaporó el solvente. El crudo se disolvió en DMSO (1 ml), se filtró y se purificó por HPLC preparativa usando un sistema Waters FractionLynx I HPLC con un colector de fracción accionado por masa, equipado con una columna Xbridge Prep C18 150 x 19 mm usando un sistema amortiguador MeCN/NH_3 al 0,2% con un gradiente desde 100% de A (5% MeCN + 95% NH_3 al 0,2%) hasta 100% de B (95% MeCN + 5% NH_3 al 0,2%) como fase móvil, seguido de la concentración al vacío para obtener el compuesto del título (0,053 g, 26%). ^{1}H-NMR* (600 MHz, DMSO-d_6, DMSO*) δ 8,95-8,83 (m, 1H); 7,76-7,64 (m, 1H); 7,48-6,87 (m, 14H); 5,18-5,08 (d, 1H); 4,84-4,78 (s, 1H); 4,2-3,95 (m); HRMS calculada para (C30 H21 F3 N2 O4+H)$^+$, 531,1532 encontrada (ES [M+H]$^+$), 531,1537

Ejemplo 33

2-(bifenil-2-ilmetil)-N-terc-butil-3-oxoisoindolina-1-carboxamida

Una mezcla de ácido 2-formilbenzoico (2,50 g, 16,7 mmol) y 1-bifenil-2-ilmetanamina (3,05 g, 16,7 mmol) en MeOH (55 ml) se agitó a temperatura ambiente durante 1 h y

después se agregó isocianuro de terc-butilo (1,38 g, 16,7 mmol). La mezcla resultante se agitó a temperatura ambiente durante toda la noche y se concentró a presión reducida. Se obtuvieron cristales por adición de etanol al residuo. Los cristales (2,06 g) se filtraron y se secaron al vacío. El filtrado se purificó por cromatografía instantánea (sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando acetato de etilo (gradiente desde 6 hasta 50 %) en heptano como eluyente. La eliminación del solvente dio 2,05 g de un sólido blanco. Los productos de la cristalización y la cromatografía se combinaron y se trituraron con metanol dando 2,88 g de un sólido blanco. El material remanente se purificó por HPLC preparativa dando una segunda tanda de 0,70 g

^{1}H NMR (500 MHz, CD_3OD) 7,71 (dm, 1H); 7,56 (m, 1H); 7,50 (m, 1H); 7,42 (dm, 1H); 7,38-7,24 (m, 9H); 5,37 (d, 1H); 4,71 (s, 1H); 4,15 (d, 1H); 1,22 (s, 9H); HRMS calculada para $(C_{26}H_{26}N_2O_2+H)^+$, 399,2066; encontrada (ESI $[M+H]^+$), 399,2073.

Ejemplo 34

(R o S) 2-(bifenil-2-ilmetil)-N-terc-butil-3-oxoisoindolina-1-carboxamida (isómero 1)

(S o R) 2-(bifenil-2-ilmetil)-N-terc-butil-3-oxoisoindolina-1-carboxamida (isómero 2)

La primera tanda (2,88 g) del ejemplo 33 anterior se separó en sus enantiómeros en una Chiralpak AI usando 2-propanol al 25% en heptano. La concentración a presión reducida dio 1,39 g de isómero 1 y 1,25 g de isómero 2.

Ejemplo 35

N-bencil-6-ciano-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida

(i) N-bencil-6-bromo-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida

Se agregó (R)-(+)-1-feniletil amina (0,12 g, 1,0 mmol) a una suspension de 5-bromo-3-hidroxi-2-benzofuran-1(3H)-ona en MeOH (5 ml). La solución se agitó durante 30 min a temperatura ambiente. Se agregó isocianuro de bencilo (0,12 g, 1,0 mmol) y la mezcla resultante se agitó a temperatura ambiente durante toda la noche y se evaporó. La purificación por cromatografía instantánea (en un sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando acetato de etilo (gradiente desde 6 hasta 50 %) en heptano como eluyente, seguida de la concentración al vacío produjo el compuesto del título (0,33 g,

72%) como un polvo blanco. ^{1}H NMR (500 MHz, CD_3OD) δ 7,68 (m, 2H); 7,52 (m, 1H); 7,44 (m, 1H); 7,36-7,20 (m, 8H); 7,68 (m, 1H); 5,61 y 5,32 (q, 1H, rotámeros); 5,22 y 4,79 (s, 1H, rotámeros); 4,37 (br s, 1H); 3,97 (m, 1H); 1,74 y 1,61 (d, 3H, rotámeros); MS (ESI) m/z 449,0 ($[M+H]^+$);

(ii) N-bencil-6-ciano-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida

Una mezcla de *N*-bencil-6-bromo-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (0,10 g, 0,22 mmol), cianuro de cinc (0,040 g, 0,34 mmol), y $Pd(PPh_3)_4$ (0,026 g, 0,022 mmol) en DMF (3 ml) se desgasificó por burbujeo de argón durante 15 min. Después la mezcla se calentó a 200 °C durante 30 min en un reactor de microondas y se concentró al vacío. La purificación por cromatografía instantánea (en un sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando acetato de etilo (gradiente desde 9 hasta 76 %) en heptano como eluyente, seguida de la concentración al vacío produjo el compuesto del título (0,064 g, 72%) como un sólido blanco. ^{1}H NMR (500 MHz, $(CD_3)_2CO$) 8,24 (br s, 1H); 7,94-7,81 (m, 3H); 7,52 (m, 1H); 7,36-7,19 (m, 8H); 7,13 (m, 1H); 5,63 y 5,21 (q, 1H); 5,41 y 5,04 (s, 1H); 4,43 (m, 1H); 4,15 (m, 1H); 1,84 y 1,67 (d, 3H, rotámeros). MS (ESI) m/z 396,0 ($[M+H]^+$); HRMS calculada para $(C_{26}H_{21}N_3O_2+H)^+$, 396,1712; encontrada (ESI $[M+H]^+$), 396,1739.

Ejemplo 36

2-(bifenil-2-ilmetil)-N-(terc-butil)-6-ciano-3-oxoisoindolina-1-carboxamida

se sintetizó de acuerdo con el procedimiento descrito en el ejemplo 35 anterior usando 1-bifenil-2-ilmetanamina en vez de (R)-(+)-1-feniletilamina e isocianuro de terc-butilo en vez de isocianuro de bencilo. HRMS calculada para $(C_{27}H_{25}N_3O_2+H)^+$, 424,2025; encontrada (ESI $[M+H]^+$), 424,2010.

Ejemplo 37

2-(2-bromobencil)-N-terc-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida

(i) N-(2-bromobencil)-N-[2-(terc-butilamino)-1-(2-furil)-2-oxoetil]but-2-inamida

Una mezcla de ácido but-2-inoico (0,42 g, 5,0 mmol) y 1-(2-bromofenil)metanamina (0,93 g, 5,0 mmol) y 2-furaldehído (0,48 g, 5,0 mmol) en MeOH (20 ml) se agitó a temperatura

ambiente durante 1 h y después se agregó isocianuro de terc-butilo (0,42 g, 5,0 mmol). La mezcla resultante se agitó a temperatura ambiente durante toda la noche y se concentró a presión reducida. El producto crudo se usó en el paso siguiente sin purificación.

(ii) 2-(2-bromobencil)-N-terc-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida

Una mezcla de N-(2-bromobencil)-N-[2-(terc butilamino)-1-(2-furil)-2-oxoetil]but-2-inamida (2,10 g, 0,487 mmol) del paso (i) anterior y trifluorometanosulfonato de iterbio(III) (0,302 g, 0,487 mmol) en xileno (100 ml) se calentó a reflujo durante 1,5 h. Se filtró un precipitado blanco que dio 0,87 g del producto puro. El filtrado se concentró y se purificó por cromatografía instantánea (sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando acetato de etilo (gradiente desde 30 hasta 70 %) en heptano como eluyente que dio una segunda tanda de 0,32 g lo que da un rendimiento total de 1,19 g (57%). ^{1}H NMR (500 MHz, (CD_3OD) δ 7,60 (m, 1H); 7,36-7,27 (m, 2H); 7,21 (m, 1H); 7,08 (m, 1H); 6,95 (m, 1H) 5,23 (d, 1H); 4,66 (s, 1H); 4,37 (d, 1H); 2,55 (s, 3H); 1,30 (s, 9H).

Ejemplo 38

2-(bifenil-2-ilmetil)-*N*-*terc*-butil-4-metil-5-[(metilsulfonil)amino]-3-oxoisoindolina-1-carboxamida

(i) N-(bifenil-2-ilmetil)-N-{2-(terc-butilamino)-1-[1-(metilsulfonil)-1H-pirrol-2-il]-2-oxoetil}but-2-inamida

Una mezcla de ácido but-2-inoico (0,050 g, 0,60 mmol), 1-bifenil-2-ilmetanamina (0,11 g, 0,60 mmol), y 1-(metilsulfonil)-1H-pirrol-2-carbaldehído (J. Am.Chem. Soc., 1998, 1741.) (0,10 g, 0,60 mmol) en MeOH (6 ml) se agitó a temperatura ambiente durante 1 h y después se agregó isocianuro de terc-butilo (0,050 g, 0,60 mmol). La mezcla resultante se agitó a temperatura ambiente durante tres días dando un precipitado blanco. El precipitado se filtró y se secó al vacío dando 0,23 g (76%) de un polvo blanco que se usó en el paso siguiente sin más purificación. MS (ESI) m/z 506,2 ($[M+H]^+$).

(ii) 2-(bifenil-2-ilmetil)-*N*-terc-butil-4-metil-5-[(metilsulfonil)amino]-3-oxoisoindolina-1-carboxamida

Se calentó una solución de N-(bifenil-2-ilmetil)-N-{2-(terc-butilamino)-1-[1-(metilsulfonil)-1H-pirrol-2-il]-2-oxoetil}but-2-inamida del paso (i) anterior (0,050 g, 0,099 mol) en dioxano (4 ml) y hexafluorofosfato de 1-butil-3-metil-1*H*-imidazol-3-io ($BMIMPF_6$, 0,2 ml) a 200 °C durante 30 min en un reactor de microondas. La mezcla se concentró a presión reducida y el residuo se particionó entre acetato de etilo y agua. Se separaron las capas y la fase acuosa se extrajo con dos porciones de acetato de etilo. Las capas orgánicas combinadas se lavaron con dos porciones de agua, se secaron sobre $MgSO_4$ y se concentraron a presión reducida. La purificación por cromatografía instantánea (en un sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando acetato de etilo (gradiente desde 12 hasta 100 %) en heptano como eluyente, seguida de la concentración al vacío produjo el compuesto del título (0,055 g, 56%) como un sólido blanco. ^{1}H NMR (500 MHz, $(CD_3)_2CO$) 8,00 (br s, 1H); 7,53 (d, 1H); 7,37-7,20 (m, 10H); 5,32 (d, 1H); 4,62 (s, 1H); 4,10 (d, 1H); 2,97 (s, 3H); 2,67 (s, 3H); 1,21 (s, 9H); MS (ESI) m/z 506,2 ($[M+H]^+$).

Ejemplo 39

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-[(metilsulfonil)amino]-3-oxoisoindolina-1-carboxamida

se sintetizó de acuerdo con el procedimiento descrito en el ejemplo 38 anterior usando ácido propiónico en vez de ácido but-2-inoico. MS (ESI) m/z 492,1 ($[M+H]^+$).

Ejemplo 40

N-(terc-butil)-2-(4-clorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida

(i) N-[2-(terc-butilamino)-1-(2-furil)-2-oxoetil]-N-(4-clorobencil)-3-(trimetilsilil)prop-2-inamida

Una mezcla de ácido 3-(trimetilsilil)prop-2-inoico (0,071 g, 0,50 mmol), 1-(4-clorofenil)metanamina (0,071 g, 0,50 mmol) y 2-furaldehído (0,048 g, 0,50 mmol) en MeOH (2 ml) se agitó a temperatura ambiente durante 1 h y después se agregó isocianuro de terc-butilo (0,042 g, 0,50 mmol). La mezcla resultante se agitó a temperatura ambiente durante 2 días y se concentró a presión reducida. El producto crudo se usó en el paso siguiente sin purificación; MS (ESI) m/z 444,9 ($[M+H]^+$).

(ii) N-(terc-butil)-2-(4-clorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida

Una mezcla de N-[2-(terc-butilamino)-1-(2-furil)-2-oxoetil]-N-(4-clorobencil)-3-(trimetilsilil)prop-2-inamida (0,223 g, 0,50 mmol) del paso (i) anterior, trifluorometanosulfonato de iterbio (III) (0,124 g, 0,40 mmol), y hexafluorofosfato de 1-butil-3-metil-1*H*-imidazol-3-io ($BMIMPF_6$, 0,3 ml) en dioxano (15 ml) se calentó a 200 °C durante 30 min en un reactor de microondas y se concentró a presión reducida. La purificación por cromatografía instantánea (en un sistema instantáneo SP1™ de Biotage™, cartucho de sílice), usando acetato de etilo (gradiente desde 30 hasta 70%) en heptano como eluyente, seguida de la concentración al vacío produjo 0,032 g (17%) del compuesto del título. ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9,87 (s, 1H); 8,13 (s, 1H); 7,41 (dm, 2H); 7,26 (dm, 1H); 7,22 (dm, 2H); 7,03 (m, 1H); 6,98 (m, 1H); 5,07 (d, 1H); 4,78 (s, 1H); 3,97 (d, 1H); 1,24 (s, 9H); MS (ESI) m/z 373,0 ($[M+H]^+$); HRMS calculada para $(C_{20}H_{21}ClN_2O_3+H)^+$, 373,1319; encontrada (ESI $[M+H]^+$), 373,1338.

Ejemplo 41

N-(terc-butil)-2-(4-clorobencil)-7-hidroxi-3-oxoisoindolina-1-carboxamida.

El compuesto del título se aisló como un subproducto en la síntesis de N-(terc-butil)-2-(4-clorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida

HRMS calculada para $(C_{20}H_{21}ClN_2O_3+H)^+$, 373,1319; encontrada (ESI $[M+H]^+$), 373,1324.

Ejemplo 42

2-(bifenil-2-ilmetil)-N-(terc-butil)-7-hidroxi-3-oxoisoindolina-1-carboxamida.

El compuesto del título se aisló como un subproducto en la síntesis de 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi- 3-oxoisoindolina-1-carboxamida,

HRMS calculada para $(C_{26}H_{26}N_2O_3+H)^+$, 415,2022; encontrada (ESI $[M+H]^+$), 415,2005.

Ejemplo 43

2-(bifenil-4-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida

(i) N-(bifenil-4-ilmetil)-N-[2-(terc-butilamino)-1-(2-furil)-2-oxoetil]but-2-inamida

Una mezcla de ácido but-2-inoico (0,025 g, 0,30 mmol), 1-bifenil-4-ilmetanamina (0,055 g, 0,30 mmol) y 2-furaldehído (0,029 g, 0,30 mmol) en MeOH (2 ml) se agitó a temperatura ambiente durante 30 min y después se agregó isocianuro de terc-butilo (0,025 g, 0,30 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 días y se concentró a presión reducida dando 0,125 g (97%) del compuesto del título. El producto crudo se usó en el paso siguiente sin purificación; MS (ESI) m/z 429,0 ($[M+H]^+$).

(ii) 2-(bifenil-4-ilmetil)-*N*-*terc*-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida

Una mezcla de N-(bifenil-4-ilmetil)-N-[2-(terc-butilamino)-1-(2-furil)-2-oxoetil]but-2-inamida (0,125 g, 0,29 mmol) del paso (i) anterior y trifluorometanosulfonato de iterbio(III) (0,037 g, 0,06 mmol) en dioxano (20 ml) se calentó a 200 °C durante 30 min en un reactor de microondas y se concentró a presión reducida. El residuo se particionó entre DCM y $NaHCO_3$ acuerdo saturado en un separador de fases. La fase acuosa se extrajo con dos porciones más de DCM y las capas orgánicas combinadas se concentraron al vacío. La purificación por HPLC preparativa usando un sistema FractionLynx I HPLC equipado con una columna Gemini 5 µ C18 110A 21,2 X 100 mm usando un gradiente desde 5 hasta 95 % de CH_3CN en NH_3 al 0,2% como fase móvil, seguida de la concentración al vacío dio 0,073 g (57%) del compuesto del título. ^1H NMR (500 MHz, $(CD_3)_2SO$) 9,61 (s, 1H); 8,10 (s, 1H); 7,61 (m, 4H); 7,59 (m, 2H); 7,32 (m, 1H); 7,26 (dm, 2H); 7,06 (dm, 1H); 6,95 (dm, 1H); 5,12 (d, 1H); 4,73 (s, 1H); 3,91 (d, 1H); 1,23 (s, 9H); MS (ESI) m/z 429,2 ($[M+H]^+$); HRMS calculada para $(C_{27}H_{28}N_2O_3+H)^+$, 429,2178; encontrada (ESI $[M+H]^+$), 429,2144.

Ejemplo 44

N-(terc-butil)-2-[(4'-fluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida

Una mezcla de 2-(2-bromobencil)-*N*-*terc*-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (ejemplo 37 anterior) (0,078 g, 0,18 mmol), ácido (4-fluorofenil)borónico (0,030 g, 0,22 mmol), $Pd(PPh_3)_4$ (0,010 g, 0,009 mmol), y Cs_2CO_3 acuoso (0,117 g en 0,2 ml de agua) en 1,2-dimetoxietano (1,0 ml) en un vial para reactor de microondas de 2 ml se desgasificó por burbujeo de argón durante 5 min. Después la mezcla se calentó a 130 °C

durante 15 min en un reactor de microondas y se concentró al vacío. Se agregó ácido clorhídrico (2 ml de una solución 2 M) al residuo y la fase acuosa se extrajo con tres porciones de DCM en un separador de fases. Las capas orgánicas combinadas se concentraron a presión reducida. La purificación por HPLC preparativa usando un sistema FractionLynx II HPLC equipado con una columna Sunfire 5 µ C18 OBD 19 X 150 mm usando un gradiente desde 5 hasta 95 % de CH_3CN en HCO_2H 0,1 M como fase móvil, seguida de la concentración al vacío dio 0,078 g (97 %) del compuesto del título. ^{1}H NMR (500 MHz, $(CD_3)_2SO$) 9,61 (s, 1H); 7,90 (s, 1H); 7,32 (m, 4H); 7,20 (m, 4H); 7,00 (dm, 1H); 6,91 (dm, 1H); 5,07 (d, 1H); 4,54 (s, 1H); 3,84 (d, 1H); 2,41 (s, 3H); 1,08 (s, 9H); MS (ESI) m/z 447,4 ($[M+H]^+$); HRMS calculada para $(C_{27}H_{27}FN_2O_3+H)^+$, 447,2084; encontrada (ESI $[M+H]^+$), 447,2092.

Ejemplo 45

N-bencil-2-[2-(4-clorofenil)etil]-1-hidroxi-3-oxoisoindolina-1-carboxamida

(i) 2-[2-(4-clorofenil)etil]isoquinolina-1,3(2*H*,4*H*)-diona

Se mezclaron 1*H*-isocromeno-1,3(4*H*)-diona (1,50 g, 6,94 mmol) y 2-(4-clorofenil)metanamina (1,08 g, 6,94 mmol) en tolueno (5 ml) en atmósfera de nitrógeno y la mezcla resultante se calentó a reflujo durante 20 horas. La mezcla se enfrió por dilución con 20 ml de tolueno lo que dio por resultado la formación de un sólido blanco, que se recogió por filtración para dar el compuesto del título (1,40 g, 67%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8,23 (d, 1H); 7,61 (t, 1H); 7,48 (t, 1H); 7,31-7,23 (m, 5H); 4,23-4,18 (m, 2H); 4,04 (s, 2H); 2,94-2,89 (m, 2H).

(ii) 2-[2-(4-clorofenil)etil]isoquinolina-1,3,4(2*H*)-triona

Se mezcló 2-[2-(4-clorofenil)etil]isoquinolina-1,3(2*H*,4*H*)-diona (0,50 g, 1,67 mmol) con SeO_2 (0,19 g, 1,67 mmol) en tolueno (10 ml) y se calentó a reflujo durante 16 horas. El material sólido se separó por filtración y el filtrado se concentró a presión reducida. El residuo se filtró a través de un tapón de gel de sílice, eluyendo con DCM. El solvente se eliminó a presión reducida para dar el compuesto del título, (0,52 g, 99%).

[M+H] (ES) 314,0

(iii) N-bencil-2-[2-(4-clorofenil)etil]-1-hidroxi-3-oxoisoindolina-1-carboxamida

Se mezclaron 2-[2-(4-clorofenil)etil]isoquinolina-1,3,4(2*H*)-triona (0,15 g, 0,47 mmol) y bencilamina (0,076 g, 0,71 mmol) en tolueno (2 ml) y la mezcla resultante se calentó a 60 °C durante 16 horas. El disolvente se eliminó a presión reducida. El residuo se purificó por cromatografía instantánea usando un SP1 de Biotage con acetato de etilo/heptano como fase móvil y después se purificó por HPLC de fase reversa equipado con una columna Kromasil C8 y MeCN/ agua (acetato de amonio 0,1 M) como fase móvil. La fracción del producto se liofilizó para dar el compuesto del título (0,023 g, 12%).
HRMS: calculada para $(C_{24}H_{21}ClN_2O_3+H)^+$ 421,1319; encontrada (ES $[M+H]^+$) 421,1336.
^{1}H-NMR (500 MHz, DMSO-d_6) δ 7,69-7,61 (m, 3H); 7,58-7,51 (m, 2H); 7,36-7,16 (m, 9H); 4,40-4,28 (m, 2H); 3,64-3,56 (m, 1H); 3,28-3,20 (m, 1H); 2,93-2,75 (m, 2H).

Ejemplo 46

N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida

Se disolvió ácido 2-formilbenzoico (9,12 mmol, 1,37 g) en metanol (10 ml) y se agregó 1-(3',4'-difluorobifenil-2-il)metanamina (9,12 mmol, 2,00 g) (prep AI) y se agitó durante 20 min. Después se agregó 2-isociano-2-metilpropano (9,12 mmol, 0,76 g) a la mezcla. La reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación. El crudo se purificó por cromatografía instantánea (se comenzó con isocrática heptano/EtOAc 90/10 y después se aumentó la concentración de EtOAc hasta 50% (gel de sílice 60 0,004-0.063 mm). Se mezclaron las fracciones que contenían el producto y el solvente se eliminó por evaporación. La sustancia no era suficientemente pura así que se purificó por HPLC preparativa (se comenzó con isocrática acetonitrilo/amortiguador 20/80 y después se aumentó la concentración de acetonitrilo hasta 95%, el amortiguador fue una mezcla de H_2O/ACN/FA (94,8/5/0,2) (0,1 M, columna KR-100-7-C8, 50 mm x 250 mm, flujo 40 ml/min). Se mezclaron las fracciones que contenían el producto y el acetonitrilo se eliminó por evaporación para dar el compuesto del título (2,10 g, 53,1 %). 1H-NMR (500 MHz, $CDCl_3$): δ 7,60-7,54 (m, 2H); 7,54-7,48 (m,1H); 7,42-7,37 (m, 1H); 7,33-7,27 (m, 3H);

7,22-7,13 (m, 2H); 7,12-7,06 (m, 1H); 7,02-6,96 (m, 1H); 6,08 (s, 1H); 5,18 (d, 1H); 4,56 (s, 1H); 4,37-4,30 (d, 1H); 1,15 (s, 9H).

Ejemplo 47

(1R o 1S)-N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida

(1S o 1R)-N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida

Se separaron N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida (ejemplo 46) (4,83 mmol, 2,10 g) mediante un sistema de HPLC preparativa, equipado con una columna Chiralpak AD, 5 µ, 250 mm x 20 mm, usando heptano/EtOH (75/25) como fase móvil, que dio fracción 1 que contenía el isómero E1, fracción 2 que contenía el isómero E2.

La fracción 1 se concentró al vacío para dar (0,903 g, 43,0 %) del isómero E1, ee = 99,9%. HRMS calculada para (C26H24F2N2O2+H)+, 435,1884; encontrada (ES [M+H]+), 435,1881.

La fracción 2 se concentró al vacío para dar (0,908 g, 43,2%) del isómero E2, ee = 99,9%. HRMS calculada para (C26H24F2N2O2+H)+, 435,1884; contado (ES [M+H]+), 435,1894.

Ejemplo 48

N-(terc-butil)-2-[(4,4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida

Se disolvió ácido 2-formilbenzoico (0,5 mmol, 75 mg) en metanol (10 ml) y se agregó 1-(4,4'-difluorobifenil-2-il)metanamina (0,50 mmol, 110 mg) y se agitó durante 20 min. Después se agregó 2-isociano-2-metilpropano (0,50 mmol, 42 mg) a la mezcla. La reacción se agitó a rt durante toda la noche. El solvente se eliminó por evaporación. El crudo se purificó por HPLC preparativa (se comenzó con isocrática acetonitrilo/amortiguador 20/80 y después se aumentó la concentración de acetonitrilo hasta 95%, el amortiguador fue una mezcla de H_2O/ACN/FA (94,8/5/0,2) (0,1 M, columna KR-100-7-C8, 50 mm x 250 mm, flujo 40 ml/min). Se mezclaron las fracciones que contenían el producto y el acetonitrilo se eliminó por evaporación para dar el compuesto del título (138 mg, 63,5 %). 1H-NMR (500

MHz, $CDCl_3$): δ 7,76-7,72 (m, 1H); 7,60-7,52 (m, 2H); 7,49-7,44 (m, 1H); 7,29-7,18 (m, 3H); 7,14-7,08 (m, 2H); 7,06-6,98 (m, 2H); 5,62 (s, 1H); 5,11 (d, 1H); 4,59 (s, 1H); 4,35 (d, 1H); 1,10 (s, 9H). HRMS calculada para $(C_{26}H_{24}F_2N_2O_2+H)+$, 435,1884; encontrada (ES [M+H]+), 435,1904.

Ejemplo 49

N-butil-2-[2-(4-clorofenil)-2-metilpropil]-3-oxo-1H-isoindol-1-carboxamida

Se mezclaron ácido 2-formilbenzoico (0,060 g, 0,40 mmol), clorhidrato de 2-(4-clorofenil)-2-metil-propan-1-amina (0,088 g, 0,40 mmol) y NEt_3 (55 µL, 0,40 mmol) en MeOH (2 ml) y la mezcla resultante se agitó a temperatura ambiente durante 20 min. Se agregó 1-isocianobutano (42 µL, 0,40 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 18 horas. La mezcla se particionó entre diclorometano (7 ml) y agua (1 ml). Las capas se separaron en un separador de fases y la capa orgánica se concentró a presión reducida. El residuo se purificó por HPLC de fase reversa usando una columna Sunfire prep C18 y 5-95% MeCN en HCO_2H acuoso 0,1 M como fase móvil, que dio el compuesto del título (0,087 g, 54%).

HRMS: calculada para $(C_{23}H_{27}ClN_2O_2+H)^+$ 399,1839; encontrada (ES $[M+H]^+$) 399,1839.

^{1}H-NMR* (500 MHz, DMSO-d_6, DMSO*) δ 8,23-8,19 (m, 1H); 7,65-7,62 (m, 1H); 7,55-7,51 (m, 1H); 7,47-7,42 (m, 2H); 7,37-7,30 (m, 4H); 4,51 (s, 1H); 4,09 (d, 1H); 3,13 (d, 1H); 3,03-2,93 (m, 2H); 1,37-1,31 (m, 2H); 1,28-1,20 (m, 8H); 0,84 (t, 3H).

Ejemplo 50

Los compuestos siguientes se prepararon, a partir de los productos intermedios apropiados (como los descritos precedentemente), de acuerdo con, o por analogía, con los métodos descritos aquí, y se identificaron con datos de espectro de masas exactas (HRMS) (especificado como HRMS calculada (M+H) y HRMS encontrada (M+H)). En algunos casos se detecta el aducto de amonio, mostrándose $(M+NH_4)$:

N-bencil-2-(1-metil-1-feniletil)-3-oxoisoindolina-1-carboxamida (385,1916; 385,1902);
N-bencil-3-oxo-2-(1-fenilpropil)isoindolina-1-carboxamida (385,1916; 385,1899);
N-[3-(difluorometoxi)bencil]-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida (437,1676; 437,1670);

N,2-dibencil-6-bromo-3-oxoisoindolina-1-carboxamida (435,0708; 435,0693);
6-bromo-2-(2-ciclopentilbencil)-N-(4,4-difluorobutil)-3-oxoisoindolina-1-carboxamida (505,1302; 505,1307);
2-(2-ciclopentilbencil)-N-(4,4-difluorobutilo)-6-fluoro-3-oxoisoindolina-1-carboxamida (445,2103; 445,2104);
6-bromo-2-(2-ciclopentilbencil)-N-metil-3-oxoisoindolina-1-carboxamida (427,1021; 427,1015);
2-(2-ciclopentilbencil)-6-fluoro-N-metil-3-oxoisoindolina-1-carboxamida (367,1821; 367,1822);
6-cloro-2-(2-ciclopentilbencil)-N-(4,4-difluorobutil)-3-oxoisoindolina-1-carboxamida (461,1807; 461,1797);
6-cloro-2-(2-ciclopentilbencil)-N-metil-3-oxoisoindolina-1-carboxamida (383,1526; 383,1523);
2-(2-ciclopentilbencil)-N-(4,4-difluorobutilo)-3-oxoisoindolina-1-carboxamida (427,2197; 427,2200);
2-(2-ciclopentilbencil)-N-metil-3-oxoisoindolina-1-carboxamida (349,1916; 349,1913);
N-bencil-6-cloro-3-oxo-2-[(1S)-1-feniletil]isoindolina-1-carboxamida (405,1369; 405,1365);
6-cloro-N-(2-metoxietil)-3-oxo-2-[2,2,2-trifluoro-1-(3-fluorofenil)etil]isoindolina-1-carboxamida (445,0942; 445,0936);
N-bencil-6-cloro-2-(dipiridin-3-ilmetil)-3-oxoisoindolina-1-carboxamida (469,1431; 469,1407);
6-cloro-N-metil-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (383,0774; 383,0798);
2-[2-(4-clorofenil)propil]-6-fluoro-N-metil-3-oxoisoindolina-1-carboxamida (361,1119; 361,1130);
6-fluoro-N-metil-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (313,1352; 313,1359);
6-cloro-2-[2-(4-clorofenil)propil]-N-metil-3-oxoisoindolina-1-carboxamida (377,0823; 377,0821);
6-cloro-N-metil-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (329,1056; 329,1062);

2-[2-(4-clorofenil)propil]-N-metil-3-oxoisoindolina-1-carboxamida (343,1213; 343,1231);
6-cloro-N-etil-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (343,1213; 343,1238);
N-bencil-5-[(metilsulfonil)amino]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (464,1644; 464,1651);
N-bencil-4-metil-5-[(metilsulfonil)amino]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (478,1800; 478,1820);
N-bencil-5-ciano-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (396,1712; 396,1734);
N-bencil-5-bromo-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (449,0864; 449,0868);
N-bencil-6-bromo-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (449,0864; 449,0872);
N-[3-(difluorometoxi)bencil]-6-fluoro-2-(3-hidroxi-2,2-dimetilpropilo)-3-oxoisoindolina-1-carboxamida (437,1688; 437,1702);
N-(3,4-diclorobencil)-6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (439,0991; 439,1017);
N-(3-clorobencil)-6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (405,1381; 405,1379);
6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida (439,1644; 439,1643);
6-cloro-N-[3-(difluorometoxi)bencil]-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (453,1392; 453,1390);
6-cloro-N-(3,4-diclorobencil)-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (455,0696; 455,0714);
6-cloro-N-(3-clorobencil)-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (421,1085; 421,1044);
6-cloro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida (455,1349; 455,1355);
N-(3,4-diclorobencil)-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (421,1085; 421,1091);
N-[3-(difluorometoxi)bencil]-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (419,1782; 419,1767);

2-(3-hidroxi-2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida (421,1739; 421,1747);
N-(4,4-difluorobutil)-6-fluoro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (445,1350; 445,1346);
6-cloro-N-(4,4-difluorobutil)-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (461,1055; 461,1014);
6-cloro-N-(4,4-difluorobutil)-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (407,1338; 407,1321);
N-(4,4-difluorobutil)-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (373,1727; 373,1748);
N-(terc-butil)-6-fluoro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (409,1539; 409,1524);
N-(terc-butil)-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (391,1633; 391,1629);
N-(terc-butil)-6-cloro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (425,1243; 425,1239);
6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (463,1256; 463,1240);
3-oxo-N-(4,4,4-trifluorobutil)-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (445,1350; 445,1341);
6-cloro-3-oxo-N-(4,4,4-trifluorobutil)-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (479,0961; 479,0967);
N-(terc-butil)-6-fluoro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (355,1821; 355,1814);
6-fluoro-3-oxo-2-[(1R)-1-feniletil]-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (409,1539; 409,1566);
N-(terc-butil)-6-cloro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (371,1526; 371,1530);
6-cloro-3-oxo-2-[(1R)-1-feniletil]-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (425,1243; 425,1255);
3-oxo-2-[(1R)-1-feniletil]-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (391,1633; 391,1649);

6-cloro-N-[4-(metilsulfonil)bencil]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (483,1145; 483,1145);

N-bencil-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (425,1477; 425,1455);

N-[(4-amino-2-metilpirimidin-5-il)metil]-6-cloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (484,1307; 484,1289);

2-(bifenil-2-ilmetil)-N-[(5-metilpirazin-2-il)metil]-3-oxoisoindolina-1-carboxamida (449,1977; 449,1978);

2-(bifenil-2-ilmetil)-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida (434,1868; 434,1839);

N-[(4-amino-2-metilpirimidin-5-il)metil]-2-(bifenil-2-ilmetil)-6-cloro-3-oxoisoindolina-1-carboxamida (498,1696; 498,1682);

N-[(4-amino-2-metilpirimidin-5-il)metil]-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida (464,2086; 464,2096);

N-butil-2-[(4-fluorofenil)(piridin-3-il)metil]-3-oxoisoindolina-1-carboxamida (418,1930; 418,1921);

N-butil-3-oxo-2-[fenil(piridin-2-il)metil]isoindolina-1-carboxamida (400,2025; 400,2018);

N-butil-2-[(4-clorofenil)(piridin-4-il)metil]-3-oxoisoindolina-1-carboxamida (434,1635; 434,1618);

2-[(4-clorofenil)(piridin-4-il)metil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida (486,1384; 486,1342);

6-cloro-2-(difenilmetil)-N-etil-3-oxoisoindolina-1-carboxamida (405,1369; 405,1332);

2-(bifenil-2-ilmetil)-6-cloro-N-etil-3-oxoisoindolina-1-carboxamida (405,1369; 405,1336);

2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-propilisoindolina-1-carboxamida (419,1526; 419,1521);

2-(difenilmetil)-N-etil-3-oxoisoindolina-1-carboxamida (371,1759; 371,1759);

2-(bifenil-2-ilmetil)-N-etil-3-oxoisoindolina-1-carboxamida (371,1759; 371,1758);

2-(bifenil-2-ilmetil)-6-fluoro-3-oxo-N-propilisoindolina-1-carboxamida (403,1821; 403,1805);

N-(4-fluorobencil)-2-[(4-fluorofenil)(piridin-3-il)metil]-3-oxoisoindolina-1-carboxamida (470,1680; 470,1664);

N-bencil-2-[(4-fluorofenil)(piridin-3-il)metil]-3-oxoisoindolina-1-carboxamida (452,1774; 452,1761);
2-[2-(4-clorofenil)propil]-N-[(5-metilpirazin-2-il)metil]-3-oxoisoindolina-1-carboxamida (435,1587; 435,1592);
6-cloro-2-[2-(4-clorofenil)propil]-N-[(5-metilpirazin-2-il)metil]-3-oxoisoindolina-1-carboxamida (469,1198; 469,1177);
2-(bifenil-2-ilmetil)-6-cloro-N-[(5-metilpirazin-2-il)metil]-3-oxoisoindolina-1-carboxamida (483,1587; 483,1582);
6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida (454,1089; 454,1069);
6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida (522,0963; 522,0932);
N-[(4-amino-2-metilpirimidin-5-il)metil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (450,1696; 450,1699);
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida (536,1352; 536,1326);
2-[2-(4-clorofenil)propil]-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida (488,1352; 488,1335);
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida (468,1478; 468,1448);
2-(bifenil-2-ilmetil)-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida (502,1742; 502,1722);
N-bencil-6-fluoro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (389,1665; 389,1656);
N-[4-(metilsulfonil)bencil]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (449,1535; 449,1510);
6-fluoro-N-[4-(metilsulfonil)bencil]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida (467,1440; 467,1443);
N-bencil-6-cloro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (459,1087; 459,1079);
N-bencil-6-fluoro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (443,1382; 443,1373);

6-cloro-N-[4-(metilsulfonil)bencil]-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (537,0862; 537,0843);

6-cloro-N-[2-cloro-4-(metilsulfonil)bencil]-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (579,0912; 579,0919);

N-[2-cloro-4-(metilsulfonil)bencil]-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (545,1301; 545,1290);

6-cloro-2-(difenilmetil)-N-[2-fluoro-4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (563,1207; 563,1201);

2-(difenilmetil)-N-[2-fluoro-4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (529,1597; 529,1584);

6-cloro-2-(difenilmetil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (545,1301; 545,1316);

2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida (468,1478; 468,1479);

6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida (454,1089; 454,1075);

2-(bifenil-2-ilmetil)-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida (434,1868; 434,1853);

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-ciano-3-oxoisoindolina-1-carboxamida (424,2025; 424,2027);

6-cloro-2-(difenilmetil)-3-oxo-N-propilisoindolina-1- carboxamida (419,1526; 419,1544);

2-[2-(4-clorofenil)propil]-N-etil-6-fluoro-3-oxoisoindolina-1-carboxamida (375,1275; 375,1263);

2-(difenilmetil)-N-etil-6-fluoro-3-oxoisoindolina-1-carboxamida (389,1665; 389,1671);

2-[2-(4-clorofenil)propil]-N-etil-3-oxoisoindolina-1-carboxamida (357,1369; 357,1374);

2-[2-(4-clorofenil)propil]-6-fluoro-3-oxo-N-propilisoindolina-1-carboxamida (389,1432; 389,1431);

2-(difenilmetil)-6-fluoro-3-oxo-N-propilisoindolina-1-carboxamida (403,1821; 403,1837);

2-(bifenil-2-ilmetil)-3-oxo-N-propilisoindolina-1-carboxamida (385,1916; 385,1903);

2-[2-(4-clorofenil)propil]-3-oxo-N-propilisoindolina-1-carboxamida (371,1526; 371,1546);

2-(difenilmetil)-3-oxo-N-propilisoindolina-1-carboxamida (385,1916; 385,1930);

2-(difenilmetil)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (471,1695; 471,1715);
2-[2-(4-clorofenil)propil]-6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (457,1306; 457,1325);
2-[2-(4-clorofenil)propil]-3-oxo-N-(4,4,4-trifluorobutilo)isoindolina-1-carboxamida (439,1400; 439,1401);
2-(bifenil-2-ilmetil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (453,1790; 453,1784);
2-(difenilmetil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (453,1790; 453,1807);
N-(terc-butil)-2-[(4-clorofenil)(piridin-4-il)metil]-3-oxoisoindolina-1-carboxamida (434,1635; 434,1620);
N-(4-fluorobencil)-3-oxo-2-[fenil(piridin-2-il)metil]isoindolina-1-carboxamida (452,1774; 452,1789);
N-bencil-2-[(4-clorofenil)(piridin-4-il)metil]-3-oxoisoindolina-1-carboxamida (468,1478; 468,1465);
N-bencil-3-oxo-2-[fenil(piridin-2-il)metil]isoindolina-1-carboxamida (434,1868; 434,1871);
2-(2,2-dimetilpropil)-N-[(5-metil-2-fenil-1,3-oxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida (418,2130; 418,2128);
2-(2,2-dimetilpropil)-N-[(1-metil-5-fenil-1H-pirazol-3-il)metil]-3-oxoisoindolina-1-carboxamida (417,2290; 417,2298);
N-bencil-2-[(1-metil-5-fenil-1H-pirazol-3-il)metil]-3-oxoisoindolina-1-carboxamida (437,1977; 437,1993);
N-bencil-2-[(5-metil-2-fenil-1,3-oxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida (438,1817; 438,1825);
N-bencil-2-(bifenil-2-ilmetil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (463,2021; 463,2019);
2-(bifenil-2-ilmetil)-5-hidroxi-4-metil-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (483,1895; 483,1881);
2-(bifenil-2-ilmetil)-5-hidroxi-4-metil-3-oxo-N-propilisoindolina-1-carboxamida (415,2021; 415,2033);

2-(bifenil-2-ilmetil)-N-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (429,2178; 429,2196);

2-(bifenil-2-ilmetil)-N-etil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (401,1865; 401,1870);

N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (465,1989; 465,2002);

N-(terc-butil)-2-[(2',4'-diclorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (497,1398; 497,1393);

N-(terc-butil)-2-[(3',4'-diclorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (497,1398; 497,1392);

N-(terc-butil)-2-[(2'-clorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (463,1788; 463,1804);

N-(terc-butil)-2-[(3'-cloro-4'-fluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (481,1694; 481,1681);

N-(terc-butil)-2-[(4'-clorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (463,1788; 463,1764);

N-(terc-butil)-2-[(4'-fluoro-2'-metilbifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (461,2240; 461,2221);

N-(terc-butil)-2-[(2',4'-difluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (465,1989; 465,1987);

N-(terc-butil)-2-[(2',5'-difluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (465,1989; 465,1998);

N-(terc-butil)-2-[(3'-fluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (447,2084; 447,2097);

N-butil-3-oxo-2-(2-(fenoxibencil)isoindolina-1-carboxamida (415,2021; 415,2060);

N-[3-(difluorometoxi)bencil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (417,1989; 417,2034);

2-(3,3-dimetilbutil)-3-oxo-N-[3-(trifluorometoxi)bencil]isoindolina-1-carboxamida (435,1895; 435,1855);

2-(2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometoxi)bencil]isoindolina-1-carboxamida (421,1739; 421,1717);

N-[3-(difluorometoxi)bencil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (403,1833; 403,1873);

6-cloro-2-(difenilmetil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (487,1400; 487,1445);

6-cloro-2-(difenilmetil)-N-(2-hidroxibencil)-3-oxoisoindolina-1-carboxamida (483,1475; 483,1472);

N-bencil-6-cloro-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (467,1526; 467,1544);

N-(terc-butil)-6-cloro-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (433,1682; 433,1709);

2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (487,1400; 487,1390);

2-(bifenil-2-ilmetil)-6-cloro-N-(3-cianobencil)-3-oxoisoindolina-1-carboxamida (492,1478; 492,1513);

N-bencil-2-(bifenil-2-ilmetil)-6-cloro-3-oxoisoindolina-1-carboxamida (467,1526; 467,1513);

2-(bifenil-2-ilmetil)-N-(terc-butil)-6-cloro-3-oxoisoindolina-1-carboxamida (433,1682; 433,1723);

6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (473,1010; 473,1010);

6-cloro-2-[2-(4-clorofenil)propil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (531,0912; 531,0937);

N-(terc-butil)-6-cloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (419,1293; 419,1326);

N-bencil-6-cloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (453,1136; 453,1156);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-4,5-dimetoxi-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida (488,1934; 488,1938);

2-[1-(1,5-dimetil-1H-pirazol-4-il)etil]-5,7-dimetoxi-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (517,2062; 517,2051);

5,7-dimetoxi-2-(2-metoxibencil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (515,1793; 515,1784);

2-(2-fluorobencil)-5,7-dimetoxi-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (503,1594; 503,1598);

N-(terc-butil)-5,7-dimetoxi-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida (413,2076; 413,2094);

3-oxo-2-(2-fenoxibencil)-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (469,1739; 469,1732);

2-[2-(4-clorofenil)propil]-N-[(2,2-difluoro-1,3-benzodioxol-5-il)metil]-3-oxoisoindolina-1-carboxamida (499,1236; 499,1221);

N-(3,4-diclorobencil)-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (405,1136; 405,1137);

2-(2,2-dimetilpropil)-N-(1H-indol-3-ilmetil)-3-oxoisoindolina-1-carboxamida (376,2025; 376,2009);

2-(2,2-dimetilpropil)-3-oxo-N-{2-[3-(trifluorometil)fenil]etil}isoindolina-1-carboxamida (419,1946; 419,1918);

2-(bifenil-2-ilmetil)-N-(terc-butil)-6-fluoro-3-oxoisoindolina-1-carboxamida (417,1978; 417,1967);

N-bencil-2-(bifenil-2-ilmetil)-6-fluoro-3-oxoisoindolina-1-carboxamida (451,1821; 451,1820);

2-[2-(4-clorofenil)etil]-N-[(2,2-difluoro-1,3-benzodioxol-5-il)metil]-6-fluoro-3-oxoisoindolina-1-carboxamida (503,0985; 503,0987);

2-[2-(4-clorofenil)etil]-6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (443,1149; 443,1151);

N-(terc-butil)-2-[2-(4-clorofenil)etil]-6-fluoro-3-oxoisoindolina-1carboxamida (389,1432; 389,1446);

N-bencil-2-[2-(4-clorofenil)etil]-6-fluoro-3-oxoisoindolina-1-carboxamida (423,1275; 423,1266);

6-fluoro-2-[2-(4-fluorofenil)etil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (427,1445; 427,1434);

N-bencil-6-fluoro-2-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida (407,1571; 407,1566);

6-fluoro-2-[2-(4-fluorofenil)propil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida (441,1601; 441,1592);

N-bencil-6-fluoro-2-[2-(4-fluorofenil)propil]-3-oxoisoindolina-1-carboxamida (421,1727; 421,1709);

N-(terc-butil)-6-fluoro-2-[2-(4-fluorofenil)propil]-3-oxoisoindolina-1-carboxamida (387,1884; 387,1868);

2-(bifenil-2-ilmetil)-1-metil-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (525,1848; 525,1854);

2-[2-(4-clorofenil)propil]-4,7-difluoro-1-metil-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;

N-butil-2-[2-(4-clorofenil)propil]-1-metil-3-oxoisoindolina-1-carboxamida (399,1839; 399,1825);

2-(bifenil-2-ilmetil)-N-(terc-butil)-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida (459,2283; 459,2263);

N-bencil-2-(difenilmetil)-5-metoxi-3-oxoisoindolina-1-carboxamida (463,2021; 463,1992);

2-(difenilmetil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (501,1790; 501,1780);

N-(terc-butil)-2-[2-(4-clorofenil)propil]-1-metil-3-oxoisoindolina-1-carboxamida (399,1839; 399,1826);

N-butil-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (399,2072; 399,2089);

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-metoxi-4-metil-3-oxoisoindolina-1-carboxamida (443,2334; 443,2317);

dimetilcarbamato de 2-(bifenil-2-ilmetil)-1-[(terc-butilamino)carbonil]-4-metil-3-oxo-2,3-dihidro-1H-isoindol-5-ilo (500,2549; 500,2561);

2-(bifenil-2-ilmetil)-5-hidroxi-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (463,2021; 463,1998);

5-hidroxi-2-[2-(4-metoxifenil)etil]-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (431,1970; 431,1963);

2-(4-clorobencil)-5-hidroxi-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (421,1319; 421,1311);

N-(4-fluorobencil)-5-hidroxi-2-[2-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (435,1720; 435,1714);

2-[2-(3,4-diclorofenil)etil]-N-(4-fluorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida (473,0835; 473,0795);

2-(4-clorobencil)-N-(4-fluorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida (425,1068; 425,1054);

2-(bifenil-2-ilmetil)-N-(4-fluorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida (467,1771; 467,1772);

N-(terc-butil)-2-[2-(3,4-diclorofenil)etil]-5-hidroxi-3-oxoisoindolina-1-carboxamida (421,1085; 421,1022);

N-(3,4-diclorobencil)-2-isobutil-3-oxoisoindolina-1-carboxamida (391,0980; 391,0989);

N-[2-(1H-indol-3-il)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida (376,2025; 376,2027);

N-(3-clorobencil)-2-isobutil-3-oxoisoindolina-1-carboxamida (357,1369; 357,1352);

N-[4-(difluorometoxi)bencil]-2-isobutil-3-oxoisoindolina-1-carboxamida (389,1676; 389,1673);

2-isobutil-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida (391,1633; 391,1613);

N-(1H-indol-3-ilmetil)-2-isobutil-3-oxoisoindolina-1-carboxamida (362,1868; 362,1859);

N-[2-(1,3-benzodioxol-5-il)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida (381,1814; 381,1801);

N-[2-(3-fluorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida (355,1821; 355,1813);

2-isobutil-3-oxo-N-{2-[3-(trifluorometil)fenil]etil}isoindolina-1-carboxamida (405,1790; 405,1775);

N-[2-(3,4-diclorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida (405,1136; 405,1135);

N-[2-(4-clorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida (371,1526; 371,1523);

N-[2-(3-clorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida (371,1526; 371,1520);

N-[2-(2-clorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida (371,1526; 371,1513);

N-[2-(2,4-diclorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida (405,1136; 405,1129);

N-[2-(2,6-diclorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida (405,1136; 405,1125);

2-(3,3-dimetilbutil)-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (404,2338; 404,2336);

N-(3-clorobencil)-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (385,1682; 385,1676);
N-(3,4-diclorobencil)-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (419,1293; 419,1273);
2-(3,3-dimetilbutil)-N-(1H-indol-3-ilmetil)-3-oxoisoindolina-1-carboxamida (390,2181; 390,2174);
N-[4-(difluorometoxi)bencil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (417,1989; 417,1975);
2-(3,3-dimetilbutil)-N-[2-(3-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida (383,2134; 383,2103);
N-[2-(1,3-benzodioxol-5-il)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (409,2127; 409,2125);
N-[2-(3-cianofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (390,2181; 390,2171);
2-(3,3-dimetilbutil)-3-oxo-N-{2-[3-(trifluorometil)fenil]etil}isoindolina-1-carboxamida (433,2103; 433,2092);
N-[2-(3-clorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (399,1839; 399,1830);
N-[2-(3,4-diclorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (433,1449; 433,1431);
N-[2-(4-clorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (399,1839; 399,1831);
N-[2-(2-clorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (399,1839; 399,1841);
N-[2-(2,4-diclorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (433,1449; 433,1428);
2-(2,2-dimetilpropil)-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (390,2181; 390,2172);
N-(3-clorobencil)-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (371,1526; 371,1515);
N-[4-(difluorometoxi)bencil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (403,1833; 403,1833);

2-(2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida (405,1790; 405,1787);

N-[2-(1,3-benzodioxol-5-il)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (395,1970; 395,1967);

2-(2,2-dimetilpropil)-N-[2-(3-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida (369,1978; 369,1977);

N-[2-(3-cianofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (376,2025; 376,2029);

N-[2-(2-clorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (385,1682; 385,1675);

N-[2-(3-clorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (385,1682; 385,1671);

N-[2-(2,4-diclorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (419,1293; 419,1290);

2-[2-(4-clorofenil)etil]-N-etil-3-oxo-N-(2-piridin-2-iletil)isoindolina-1-carboxamida (448,1791; 448,1776);

2-[2-(4-clorofenil)etil]-3-(1,3-dihidro-2H-isoindol-2-ilcarbonil)isoindolin-1-ona (417,1369; 417,1382);

2-[2-(4-clorofenil)etil]-N-metil-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (487,1400; 487,1352);

N-bencil-2-[2-(4-clorofenil)etil]-N-etil-3-oxoisoindolina-1-carboxamida (433,1682; 433,1662);

N-bencil-2-[2-(4-clorofenil)etil]-N-metil-3-oxoisoindolina-1-carboxamida (419,1526; 419,1516);

N-(terc-butil)-3-oxo-2-{2-[4-(trifluorometil)fenil]etil}isoindolina-1-carboxamida (405,1790; 405,1766);

N-butil-3-oxo-2-{2-[4-(trifluorometil)fenil]etil}isoindolina-1-carboxamida (405,1790; 405,1771);

N-bencil-3-oxo-2-{2-[4-(trifluorometil)fenil]etil}isoindolina-1-carboxamida (439,1633; 439,1621);

N-(terc-butil)-5-hidroxi-2-[2-(1H-indol-3-il)etil]-4-metil-3-oxoisoindolina-1-carboxamida (406,2130; 406,2102);

N-(terc-butil)-2-[2-(4-fluorofenil)propil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (399,2084; 399,2061);

2-[3,5-bis(trifluorometil)bencil]-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (489,1613; 489,1611);

N-(terc-butil)-2-(2,2-difeniletil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (443,2334; 443,2317);

N-(terc-butil)-2-(difenilmetil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (429,2178; 429,2160);

N-(terc-butil)-2-(9H-fluoren-9-il)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (427,2021; 427,2007);

N-(terc-butil)-5-hidroxi-4-metil-3-oxo-2-{2-[4-(trifluorometil)fenoxi]bencil}isoindolina-1-carboxamida (513,2001; 513,1967);

2-(bifenil-3-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (429,2178; 429,2139);

N-butil-2-[2-(4-fluorofenil)propil]-3-oxoisoindolina-1-carboxamida (369,1978; 369,1956);

N-butil-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida (371,1526; 371,1507);

N-(terc-butil)-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida (371,1526; 371,1534);

N-(terc-butil)-2-[2-(4-fluorofenil)propil]-3-oxoisoindolina-1-carboxamida (369,1978; 369,1954);

N-bencil-2-[2-(4-fluorofenil)propil]-3-oxoisoindolina-1-carboxamida (403,1821; 403,1789);

N-bencil-2-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida (389,1665; 389,1668);

N-bencil-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida (405,1369; 405,1367);

N-[2-(1H-indol-3-il)etil]-3-oxo-2-[4-(piperidin-1-ilcarbonil)bencil]isoindolina-1-carboxamida (521,2552; 521,2518);

2-(bifenil-2-ilmetil)-N-(2,4-difluorobencil)-3-oxoisoindolina-1-carboxamida (469,1727; 469,1689);

2-(bifenil-2-ilmetil)-N-(4-ciano-2,6-difluorobencil)-3-oxoisoindolina-1-carboxamida (494,1680; 494,1667);

N-(2,4-difluorobencil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (469,1727; 469,1695);

N-(2-clorobencil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (467,1526; 467,1486);
2-(difenilmetil)-N-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida (465,1978; 465,1948);
2-(bifenil-2-ilmetil)-N-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida (465,1978; 465,1957);
2-(difenilmetil)-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida (451,1821; 451,1785);
N-(2,4-difluorobencil)-3-oxo-2-(2-piridin-3-il bencil)isoindolina-1-carboxamida (470,1680; 470,1645);
N-(2-clorobencil)-3-oxo-2-(2-piridin-3-ilbencil)isoindolina-1-carboxamida (468,1478; 468,1437);
N-[2-(4-fluorofenil)etil]-3-oxo-2-(2-piridin-3-ilbencil)isoindolina-1-carboxamida (466,1930; 466,1917);
N-bencil-3-oxo-2-(2-piridin-3-ilbencil)isoindolina-1-carboxamida (434,1868; 434,1839);
N-(4-fluorobencil)-3-oxo-2-(2-piridin-3-ilbencil)isoindolina-1-carboxamida (452,1774; 452,1760);
N-butil-5-metoxi-2-(2-metil-2-fenilpropil)-3-oxoisoindolina-1-carboxamida (395,2334; 395,2298);
2-(bifenil-2-ilmetil)-N-butil)-5-metoxi-3-oxoisoindolina-1-carboxamida (429,2178; 429,2147);
N-butil-2-[2-(4-fluorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida (399,2084; 399,2057);
N-butil-2-[2-(4-clorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida (415,1788; 415,1772);
N-(terc-butil)-5- metoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida (431,2334; 431,2338);
N-(terc-butil)-2-[2-(4-fluorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida (399,2084; 399,2060);
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida (415,1788; 415,1774);
2-(bifenil-2-ilmetil)-N-(terc-butil)-5-metoxi-3-oxoisoindolina-1-carboxamida (429,2178; 429,2162);

N-bencil-5-metoxi-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida (465,2178; 465,2154);
N-bencil-5-metoxi-2-(2-metil-2-fenilpropil)-3-oxoisoindolina-1-carboxamida (429,2178; 429,2183),
N-bencil-2-(bifenil-2-ilmetil)-5-metoxi-3-oxoisoindolina-1-carboxamida (463,2021; 463,1988);
N-butil-5,6-dimetoxi-2-(2-metil-2-fenilpropil)-3-oxoisoindolina-1-carboxamida (425,2440; 425,2408);
N-bencil-2-[2-(4-clorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida (449,1632; 449,1597);
N-butil-5,6-dimetoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida (461,2440; 461,2424);
N-butil-2-[2-(4-fluorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida (429,2189; 429,2148);
2-(bifenil-2-ilmetil)-N-butil)-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida (459,2283; 459,2237);
N-butil-2-[2-(4-clorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida (445,1894; 445,1857);
N-(terc-butil)-5,6-dimetoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida (461,2440; 461,2417);
N-bencil-5,6-dimetoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida (495,2283; 495,2259);
N-bencil-5,6-dimetoxi-2-(2-metil-2-fenilpropil)-3-oxoisoindolina-1-carboxamida (459,2283; 459,2267),
N-bencil-2-[2-(4-fluorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida (463,2033; 463,2008);
N-bencil-2-(bifenil-2-ilmetil)-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida (493,2127; 493,2099);
N-bencil-2-(difenilmetil)-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida (493,2127; 493,2092);
N-bencil-2-[2-(4-clorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida (479,1737; 479,1711);

2-(bifenil-2-ilmetil)-N-(terc-butil)-1-metil-3-oxoisoindolina-1-carboxamida (413,2229; 413,2210);

2-(bifenil-2-ilmetil)-N-butil-1-metil-3-oxoisoindolina-1-carboxamida (413,2229; 413,2204);

N-bencil-N-({2-[2-(4-clorofenil)etil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de etilo (491,1737; 491,1708);

2-[2-(4-clorofenil)etil]-N-metil-3-oxo-N-[(2-feniletil)isoindolina-1-carboxamida (433,1682; 433,1641);

2-[2-(4-clorofenil)etil]-N,N-dietil-3-oxoisoindolina-1-carboxamida (371,1526; 371,1500);

N-bencil-N-butil-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida (461,1995; 461,1977);

N-[2-(2,6-diclorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida (433,1449; 433,1440);

N-[2-(4-clorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (385,1682; 385,1677);

N-[2-(2,6-diclorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (419,1293; 419,1270);

N-butil-5-metoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida (431,2334; 431,2332);

N-bencil-2-[2-(4-fluorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida (433,1927; 433,1907);

N-(terc-butil)-2-[2-(4-clorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida (445,1894; 445,1870);

N-(terc-butil)-2-[(4'-fluoro-2'-metilbifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida (431,2134; 431,2122);

N-(terc-butil)-2-[(4'-metilbifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida (413,2229; 413,2214);

N-(terc-butil)-2-[(4'-metoxibifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida (429,2178; 429,2179);

N-(terc-butil)-2-[(4'-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida (417,1978; 417,1974);

N-({2-[(3',4'-difluorobifenil-2-il)metil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo (451,1469; 451,1465);

N-({2-[(4'-fluoro-2'-metilbifenil-2-il)metil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo (447,1720; 447,1724);

N-({2-[(4'-fluorobifenil-2-il)metil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo (433,1563; 433,1558);

N-({2-[(4'-metilbifenil-2-il)metil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo (429,1814; 429,1809);

2-[(3',4'-difluorobifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (547,1503; 547,1497);

2-[(4'-fluoro-2'-metilbifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (543,1753; 543,1778);

2-[(4'-metoxibifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (541,1797; 541,1797);

2-[(4'-fluorobifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (529,1597; 529,1594);

2-[(4'-metilbifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (525,1848; 525,1854);

N-(terc-butil)-2-(4-clorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (387,1475; 387,1486);

N-(terc-butil)-5-hidroxi-2-[2-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (383,1970; 383,2007);

2-[2-(4-clorofenil)propil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (472,1791; 472,1816);

N-(terc-butil)-7-hidroxi-2-[2-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (383,1970; 383,1978);

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-3-oxoisoindolina-1-carboxamida (415,2021; 415,2018);

2-[2-(3,4-diclorofenil)etil]-5-hidroxi-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (469,1085; 469,1005);

N-(3,4-difluorobencil)-2-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida (409,1363; 409,1375);

N-(3-clorobencil)-2-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida (407,1162; 407,1162);
2-(4-hidroxibencil)-3-oxo-N-[4-(trifluorometil)bencil]isoindolina-1-carboxamida (441,1426; 441,1477);
N-[3,5-bis(trifluorometil)bencil]-2-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida (509,1300; 509,1384);
N-(3-clorobencil)-2-(3-cianobencil)-3-oxoisoindolina-1-carboxamida (416,1165; 416,1188);
N-[3,5-bis(trifluorometil)bencil]-2-(3-cianobencil)-3-oxoisoindolina-1-carboxamida (518,1303; 518,1320);
2-(3-cianobencil)-N-(3,4-difluorobencil)-3-oxoisoindolina-1-carboxamida (418,1367; 418,1381);
2-(3-cianobencil)-3-oxo-N-[4-(trifluorometil)bencil]isoindolina-1-carboxamida (450,1429; 450,1442);
N-[4-(aminocarbonil)bencil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (462,1584; 462,1599);
N-[4-(aminocarbonil)bencil]-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida (476,1974; 476,1927);
2-(3,4-difluorobencil)-N-{4-[(dimetilamino)metil]bencil}-3-oxoisoindoline-1-carboxamida;
2-(3-clorobencil)-N-{4-[(dimetilamino)metil]bencil}-3-oxoisoindoline-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-{4-[(dimetilamino)metil]bencil}-3-oxoisoindolina-1-carboxamida
2-(3,4-difluorobencil)-N-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida (409,1363; 409,1383);
2-(3-clorobencil)-N-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida (407,1162; 407,1158);
2-[3,5-bis(trifluorometil)bencil]-N-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida (509,1300; 509,1281);
2-(3-clorobencil)-N-(3-cianobencil)-3-oxoisoindolina-1-carboxamida (416,1165; 416,1172);

N-(3-cianobencil)-2-(3,4-difluorobencil)-3-oxoisoindolina-1-carboxamida (418,1367; 418,1353);

2-[2-(4-clorofenil)propil]-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida (444,1478; 444,1504);

2-[3,5-bis(trifluorometil)bencil]-N-(3-cianobencil)-3-oxoisoindolina-1-carboxamida (518,1303; 518,1278);

N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-hidroxi-3-oxoisoindolina-1-carboxamida (401,1632; 401,1666);

N-{4-[(dimetilamino)metil]bencil}-3-oxo-2-[4-(trifluorometoxi)bencil]isoindolina-1-carboxamida (482,2055; 482,2060);

N-(4-hidroxibencil)-3-oxo-2-[4-(trifluorometil)bencil]isoindolina-1-carboxamida (441,1426; 441,1414);

N-(3-cianobencil)-3-oxo-2-[4-(trifluorometil)bencil]isoindolina-1-carboxamida (450,1429; 450,1461);

2-(bifenil-3-ilmetil)-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida (458,1868; 458,1872);

2-(bifenil-4-ilmetil)-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida (458,1868; 458,1894);

N-butil-3-oxo-2-[2-(2-fenoxifenil)etil]isoindolina-1-carboxamida (429,2178; 429,2170);

N-butil-2-(2-{4-[(dimetilamino)carbonil]fenil}etil)-3-oxoisoindolina-1-carboxamida (436,2600; 436,2588);

N-butil-2-[2-(3-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida (355,1821; 355,1839);

N-butil-3-oxo-2-{2-[2-(trifluorometoxi)fenil]etil}isoindolina-1-carboxamida (421,1739; 421,1722);

2-(2-bifenil-4-iletil)-N-butil-3-oxoisoindolina-1-carboxamida (413,2229; 413,2253);

N-butil-2-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida (355,1821; 355,1834);

N-butil-2-[2-(3,5-dimetoxifenil)etil]-3-oxoisoindolina-1-carboxamida (397,2127; 397,2129);

N-butil-3-oxo-2-[2-(4-fenoxifenil)etil]isoindolina-1-carboxamida (429,2178; 429,2179);

N-butil-2-[2-(2-etoxifenil)etil]-3-oxoisoindolina-1-carboxamida (381,2178; 381,2173);

2-[2-(1,3-benzodioxol-5-il)etil]-N-butil-3-oxoisoindolina-1-carboxamida (381,1814; 381,1814);

N-(terc-butil)-3-oxo-2-[2-(2-fenoxifenil)etil]isoindolina-1-carboxamida (429,2178; 429,2170);

N-(terc-butil)-3-oxo-2-{2-[2-(trifluorometoxi)fenil]etil}isoindolina-1-carboxamida (421,1739; 421,1741);

2-(2-bifenil-4-iletil)-N-(terc-butil)-3-oxoisoindolina-1-carboxamida (413,2229; 413,2261);

N-(terc-butil)-2-[2-(3,5-dimetoxifenil)etil]-3-oxoisoindolina-1-carboxamida (397,2127; 397,2129);

N-(terc-butil)-3-oxo-2-[2-(4-fenoxifenil)etil]isoindolina-1-carboxamida (429,2178; 429,2147);

N-(terc-butil)-2-[2-(2-etoxifenil)etil]-3-oxoisoindolina-1-carboxamida (381,2178; 381,2169);

2-[2-(1,3-benzodioxol-5-il)etil]-N-(terc-butil)-3-oxoisoindolina-1-carboxamida (381,1814; 381,1810);

N-[2-(1H-indol-3-il)etil]-3-oxo-2-[2-(2-fenoxifenil)etil]isoindolina-1-carboxamida (516,2287; 516,2333);

2-(2-{4-[(dietilamino)carbonil]fenil}etil)-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (523,2709; 523,2714);

2-[2-(3-fluorofenil)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (442,1930; 442,1936);

N-[2-(1H-indol-3-il)etil]-3-oxo-2-{2-[2-(trifluorometoxi)fenil]etil}isoindolina-1-carboxamida (508,1848; 508,1853);

2-[2-(4-fluorofenil)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (442,1930; 442,1929);

2-[2-(3,5-dimetoxifenil)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (484,2236; 484,2237);

2-(2-bifenil-4-iletil)-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (500,2338; 500,2371);

N-[2-(1H-indol-3-il)etil]-3-oxo-2-[2-(4-fenoxifenil)etil]isoindolina-1-carboxamida (516,2287; 516,2280);

2-[2-(2-etoxifenil)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (468,2287; 468,2276);

2-[2-(1,3-benzodioxol-5-il)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (468,1923; 468,1899);

(1R)-2-[(1S)-1-(4-fluorofenil)etil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;

N-[4-(dimetilamino)bencil]-2-[2-(dimetilamino)-2-feniletil]-3-oxoisoindolina-1-carboxamida (457,2603; 457,2610);

N-[4-(dimetilamino)bencil]-2-(2,2-difeniletil)-3-oxoisoindolina-1-carboxamida (490,2494; 490,2497);

2-(1-bencil-2-fluoroetil)-N-[(5-metilisoxazol-3-il)metil]-3-oxoisoindolina-1-carboxamida (408,1723; 408,1700);

N-(terc-butil)-2-(2-cloro-4-clorobencil)-3-oxoisoindolina-1-carboxamida (375,1275; 375,1276);

2-(3,4-difluorobencil)-N-(4-fluorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (441,1426; 441,1414);

2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida (424,1472; 424,1458);

2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (437,1676; 437,1667);

2-(3,4-difluorobencil)-5-hidroxi-3-oxo-4-fenil-N-(2-feniletil)isoindolina-1-carboxamida (499,1833; 499,1788);

N-(2-clorobencil)-2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (457,1130; 457,1088);

2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (491,1394; 491,1378);

N-(terc-butil)-2-(2-clorobencil)-5-hidroxi-3-oxo-4-(trimetilsilil)isoindolina-1-carboxamida;

N-(terc-butil)-2-(2-clorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (387,1475; 387,1461);

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida (491,2334; 491,2325);

2-[3,5-bis(trifluorometil)bencil]-N-(terc-butil)-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida (551,1769; 551,1776);

2-[2-(4-clorofenil)propil]-N-{3-[(dimetilamino)carbonil]-4-fluorobencil}-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-(4-cianofenil)-3-oxoisoindolina-1-carboxamida;
2-(1-bencil-2-fluoroetil)-N-butil-3-oxoisoindolina-1-carboxamida (369,1978; 369,1972);
2-(1-bencil-2-fluoroetil)-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida (421,1727; 421,1689);
2-(1-bencil-2-fluoroetil)-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida (446,2243; 446,2229);
N-[4-(aminometil)fenil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (434,1635; 434,1641);
2-[2-(4-clorofenil)propil]-N-(4-{[(difluoroacetil)amino]metil}fenil)-3-oxoisoindolina-1-carboxamida (512,1552; 512,1567);
N-[4-(aminocarbonil)fenil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (448,1428; 448,1418);
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-(fluorometoxi)-4-metil-3-oxoisoindolina-1-carboxamida (447,1850; 447,1835);
N-[4-(dimetilamino)bencil]-3-oxo-2-(4-fenilbutil)isoindolina-1-carboxamida (442,2494; 442,2494);
N-[4-(dimetilamino)bencil]-2-(2-hidroxi-2-feniletil)-3-oxoisoindolina-1-carboxamida (430,2130; 430,2120);
N-[4-(dimetilamino)bencil]-3-oxo-2-[2-(1H-pirazol-1-il)bencil]isoindolina-1-carboxamida (466,2243; 466,2235);
N-[4-(dimetilamino)bencil]-3-oxo-2-(4-fenoxibencil)isoindolina-1-carboxamida ;N-[4-(dimetilamino)bencil]-3-oxo-2-[1-(1-fenil-1H-pirazol-4-il)metil]isoindolina-1-carboxamida (466,2243; 466,2254);
N-[4-(dimetilamino)bencil]-2-[1-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (476,2338; 476,2325);
2-(2-cloro-4-fluorobencil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (487,0894; 487,0908);

N-[4-(dimetilamino)bencil]-3-oxo-2-(1-fenilpropil)isoindolina-1-carboxamida (428,2338; 428,2318);
N-[4-(metilsulfonil)bencil]-3-oxo-2-[2-(1H-pirazol-1-il)bencil]isoindolina-1-carboxamida (501,1596; 501,1581);
2-(2-hidroxi-2-feniletil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (465,1484; 465,1487);
2-(2,2-difeniletil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (525,1848; 525,1848);
2-(difenilmetil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (511,1691; 511,1691);
2-[2-(4-clorofenil)propil]-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida (420,1478; 420,1482);
N-[4-(metilsulfonil)bencil]-3-oxo-2-(1,2,3,4-tetrahidronaftalen-1-il)isoindolina-1-carboxamida (475,1691; 475,1682);
2-(2-cloro-4-fluorobencil)-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida (410,1071; 410,1057);
2-[1-(4-fluorofenil)etil]-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida (390,1617; 390,1623);
(1S)-2-[(2R)-2-(4-clorofenil)propil]-N-(3-metoxipropil)-1-metil-3-oxoisoindolina-1-carboxamida (415,1788; 415,1790);
(1R)-2-[(2R)-2-(4-clorofenil)propil]-N-(3-metoxipropil)-1-metil-3-oxoisoindolina-1-carboxamida (415,1788; 415,1797);
2-[2-(4-clorofenil)propil]-N-(3-metoxipropil)-1-metil-3-oxoisoindolina-1-carboxamida (415,1788; 415,1776);
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-hidroxi-3-oxo-4-(trimetilsilil)isoindolina-1-carboxamida (473,2027; 473,2016);
N-(terc-butil)-2-(3,4- difluorobencil)-5-hidroxi-3-oxo-4-(trimetilsilil)isoindolina-1-carboxamida (447,1915; 447,1912);
N-(terc-butil)-2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (389,1676; 389,1661);
N-(terc-butil)-2-(3,4-difluorobencil)-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida (451,1833; 451,1846);

N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (415,1788; 415,1793);

2-(2-cloro-4-fluorobencil)-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida (452,0977; 452,0974);

2-[3,5-bis(trifluorometil)bencil]-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;

N,2-bis(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida; (443,1319; 443,1297);

N-(3-ciano-4-fluorobencil)-3-oxo-2-(2-feniletil)isoindolina-1-carboxamida (414,1617; 414,1617);

N-(3-ciano-4-fluorobencil)-2-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida (418,1367; 418,1362);

2-bencil-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida (400,1461; 400,1465);

N-(3-ciano-4-fluorobencil)-2-(3,4-difluorobencil)-3-oxoisoindolina-1-carboxamida (436,1273; 436,1272);

2-(bifenil-2-ilmetil)-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida (476,1774; 476,1775);

2-[2-(4-clorofenil)propil]-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida (462,1384; 462,1371);

2-(2-cloro-4-fluorobencil)-N-(3-{[(difluoroacetil)amino]metil}-4-fluorobencil)-3-oxoisoindolina-1-carboxamida (534,1207; 534,1210);

2-[2-(4-clorofenil)propil]-N-(3-{[(difluoroacetil)amino]metil}-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;

N-[3-(aminometil)-4-fluorobencil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (466,1697; 466,1700);

N-[3-(aminocarbonil)-4-fluorobencil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (480,1490; 480,1479);

N-[3-(aminocarbonil)-4-fluorobencil]-2-(2-cloro-4-fluorobencil)-3-oxoisoindolina-1-carboxamida (470,1083; 470,1077);

N-(terc-butil)-3-oxo-2-(4-fenilbutil)isoindolina-1-carboxamida (365,2229; 365,2231);

N-(terc-butil)-3-oxo-2-(1,2,3,4-tetrahidronaftalen-1-il)isoindolina-1-carboxamida (363,2072; 363,2064);

N-(terc-butil)-3-oxo-2-(4-fenoxibencil)isoindolina-1-carboxamida (415,2021; 415,2055);
N-(terc-butil)-3-oxo-2-[2-(1H-pirazol-1-il)bencil]isoindolina-1-carboxamida (389,1977; 389,1992);
N-(terc-butil)-2-(2,2-difeniletil)-3-oxoisoindolina-1-carboxamida (413,2229; 413,2237);
N-(terc-butil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (399.2072; 399.2099);
N-(1,3-benzodioxol-5-ilmetil)-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (381,1814; 381,1772);
2-(2-cloro-4-fluorobencil)-N-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida (412,1228; 412,1213);
N-(1,3-benzodioxol-5-ilmetil)-2-(2-cloro-4-fluorobencil)-3-oxoisoindolina-1-carboxamida (453,1017; 453,0986);
2-(2-cloro-4-fluorobencil)-N-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida (475,1036; 475,1006);
2-[3,5-bis(trifluorometil)bencil]-3-oxo-N-(2-piridin-4-iletil)isoindolina-1-carboxamida (508,1459; 508,1463);
2-[2-(4-clorofenil)propil]-3-oxo-N-(2-piridin-4-iletil)isoindolina-1-carboxamida (434,1635; 434,1630);
2-[3,5-bis(trifluorometil)bencil]-N-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida (496,1459; 496,1419);
2-[2-(4-clorofenil)propil]-N-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida (422,1635; 422,1634);
2-[2-(4-clorofenil)propil]-N-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida (485,1443; 485,1420);
2-[3,5-bis(trifluorometil)bencil]-N-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida;
N-(1,3-benzodioxol-5-ilmetil)-2-[3,5-bis(trifluorometil)bencil]-3-oxoisoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida;
N-(1-bencilpirrolidin-3-il)-2-(2-cloro-4-fluorobencil)-3-oxoisoindolina-1-carboxamida (478,1697; 478,1697);
N-(1-bencilpirrolidin-3-il)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (488,2104; 488,2104);

2-(2-cloro-4-fluorobencil)-N-{[5-(2-furil)isoxazol-3-il]metil}-3-oxoisoindolina-1-carboxamida (466,0970; 466,0988);
2-(2,2-dimetilpropil)-N-{[5-(2-furil)isoxazol-3-il]metil}-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-{[5-(2-furil)isoxazol-3-il]metil}-3-oxoisoindolina-1-carboxamida (550,1201; 550,1180);
2-[2-(4-clorofenil)propil]-N-[3-(1H-imidazol-1-il)propil]-3-oxoisoindolina-1-carboxamida (437,1744; 437,1733);
2-[3,5-bis(trifluorometil)bencil]-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida (536,1772; 536,1783);
2-[2-(4-clorofenil)propil]-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida (462,1948; 462,1909);
N-(1-bencilpirrolidin-3-il)-2-[3,5-bis(trifluorometil)bencil]-3-oxoisoindolina-1-carboxamida (562,1929; 562,1935);
2-[2-(4-clorofenil)propil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida (497,1301; 497,1281);
N-(terc-butil)-3-oxo-2-[(1-fenil-1H-tetrazol-5-il)metil]isoindolina-1-carboxamida (391,1882; 391,1883);
2-[2-(4-clorofenil)propil]-N-[3-(dimetilamino)propil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[2-(dimetilamino)etil]-3-oxoisoindolina-1-carboxamida (400,1791; 400,1766);
2-[2-(4-clorofenil)propil]-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida (420,1478; 420,1465);
N-[2-(4-benzoilpiperazin-1-il)etil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-(1-piridin-3-iletil)isoindolina-1-carboxamida (434,1635; 434,1627);
2-[2-(4-clorofenil)propil]-N-(3-metoxifenil)-3-oxoisoindolina-1-carboxamida (435,1475; 435,1462);
2-[2-(4-clorofenil)propil]-3-oxo-N-(1-piridin-4-iletil)isoindolina-1-carboxamida (434,1635; 434,1620);
2-[2-(4-clorofenil)propil]-N-(4-cianofenil)-3-oxoisoindolina-1-carboxamida (430,1322; 430,1315);

2-[2-(4-clorofenil)propil]-N-(3-metoxipropil)-3-oxoisoindolina-1-carboxamida (401,1632; 401,1633);

N-(1,3-benzodioxol-5-ilmetil)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (463,1424; 463,1411);

2-[2-(4-clorofenil)propil]-N-(3,4-dimetoxibencil)-3-oxoisoindolina-1-carboxamida (479,1737; 479,1748);

2-[2-(4-clorofenil)propil]-N-[(3-metil-5-fenilisoxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida (500,1741; 500,1745);

N-butil-2-[2-(4-clorofenil)propil]-7-fluoro-3-oxoisoindolina-1-carboxamida (403,1588; 403,1577);

N-(terc-butil)-2-[2-(4-clorofenil)propil]-7-fluoro-3-oxoisoindolina-1carboxamida (403,1588; 403,1569);

N-(terc-butil)-3-oxo-2-[2-(fenilsulfonil)etil]isoindolina-1-carboxamida;

N-(terc-butil)-2-[2-(4-fluorofenoxi)propil]-3-oxoisoindolina-1-carboxamida (385,1927; 385,1899);

N-(terc-butil)-3-oxo-2-(2-fenoxipropil)isoindolina-1-carboxamida (367,2021; 367,2033);

N-bencil-2-[(5-metilisoxazol-3-il)metil]-3-oxoisoindolina-1-carboxamida;

N-bencil-2-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;

N-bencil-3-oxo-2-[2-(fenilsulfonil)etil]isoindolina-1-carboxamida (435,1378; 435,1366);

N-bencil-3-oxo-2-(2-fenoxietil)isoindolina-1-carboxamida (387,1708; 387,1705);

N-bencil-3-oxo-2-(2-fenoxipropil)isoindolina-1-carboxamida (401,1865; 401,1888);

N-bencil-2-[2-(4-fluorofenoxi)propil]-3-oxoisoindolina-1-carboxamida (419,1771; 419,1798);

N-bencil-2-[(1-bencil-1H-pirazol-4-il)metil]-3-oxoisoindolina-1-carboxamida (437,1977; 437,1988);

N-bencil-2-[(5-metil-3-fenilisoxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida (438,1817; 438,1818);

N-bencil-3-oxo-2-[(3-fenilisoxazol-5-il)metil]isoindolina-1-carboxamida (424,1661; 424,1669);

N-(terc-butil)-5,6-dicloro-2-(4-cianobencil)-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-5,6-dicloro-2-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida (409,0886; 409,0912);

N-(terc-butil)-5,6-dicloro-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida (421,1085; 421,1078);

N-(terc-butil)-5,6-dicloro-2-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida (457,0897; 457,0864);

N-(terc-butil)-5-fluoro-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida (371,1771; 371,1768);

N-(4-fluorobencil)-3-oxo-2-(2-piridin-4-iletil)isoindolina-1-carboxamida (390,1617; 390,1628);

2-[(1-metil-1H-pirrol-2-il)metil]-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida (428,1586; 428,1586);

N-(2-furilmetil)-3-oxo-2-(2-fenilpropil)isoindolina-1-carboxamida (375,1708; 375,1698);

2-[2-(4-clorofenil)etil]-N-[(5-metil-2-furil)metil]-3-oxoisoindolina-1-carboxamida (409,1319; 409,1317);

N-(4-fluorobencil)-2-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida (378,1617; 378,1609);

N-(2-clorobencil)-2-[2-(1H-indol-3-il)-1-metiletil]-3-oxoisoindolina-1-carboxamida (458,1635; 458,1631);

N-(terc-butil)-5,6-dicloro-2-[2-(4-cloro-2-metilfenil)-2,2-difluoroetil]-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-5,6-dicloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (453,0903; 453,0917);

N-(terc-butil)-2-[2-(4-cloro-2-metilfenil)-2,2-difluoroetil]-3-oxoisoindolina-1-carboxamida (421,1494; 421,1518);

N-bencil-2-[2-(4-cloro-2-metilfenil)-2,2-difluoroetil]-3-oxoisoindolina-1-carboxamida (455,1338; 455,1351);

2-[2-(4-clorofenil)propil]-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (487,1400; 487,1414);

2-[3-(difluorometoxi)bencil]-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida (419,1602; 419,1599);

N-(2-clorobencil)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (453,1136; 453,1123);

2-[4-(difluorometoxi)bencil]-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida (419,1602; 419,1601);

N-(2-clorobencil)-2-(2,5-dimetilbencil)-3-oxoisoindolina-1-carboxamida (419,1526; 419,1513);

2-(bifenil-2-ilmetil)-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida (451,1821; 451,1804);

N-(2-clorobencil)-2-[(1R)-1-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (435,1475; 435,1466);

N-(2-clorobencil)-2-[(1R)-1-(3-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (435,1475; 435,1469);

N-(2-clorobencil)-2-[(1S)-1-(1-naftil)etil]-3-oxoisoindolina-1-carboxamida (455,1526; 455,1518);

N-bencil-3-oxo-2-(4-fenoxibencil)isoindolina-1-carboxamida (449,1865; 449,1849);

N-(2-clorobencil)-3-oxo-2-(3-fenilpropil)isoindolina-1-carboxamida (419,1526; 419,1524);

N-(2-clorobencil)-3-oxo-2-(2-feniletil)isoindolina-1-carboxamida (405,1369; 405,1336);

N-(2-clorobencil)-3-oxo-2-(1-fenilpropil)isoindolina-1-carboxamida (419,1526; 419,1520);

N-(2-clorobencil)-2-(1-metil-3-fenilpropil)-3-oxoisoindolina-1-carboxamida (433,1682; 433,1693);

N-(2-clorobencil)-3-oxo-2-(2-fenilpropil)isoindolina-1-carboxamida (419,1526; 419,1516);

2-(bifenil-2-ilmetil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (501,1790; 501,1790);

2-(bifenil-2-ilmetil)-N-(2-clorobencil)-3-oxoisoindolina-1-carboxamida (467.1526; 467.1514);

3-oxo-2-(1-fenilpropil)-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (453,1790; 453,1809);

3-oxo-2-(2-fenilpropil)-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (453,1790; 453,1777);

2-(1-metil-3-fenilpropil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (467,1946; 467,1926);

3-oxo-2-(2-feniletil)-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (439,1633; 439,1626);

N-bencil-2-[2-(5-bromo-2-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (479,0970; 479,0968);

3-oxo-2-(3-fenilpropil)-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (453,1790; 453,1769);

N-bencil-2-[2-(3-bromo-4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (479,0970; 479,0972);

2-(2-metilbutil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (405,1790; 405,1786);

N-bencil-2-(2,4-difluorobencil)-3-oxoisoindolina-1-carboxamida (393,1414; 393,1432);

2-(ciclohexilmetil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (431,1946; 431,1945);

2-(3-fluorobencil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (443,1382; 443,1384);

2-(2-etoxibencil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida (469,1739; 469,1753);

3-oxo-2-[4-(trifluorometoxi)bencil]-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;

2-[2-(4-clorofenil)propil]-N-[2-(3,4-dimetoxifenil)etil]-3-oxoisoindolina-1-carboxamida (493,1894; 493,1895);

2-[2-(4-clorofenil)propil]-3-oxo-N-[2-(2-tienil)etil]isoindolina-1-carboxamida (439,1247; 439,1242);

2-[2-(4-clorofenil)propil]-N-[2-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (463,1788; 463,1794);

2-[2-(4-clorofenil)propil]-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (433,1682; 433,1679);

2-[2-(4-clorofenil)propil]-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida (387,1475; 387,1483);

2-[2-(4-clorofenil)propil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida (437,1432; 437,1448);

N-bencil-2-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida (423.1520; 423.1511);

N-bencil-2-[3-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida (423,1520; 423,1518);

N-butil-2-(1-naftilmetil)-3-oxoisoindolina-1-carboxamida (373,1916; 373,1883);

N-bencil-2-cicloheptil-3-oxoisoindolina-1-carboxamida (363,2072; 363,2062);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-[2-(4-bromofenil)etil]-3-oxoisoindolina-1-carboxamida;

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(1-etilpropil)-3-oxoisoindolina-1-carboxamida;

N-bencil-3-oxo-2-[3-(1H-pirrol-1-il)bencil]isoindolina-1-carboxamida (422.1868; 422.1874);

N-bencil-2-(3-fluorobencil)-3-oxoisoindolina-1-carboxamida (375,1508; 375,1501);

N-bencil-2-[2-(2-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (401,1865; 401,1854);

N-bencil-2-(2-etoxibencil)-3-oxoisoindolina-1-carboxamida (401,1865; 401,1869);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-3-oxo-2-(2-fenilpropil)isoindolina-1-carboxamida;

N-bencil-2-(4-cianobencil)-3-oxoisoindolina-1-carboxamida (382,1555; 382,1558);

N-bencil-2-(3,5-dimetoxibencil)-3-oxoisoindolina-1-carboxamida (417,181; 417,1806);

N-bencil-2-[1-(1-naftil)etil]-3-oxoisoindolina-1-carboxamida (421,1916; 421,1899);

N-bencil-3-oxo-2-[4-(trifluorometil)bencil]isoindolina-1-carboxamida (425,1477; 425,1482);

N-({2-[3,5-bis(trifluorometil)bencil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)-beta-alaninato de etilo (503,1405; 503,1403);

2-(1-naftilmetil)-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida (403,1841; 403.1844);

N-({2-[2-(3,4-diclorofenil)etil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)-beta-alaninato de etilo (449,1035; 449,1038);

4-({1-[(bencilamino)carbonil]-3-oxo-1,3-dihidro-2H-isoindol-2-il}metil)benzoato de metilo (415,1657; 415,1665);

3-oxo-2-[3-(trifluorometil)bencil]-N-[(trimetilsilil)metil]isoindolina-1-carboxamida (421,1559; 421,1552);

2-[1-(1-naftil)etil]-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida (417,1998; 417,1983);

3-oxo-2-[4-(trifluorometil)bencil]-N-[(trimetilsilil)metil]isoindolina-1-carboxamida (421,1559; 421,1546);

2-[2-(4-bromo fenil)etil]-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida (445,0947; 445,0931);

2-(2-cloro-6-fenoxibencil)-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida (479,1557; 479,1568);

2-(3,4-diclorobencil)-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida (421,0906; 421,0896);

N-bencil-2-(1-bencilpirrolidin-3-il)-3-oxoisoindolina-1-carboxamida (426,2181; 426,2169);

N-bencil-2-(1-bencilpirrolidin-3-il)-4,5-dimetoxi-3-oxoisoindolina-1-carboxamida (486,2392; 486,2405);

N-bencil-2-(3,4-difluorobencil)-4,5-dimetoxi-3-oxoisoindolina-1-carboxamida (453,1626; 453,1620);

N-bencil-2-[2-(4-clorofenil)propil]-4,5-dimetoxi-3-oxoisoindolina-1-carboxamida (479,1737; 479,1729);

N-bencil-4,5-dimetoxi-2-(1-metil-3-fenilpropil)-3-oxoisoindolina-1-carboxamida;

N-bencil-2-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida (360,1712; 360,1697);

N-bencil-3-oxo-2-(1-fenil-2-pirrolidin-1-iletil)isoindolina-1-carboxamida (440.2338; 440.2336);

N-bencil-2-[2-(4-metoxifenil)-2-oxoetil]-3-oxoisoindolina-1-carboxamida (415,1657; 415,1674);

N-bencil-2-[(1R)-1-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (401,1865; 401,1883);

N-bencil-2-(3,4-difluorobencil)-3-oxoisoindolina-1-carboxamida (393,1414; 393,1403);

N-bencil-2-[(1R)-1-(3-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida (401,1865; 401,1859);

N-bencil-2-(2,5-dimetilbencil)-3-oxoisoindolina-1-carboxamida (385,1916; 385,1924);

N-bencil-2-(1-metil-3-fenilpropil)-3-oxoisoindolina-1-carboxamida (399,2072; 399,2062);

N-bencil-3-oxo-2-{2-[3-(trifluorometil)fenil]etil}isoindolina-1-carboxamida (439,1633; 439,1634);

N-bencil-2-[3,5-bis(trifluorometil)bencil]-3-oxoisoindolina-1-carboxamida (493,1350; 493,1341);

N-bencil-2-[2-(6-cloro-1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida (444,1478; 444,1484);

N,2-dibencil-3-oxoisoindolina-1-carboxamida (357,1603; 357,1613);

N-bencil-2-(ciclohexilmetil)-3-oxoisoindolina-1-carboxamida (363,2072; 363,2079);

N-bencil-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida (363,1167; 363,1162);

2-(1,3-benzodioxol-5-ilmetil)-N-ciclohexil-3-oxoisoindolina-1-carboxamida (393,1814; 393,1807);

2-(2-metoxibencil)-N-(4-metilciclohexil)-3-oxoisoindolina-1-carboxamida (393,2178; 393,2169);

N-{[3-oxo-2-(3-pirrolidin-1-ilpropil)-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo (402,2392; 402,2388);

N-(terc-butil)-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida (353,1865; 353,1861);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(2-bromobencil)-3-oxoisoindolina-1-carboxamida;

2-[2-(4-clorofenil)etil]-N-ciclohexil-3-oxoisoindolina-1-carboxamida (397,1682; 397,1648);

N-(2,3-dimetilciclohexil)-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida (383,1793; 383,1778);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida (474,1930; 474,1937);

2-(2-clorobencil)-N-(4-metilciclohexil)-3-oxoisoindolina-1-carboxamida (397,1682; 397,1671);

N-butil-2-(2-ciclohex-1-en-1-iletil)-3-oxoisoindolina-1-carboxamida (341,2229; 341,2213);

N-bencil-2-[(2R)-2-hidroxi-1,2-difeniletil]-3-oxoisoindolina-1-carboxamida (463,2021; 463,2000);

2-(bifenil-2-ilmetil)-N-butil-3-oxoisoindolina-1-carboxamida (399,2072; 399,2090);

2-(bifenil-2-ilmetil)-N-isopropil-3-oxoisoindolina-1-carboxamida (385,1916; 385,1915);

N-{[2-(2-bromobencil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo (459,0919; 459,0904);

2-[2-(4-clorofenil)propil]-N-isopropil-3-oxoisoindolina-1-carboxamida (371,1526; 371,1545);

N-{[3-oxo-2-(2-feniletil)-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de metilo (353,1501; 353,1496);

N-(terc-butil)-2-[1-(2-naftil)etil]-3-oxoisoindolina-1-carboxamida (387,2072; 387,2083);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-[1-(2-naftil)etil]-3-oxoisoindolina-1-carboxamida (462,1930; 462,1919);

2-[2-(3,4-dietoxifenil)etil]-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (473,2440; 473,2461);

2-bencil-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (371,1759; 371,1755);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida (441,2039; 441,2030);

N-bencil-2-(3-metoxibencil)-3-oxoisoindolina-1-carboxamida (387,1708; 387,1705);

2-(2-cloro-4-fluorobencil)-N-ciclopentil-3-oxoisoindolina-1-carboxamida (387,1275; 387,1291);

2-(2-cloro-4-fluorobencil)-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida (410,1071; 410,1057);

2-(2,5-dimetoxibencil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (431,1970; 431,1964);

N-(sec-butil)-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida (371,1526; 371,1496);

N-bencil-2-(2,3-difluorobencil)-3-oxoisoindolina-1-carboxamida (393,1414; 393,1390);

2-(2-cloro-4-fluorobencil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (423,1275; 423,1260);

2-[2-(4-clorofenil)etil]-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (419,1526; 419,1539);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(2-metilbencil)-3-oxoisoindolina-1-carboxamida (412,1773; 412,1747);

N-(terc-butil)-2-(ciclohexilmetil)-3-oxoisoindolina-1-carboxamida (329,2229; 329,2238);

2-(1-metil-3-fenilpropil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida (413,2229; 413,2227);

N-bencil-2-ciclohexil-3-oxoisoindolina-1-carboxamida (349,1916; 349,1906);

N-(terc-butil)-2-(2-ciclohex-1-en-1-iletil)-3-oxoisoindolina-1-carboxamida (341,2229; 341,2216);

N-(terc-butil)-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;

N-{[2-(ciclohexilmetil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo (387,2283; 387,2270);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(2-ciclohex-1-en-1-iletil)-3-oxoisoindolina-1-carboxamida (416,2086; 416,2081);

N-{[2-(bifenil-2-ilmetil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo (457,2127; 457,2120);

N-bencil-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida (337,1916; 337,1917);

N-bencil-2-(3-metilbutil)-3-oxoisoindolina-1-carboxamida (337,1916; 337,1907);

N-bencil-3-oxo-2-[2-(2-tienil)etil]isoindolina-1-carboxamida (377,1323; 377,1326);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-3-oxo-2-(2-feniletil)isoindolina-1-carboxamida (412,1773; 412,1770);

N-bencil-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (419,1526; 419,1497);

N-(terc-butil)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (385,1682; 385,1663);

N-bencil-2-(2-metilbencil)-3-oxoisoindolina-1-carboxamida (371,1759; 371,1779);

N-bencil-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida (387,1708; 387,1711);

N-bencil-3-oxo-2-(2-feniletil)isoindolina-1-carboxamida (371,1759; 371,1746);

N-bencil-2-[1-(2-naftil)etil]-3-oxoisoindolina-1-carboxamida (421,1916; 421,1919);

N-({2-[2-(4-clorofenil)propil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo (401,1268; 401,1258);

N-({2-[1-(2-naftil)etil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de terc-butilo (445,2127; 445,2119);

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (460,1540; 460,1520);

N-butil-2-[1-(2-naftil)etil]-3-oxoisoindolina-1-carboxamida (387,2072; 387,2103);

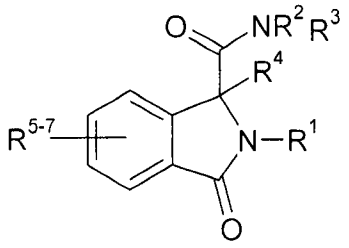
N-bencil-2-(2-bromobencil)-3-oxoisoindolina-1-carboxamida (435,0708; 435,0700);

N-bencil-2-(2-ciclohex-1-en-1-iletil)-3-oxoisoindolina-1-carboxamida (375,2072; 375,2065);
N-bencil-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida (433,1916; 433,1916);
N-butil-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida (385,1682; 385,1676);
2-[2-(4-clorofenil)-2-metilpropil]-N-[(1-isopropil-5-oxopirrolidin-3-il)metil]-3-oxoisoindolina-1-carboxamida (482,221; 482,218);
2-[2-(4-clorofenil)propil]-N-[(1-isopropil-5-oxopirrolidin-3-il)metil]-3-oxoisoindolina-1-carboxamida;
1H-isoindol-1-carboxamida, 2-[2-(4-clorofenil)propil]-2,3-dihidro-N-[2-[(1-metiletil)amino]-2-oxoetil]-3-oxo- (428,1741; 428,174);
N-(terc-butil)-2-[(4',5-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida (435,1884; 435,1892);
N-(terc-butil)-2-[(5-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida (417,1978; 417,1976);
N-(terc-butil)-2-[(4-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida (417,1978; 417,1978);
2-[2-(4-clorofenil)-2-metilpropil]-N-[(1-isopropil-5-oxopirrolidin-3-il)metil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[(1-isopropil-5-oxopirrolidin-3-il)metil]-3-oxoisoindolina-1-carboxamida;
1H-isoindol-1-carboxamida, 2-[2-(4-clorofenil)propil]-2,3-dihidro-N-[2-[(1-metiletil)amino]-2-oxoetil]-3-oxo-;
2-(2,2-dimetilpropil)-6-fluoro-3-oxo-N-(1-feniletil)isoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-6-fluoro-N-(3-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-6-fluoro-N-(2-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-(3-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-(2-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(1-metil-1-feniletil)-3-oxo-N-(1-feniletil)isoindolina-1-carboxamida;
6-fluoro-3-oxo-N,2-bis(1-feniletil)isoindolina-1-carboxamida;
N-(1-metil-1-feniletil)-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;
3-oxo-N,2-bis(1-feniletil)isoindolina-1-carboxamida;
N-(3-fluorobencil)-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;

N-(2-fluorobencil)-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;
(1R o 1S)-2-[(2S o 2R)-2-(4-clorofenil)propil]-3-oxo-N-propilisoindolina-1-carboxamida;
(1S o 1R)-2-[(2R o 2S)-2-(4-clorofenil)propil]-3-oxo-N-propilisoindolina-1-carboxamida;
(1R o 1S)-2-[(2R o 2S)-2-(4-clorofenil)propil]-3-oxo-N-propilisoindolina-1-carboxamida;
(R o S) 2-(bifenil-2-ilmetil)-6-cloro-N-etil-3-oxoisoindolina-1-carboxamida;
(S o R) 2-(bifenil-2-ilmetil)-6-cloro-N-etil-3-oxoisoindolina-1-carboxamida;
N-(4-fluorobencil)-2-[1-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
2-[1-(4-clorofenil)etil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[1-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
2-[1-(4-clorofenil)-1-metiletil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-6-fluoro-2-[1-(4-fluorofenil)-1-metiletil]-3-oxoisoindolina-1-carboxamida;
2-[1-(4-clorofenil)-1-metiletil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
N-(4-fluorobencil)-2-[1-(4-fluorofenil)-1-metiletil]-3-oxoisoindolina-1-carboxamida;
N-bencil-6-fluoro-2-(1-metil-1-feniletil)-3-oxoisoindolina-1-carboxamida;
2-[1-(4-fluorofenil)-1-metiletil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
N-(4-fluorobencil)-2-(1-metil-1-feniletil)-3-oxoisoindolina-1-carboxamida;
2-(1-metil-1-feniletil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(5-cianopentil)-6-fluoro-3-oxoisoindolina-1-carboxamida;
N-bencil-6-bromo-3-oxo-2-(1-fenilpropil)isoindolina-1-carboxamida
N-bencil-2-[2-(4-clorofenil)propil]-4-fluoro-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(4,4-difluorobutil)-4-fluoro-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-4-fluoro-3-oxo-N-propilisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-etil-4-fluoro-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(bifenil-2-ilmetil)-4-fluoro-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(4,4-difluorobutil)-4-fluoro-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-4-fluoro-3-oxo-N-propilisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-etil-4-fluoro-3-oxoisoindolina-1-carboxamida;
N-bencil-4-fluoro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;

Reivindicaciones

1. Un compuesto de fórmula I:



I

o una de sus sales farmacéuticamente aceptables, donde

R^1 representa C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, $-OR^8$, $-COR^9$, $-SR^{10}$, $-COXR^{11}$, $-N(R^{12a})(R^{12b})$, $-N(R^{13a})C(O)OR^{13b}$, $-OC(O)N(R^{14a})(R^{14b})$, $-SO_2R^{15}$, arilo o Het^1); además R^1 representa arilo o Het^2;

R^8 a R^{11}, R^{13a}, R^{13b}, R^{15} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^9 (donde los grupos C_1-C_6 alquilo, arilo y Het^9 están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{10});

R^{12a} y R^{12b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{11} (donde los grupos C_1-C_6 alquilo, arilo y Het^{11} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{12}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{14a} y R^{14b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{13} (donde los grupos C_1-C_6 alquilo, arilo y Het^{13} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{14}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^2 representa C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, -OR^{16}, -COR^{17}, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, trialquilsililo, –$COXR^{18}$, arilo o Het^3); además R^2 representa -$(CH_2)_kN(R^{19a})(R^{19b})$, -$(CH_2)_kNR^{20a}C(O)N(R^{20b})(R^{20c})$, -$(CH_2)_nNR^{21a}SO_2R^{21b}$, -$(CH_2)_nSO_2R^{22}$, -$(CH_2)_kN(R^{23a})C(O)OR^{23b}$, -$OC(O)N(R^{24a})(R^{24b})$, C_3-C_8 cicloalquilo, arilo o Het^4;

R^{16} a R^{18}, R^{21}, R^{22}, R^{23a}, R^{23b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{15} (donde los grupos C_1-C_6 alquilo, arilo y Het^{15} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{16});

R^{19a} y R^{19b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{19} (donde los grupos C_1-C_6 alquilo, arilo y Het^{19} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{20}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{20a}, R^{20b} y R^{20c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{21} (donde los grupos C_1-C_6 alquilo, arilo y Het^{21} están opcionalmente sustituidos con uno o más sustituyentes selecionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{22});
R^{20b} y R^{20c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^3 representa hidrógeno, C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, -OR^{25}, -COR^{26}, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, trialquilsililo, –$COXR^{27}$, arilo o Het^5); además R^3 representa -$(CH_2)_kN(R^{28a})(R^{28b})$, -$(CH_2)_kN(R^{29a})C(O)N(R^{29b})(R^{29c})$, -$(CH_2)_nNR^{30a}SO_2R^{30b}$, -$(CH_2)_nSO_2R^{31}$, -$(CH_2)_kN(R^{32a})C(O)OR^{32b}$, -$OC(O)N(R^{33a})(R^{33b})$, C_3-C_8 cicloalquilo, arilo o Het^6;

R^{25} a R^{27}, R^{30}, R^{31}, R^{32a}, R^{32b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{23} (donde los grupos C_1-C_6 alquilo, arilo y Het^{23} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{24});

R^{28a} y R^{28b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{25} (donde los grupos C_1-C_6 alquilo, arilo y Het^{25} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{26}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{33a} y R^{33b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{27} (donde los grupos C_1-C_6 alquilo, arilo y Het^{27} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{28}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{29a}, R^{29b} y R^{29c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{29} (donde los grupos C_1-C_6 alquilo, arilo y Het^{29} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{30}); R^{29b} y R^{29c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

$\mathbf{R^4}$ representa hidrógeno, –OH, arilo, C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, hidroxi, C_2-C_4 alquenilo, trialquilsililo), $-OR^{34}$, $-(CH_2)_mR^{35}$;

R^{34} representa independientemente, cada vez que aparece, hidrógeno, C_1-C_6 alquilo, arilo o Het^{31} (donde los grupos C_1-C_6 alquilo, arilo y Het^{31} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{32});

R^{35} representa independientemente arilo o Het^{33}(donde los grupos arilo y Het^{33} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{34});

R^5 a R^7 representan independientemente, cada vez que aparecen, hidrógeno, -OH, halógeno, ciano, nitro, C_{1-6} alquilo, $-OR^{36}$, $-N(R^{37a})(R^{37b})$, $-C(O)R^{38}$, $-C(O)OR^{39}$, $-C(O)N(R^{40a})(R^{40b})$, $-NC(O)OR^{41}$, $-OC(O)N(R^{42a})(R^{42b})$, $-N(R^{43a})C(O)R^{43b}$, $-N(R^{44a})S(O)_2R^{44b}$, $-S(O)_2R^{45}$, $-OS(O)_2R^{46}$, $-(CH_2)_nN(R^{47a})(R^{47b})$, $-(CH_2)_nNR^{48a}C(O)N(R^{48b})(R^{48c})$, $-(CH_2)_nNR^{49a}SO_2R^{49b}$, trialquilsililo, arilo o Het^7;

R^{36}, R^{38}, R^{39}, R^{41}, R^{43}, R^{44a}, R^{44b}, R^{45}, R^{46}, R^{49a} y R^{49b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{35} (donde los grupos C_1-C_6 alquilo, arilo y Het^{35} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{36});

R^{37a} y R^{37b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{37} (donde los grupos C_1-C_6 alquilo, arilo y Het^{37} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{38}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{40a} y R^{40b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{39} (donde los grupos C_1-C_6 alquilo, arilo y Het^{39} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{40}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{42a} y R^{42b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{41} (donde los grupos C_1-C_6 alquilo, arilo y Het^{41} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{42}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{47a} y R^{47b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{43} (donde los grupos C_1-C_6 alquilo, arilo y Het^{43} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{44}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{48a}, R^{48b} y R^{48c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{45} (donde los grupos C_1-C_6 alquilo, arilo y Het^{45} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{46}) R^{48b} y R^{48c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

arilo está independientemente, cada vez que aparece, opcionalmente sustituido con –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, C_3-C_8 cicloalquilo, C_2-C_6 alquenilo, fenilo, Het^8, -OR^{50}, -$(CH_2)_mR^{51}$, -SR^{52}, -$C(O)R^{53}$, -$COXR^{54}$, -$N(R^{55a})(R^{55b})$, -SO_2R^{56}, -$OS(O)_2R^{57}$, -$(CH_2)_mN(R^{58a})(R^{58b})$, -$CH_2)_mNR^{59a}C(O)N(R^{59b})(R^{59c})$, -$C(O)OR^{60}$, -$C(O)N(R^{61a})(R^{61b})$, -$N(R^{62a}C(O)R^{62b}$, -$N(R^{63a})C(O)OR^{63b}$, -$OC(O)N(R^{64a})(R^{64b})$, -$N(R^{65a})S(O)_2R^{65b}$ y $OC(O)R^{66}$;

R^{50} a R^{54}, R^{56}, R^{57}, R^{60}, R^{62a}, R^{62b}, R^{63a}, R^{63b}, R^{65a}, R^{65b} y R^{66} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{47} (donde los grupos C_1-C_6 alquilo, arilo y Het^{47} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{48});

R^{51} representa independientemente arilo o Het^{49} (donde los grupos arilo y Het^{49} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{50});

R^{55a} y R^{55b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{51} (donde los grupos C_1-C_6 alquilo, arilo y Het^{51} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro,

C_1-C_6 alquilo, arilo y Het^{52}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{58a} y R^{58b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{53} (donde los grupos C_1-C_6 alquilo, arilo y Het^{53} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{54}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{59a} representa independientemente, cada vez que aparece, hidrógeno, C_1-C_6 alquilo, arilo o Het^{55} (donde los grupos C_1-C_6 alquilo, arilo y Het^{55} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{56});
R^{59b} y R^{59c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{61a} y R^{61b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{57} (donde los grupos C_1-C_6 alquilo, arilo y Het^{57} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{58});
o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{64a} y R^{64b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{59} (donde los grupos C_1-C_6 alquilo, arilo y Het^{59} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{60});

Het^1 a Het^{60} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde los grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro, C_{1-6} alquilo, C_{2-6} alquenilo, arilo, otro Het, $-OR^{67}$,

$-(CH_2)_mR^{68}$, $-SR^{69}$, $-COXR^{70}$, $-N(R^{71a})(R^{71b})$, $-SO_2R^{72}$, $-(CH_2)_mN(R^{73a})(R^{73b})$, $-(CH_2)_mNR^{74a}C(O)N(R^{74b})(R^{74c})$, $-C(O)R^{75}$, $-C(O)OR^{76}$, $-C(O)N(R^{77a})(R^{77b})$, $-N(R^{78a})C(O)R^{78b}$, $-N(R^{79a})S(O)_2R^{79b}$, $OC(O)R^{80}$, $-NC(O)OR^{81}$, $-OC(O)N(R^{82a})(R^{82b})$;

R^{67}, R^{69}, R^{70}, R^{72}, R^{75}, R^{76}, R^{78a}, R^{78b}, R^{79a}, R^{79b}, R^{80} o R^{81} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{61} (donde los grupos C_1-C_6 alquilo, arilo y Het^{61} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{62});

R^{68} representa independientemente arilo o Het^{63}(donde los grupos arilo y Het^{63} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{64});

R^{71a} y R^{71b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{65} (donde los grupos C_1-C_6 alquilo, arilo y Het^{65} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{66}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{73a} y R^{73b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{67} (donde los grupos C_1-C_6 alquilo, arilo y Het^{67} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{68});
o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{74a}, R^{74b} y R^{74c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{69} (donde los grupos C_1-C_6 alquilo, arilo y Het^{69} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{70});
R^{74b} y R^{74c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

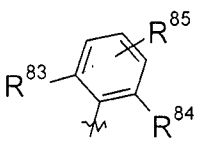
R^{77a} y R^{77b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{71} (donde los grupos C_1-C_6 alquilo, arilo y Het^{71} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{72});
o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{82a} y R^{82b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{73} (donde los grupos C_1-C_6 alquilo, arilo y Het^{73} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{74}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

Het^{61} a Het^{74} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde los grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro y C_{1-6} alquilo;

X representa un átomo de nitrógeno u oxígeno;
m es un número entero entre 0 y 10;
n es un número entero entre 0 y 4;
k es un número entero entre 1 y 5;
siempre que:

a) R^2 o R^3 no representen un fragmento de fórmula



donde

R^{83} y R^{84} representan independientemente, cada vez que aparecen, halógeno, C_1-C_{12} alquilo, C_1-C_{12} alcoxi, C_1-C_{12} haloalquilo, C_1-C_{12} haloalcoxi, ciano, $-SR^{86}$, $-N(R^{87a})R^{87b}$, C_2-C_6 alquinilo, arilo o Het^{75};

R^{85} representa hidrógeno, un grupo C_1-C_{12} alquilo o un grupo C_1-C_{12} alcoxi (donde los grupos C_1-C_{12} alquilo y C_1-C_{12} alcoxi están opcionalmente sustituidos con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_2-C_6 alquinilo, ciano, oxo, arilo, Het^{76}, $-OR^{88}$, $-SR^{89}$, $-COXR^{90}$, $-N(R^{91a})R^{91b}$ y $-SO_2R^{92}$);

Het^{75} a Het^{76} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde los grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro, C_{1-6} alquilo, C_{1-6} alcoxi, arilo, ariloxi, $-N(R^{93a})R^{93b}$, $-C(O)R^{93c}$, $-C(O)OR^{93d}$, $-C(O)N(R^{93e})R^{93f}$, $-N(R^{93g})C(O)R^{93h}$ y $-N(R^{93i})S(O)_2R^{93j}$, $OC(O)R^{93k}$ y otro Het;
R^{86} a R^{93} representan independientemente, cada vez que aparecen, hidrógeno o C_{1-6} alquilo;

b) el compuesto no sea:
2-(4-nitrofenil)-3-(pirrolidin-1-ilcarbonil)isoindolin-1-ona;
N,2-dibencil-3-oxoisoindolina-1-carboxamida;
N,2-dietil-3-oxoisoindolina-1-carboxamida;
N,2-dibutil-3-oxoisoindolina-1-carboxamida;
N,2-didodecil-3-oxoisoindolina-1-carboxamida;
N,2-bis(4-metoxibencil)-3-oxoisoindolina-1-carboxamida;
3-oxo-N,2-dipropilisoindolina-1-carboxamida;
N,2-diheptil-3-oxoisoindolina-1-carboxamida;
3-oxo-N,2-difenilisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-propilisoindolina-1-carboxamida;
N-(terc-butil)-1-metil-3-oxo-2-propilisoindolina-1-carboxamida;
N,1-dimetil-3-oxo-2-propilisoindolina-1-carboxamida;
N-ciclohexil-3-oxo-2-propilisoindolina-1-carboxamida;
N-(fenil)-3-oxo-2-propilisoindolina-1-carboxamida;

2-bencil-N-terc-butil-3-oxoisoindolina-1-carboxamida:
2-bencil-N,1-dimetil-3-oxoisoindolina-1-carboxamida;
2-bencil-N-terc-butil-1-metil-3-oxoisoindolina-1-carboxamida;
2-bencil-N,1-dimetil-3-oxoisoindolina-1-carboxamida;
(4-{1-[(terc-butilamino)carbonil]-3-oxo-1,3-dihidro-2H-isoindol-2-il}butil)carbamato de terc-butilo;
2-bencil-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
2-bencil-N-butil-3-oxoisoindolina-1-carboxamida;
2-bencil-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida;
2-(2-hidroxietil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
N-butil-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida;
2-(2-hidroxietil)-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida;
2-(3-(1H-imidazol-1-il)propil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
N-butil-2-[3-(1H-imidazol-1-il)propil]-3-oxoisoindolina-1-carboxamida;
2-[3-(1H-imidazol-1-il)propil]-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida
2-(ciclohexil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
N-butil-2-ciclohexil-3-oxoisoindolina-1-carboxamida;
2-ciclohexil-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida;
N,2-dibencil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-bencil-2-terc-butil-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida;
N-bencil-2-terc-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N,2-dibencil-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida;
N-bencil-2-terc-butil-5-hidroxi-3-oxoisoindolina-1-carboxamida;
2-ciclohexil-N-hexil-3-oxoisoindolina-1-carboxamida;
N,2-dihexil-3-oxoisoindolina-1-carboxamida;
N-hexil-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida;
N-hexil-2-(4-hidroxibutil)-3-oxoisoindolina-1-carboxamida;
N,2-diciclohexil-3-oxoisoindolina-1-carboxamida;
N-ciclohexil-2-hexil-3-oxoisoindolina-1-carboxamida;
N-ciclohexil-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida;
N-ciclohexil-2-(4-hidroxibutil)-3-oxoisoindolina-1-carboxamida;

(4-{1-[(ciclohexilamino)carbonil]-3-oxo-1,3-dihidro-2H-isoindol-2-il}butil)carbamato de terc-butilo;

N-adamantan-1-il-2-ciclohexil-3-oxoisoindolina-1-carboxamida;

N-adamantan-1-il-2-hexil-3-oxoisoindolina-1-carboxamida;

N-adamantan-1-il-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida;

N-adamantan-1-il-2-(2-morfolin-4-iletil)-3-oxoisoindolina-1-carboxamida

N,2-dibencil-5-{[(2-nitrofenil)sulfonil]amino}-3-oxoisoindolina-1-carboxamida;

[1-(terc-butilcarbamoil)-3-oxo-1,3-dihidro-2H-isoindol-2-il]acetato de etilo;

N-[2-(3,4-dimetoxifenil)etil]-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida

N-ciclopentil-2-(3-metoxibencil)-3-oxoisoindolina-1-carboxamida;

2-(1,3-benzodioxol-5-ilmetil)-N-{[(4-metilfenil)sulfonil]metil}-3-oxoisoindolina-1-carboxamida;

N-ciclohexil-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida;

2-bencil-N-ciclohexil-3-oxoisoindolina-1-carboxamida;

N-{[(4-metilfenil)sulfonil]metil}-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida;

2-(4-clorobencil)-N-{[(4-metilfenil)sulfonil]metil}-3-oxoisoindolina-1-carboxamida;

N-ciclohexil-2-(2-furilmetil)-3-oxoisoindolina-1-carboxamida;

2-(4-clorobencil)-N-ciclohexil-3-oxoisoindolina-1-carboxamida;

{1-bencil-2-hidroxi-3-[(2-hidroxi-3-{[(3-oxo-2,3-dihidro-1H-isoindol-1-il)carbonil]amino}-4-fenilbutil)amino]propil}carbamato de terc-butilo;

1-hidroxi-2-metil-3-oxo-N-(piridin-2-ilmetil)isoindolina-1-carboxamida;

N-[3-(dimetilamino)propil]-1-hidroxi-2-(2-hidroxietil)-3-oxoisoindolina-1-carboxamida;

N-(3-azepan-1-ilpropil)-1-hidroxi-3-oxo-2-fenilisoindolina-1-carboxamida;

2-benzoil-1-hidroxi-3-oxo-N-fenilisoindolina-1-carboxamida;

3-oxo-N,2-difenilisoindolina-1-carboxamida;

ácido 6-{[(1-metil-2-octil-3-oxo-2,3-dihidro-1H-isoindol-1-il)carbonil]amino}hexanoico;

N-(metil)-2-benzoil-1-hidroxi-3-oxoindolina-1-carboxamida;

N-(fenil)-2-benzoil-1-hidroxi-3-oxoisoindolina-1-carboxamida;ácido 6-[(2-alil-1-metil-3-oxoisoindolina-1-carbonil)-amino]-hexanoico;N-{(1S,2R)-1-(3,5-difluorobencil)-3-[(3-etilbencil)amino]-2-hidroxipropil}-2-etil-3-oxoisoindolina-1-carboxamida;

N1-ciclopentil-N4-(2,6-difluorofenil)-2-(2,4-dimetilfenil)-5-metil-3-oxoisoindolina-1,4-dicarboxamida;

[1-(terc-butilcarbamoil)-3-oxo-1,3-dihidro-2H-isoindol-2-il]acetato de metilo;
1-hidroxi-2-metil-3-oxoisoindolina-1-carbohidrazida;
1-hidroxi-3-oxo-fenilisoindolina-1-carbohidrazida;
o una de sus sales farmacéuticamente aceptables;

c) el compuesto no sea:
2-(2-etoxietil)-N-isopropil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-(3-pirrolidin-1-ilpropil)isoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-(tetrahidrofuran-2-ilmetil)isoindolina-1-carboxamida;
2-[1-(hidroximetil)butil]-N-isopropil-3-oxoisoindolina-1-carboxamida;
N-isopropil-2-(3-metilbutil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-ciclohexil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(3-metilbutil)-3-oxoisoindolina-1-carboxamida;
N-{[2-(3-metilbutil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de metilo;
N-({2-[1-(hidroximetil)butil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de terc-butilo;
N-{[2-(3-metilbutil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
N-(terc-butil)-2-[1-(metoximetil)propil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(dietilamino)etil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[1-(hidroximetil)butil]-3-oxoisoindolina-1-carboxamida;
N-{[3-oxo-2-(2-tienilmetil)-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
N-({2-[2-(metiltio)etil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de terc-butilo;
N-{[2-(ciclopropilmetil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de metilo;
o
2-(2,2-dimetilpropil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida.

2. Un compuesto de acuerdo con la reivindicación 1 donde R^1 representa C_1-C_7 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, -OR^8, -$COXR^{10}$, arilo o Het^1); además R^1 representa Het^2.

3. Un compuesto de acuerdo con la reivindicación 1 donde R^1 representa C_1-C_7 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, -OR^8, -$COXR^{10}$, fenilo, naftaleno o Het^1).

4. Un compuesto de acuerdo con la reivindicación 1, donde R^1 representa (1-bencilpirrolidin-3-ilo); (1-fluoro-3-fenil-propan-2-ilo); (1-metil-5-fenil-pirazol-3-il)metilo; (1-metilpirrol-2-il)metilo; (2,3-difluorofenil)metilo; (2,4-difluorofenil)metilo; (2,5-dimetoxifenil)metilo
(2,5-dimetilfenil)metilo; (2-bromofenil)metilo; (2-cloro-4-fluorofenil)metilo
(2-cloro-6-fenoxifenil)metilo; (2-clorofenil)metilo; (2-dimetilamino-2-feniletilo); (2-etoxifenil)metilo; (2-fluorofenil)metilo; (2-metoxifenil)metilo;
(2-metil-2-fenilpropilo); (2-metilfenil)metilo; (2-fenoxifenil)metilo; (2-fenilfenil)metilo;
(2-piridin-3-ilfenil)metilo; (3,4-diclorofenil)metilo; (3,4-difluorofenil)metilo; (3,5-dimetoxifenil)metilo; (3-clorofenil)metilo;
(3-ciano-4-fluorofenil)metilo; (3-cianofenil)metilo; (3-fluorofenil)metilo; (3-hidroxi-2,2-dimetilpropilo); (3-metoxifenil)metilo; (3-fenil-1,2-oxazol-5-il)metilo; (3-fenilfenil)metilo;
(3-pirrol-1-ilfenil)metilo; (4-clorofenil)metilo;
(4-dimetilaminofenil)metilo; (4-fluorofenil)metilo; (4-hidroxifenil)metilo;
(4-metoxicarbonilfenil)metilo; (4-fenoxifenil)metilo; (4-fenilfenil)metilo; (5-metil-2-fenil-1,3-oxazol-4-il)metilo; (5-metil-3-fenil-1,2-oxazol-4-il)metilo;
(fenilpiridin-2-ilmetilo); [(1R)-1-(4-metoxifenil)etilo]; [(1S)-1-feniletilo]; [(1R)-1-feniletilo]; [(1R)-2-(4-clorofenil)-1-(4,4,4- trifluorobutilcarbamoil)etilo]; [(1R)-2-(4-clorofenil)-1-metoxicarbonil-etilo]; [(1S)-1-naftalen-1-iletilo]; [(2R)-2-(4-clorofenil)propilo]; [(2S)-2-(4-clorofenil)propilo]; [(4-clorofenil)-piridin-4-ilmetilo]; [(4-fluorofenil)-piridin-3-ilmetilo]; [(4-fluorofenil)-piridin-3-ilmetilo]; [(4-fluorofenil)-piridin-3-ilmetilo]; [2-(2,4-diclorofenil)fenil]metilo; [2-(2,4-difluorofenil)fenil]metilo; [2-(2,5-difluorofenil)fenil]metilo; [2-(2-clorofenil)fenil]metilo; [2-(3,4-diclorofenil)fenil]metilo; [2-(3,4-difluorofenil)fenil]metilo; [2-(3-cloro-4-fluorofenil)fenil]metilo; [2-(3-fluorofenil)fenil]metilo; [2-(4-cloro-2-metilfenil)-2,2-difluoroetilo]; [2-(4-cloro-2-metilfenil)-2,2-difluoroetilo]; [2-(4-clorofenil)fenil]metilo; [2-(4-fluoro-2-metilfenil)fenil]metilo; [2-(4-fluorofenoxi)fenil]metilo; [2-(4-fluorofenil)fenil]metilo; [2-

(4-metoxifenil)-2-oxo-etilo]; [2-(4-metoxifenil)fenil]metilo; [2-(4-metilfenil)fenil]metilo; [2-(trifluorometil)fenil]metilo; [2-[4-(trifluorometil)fenoxi]fenil]metilo; [3-(difluorometoxi)fenil]metilo; [3,5-bis(trifluorometil)fenil]metilo; [4-(difluorometoxi) fenil]metilo; [4-(trifluorometil)fenil]metilo; 1-(1H-indol-3-il)propan-2-ilo; 1-(4-fluorofenil)etilo; 1-naftalen-1-iletilo; 1-naftalen-2-iletilo; 1-feniletilo; 1-fenilpropilo; 2-(1-ciclohexenil)etilo; 2-(2-etoxifenil)etilo; 2-(2-metoxifenil)etilo; 2-(2-fenoxifenil)etilo; 2-(3,4-diclorofenil)etilo; 2-(3,5-dimetoxifenil)etilo; 2-(3-bromo-4-metoxifenil)etilo; 2-(3-fluorofenil)etilo; 2-(4-bromofenil)etilo; 2-(4-clorofenil)etilo; 2-(4-clorofenil)propilo; 2-(4-fluorofenoxi)propilo; 2-(4-fluorofenil)etilo; 2-(4-fluorofenil)propilo; 2-(4-fenoxifenil)etilo; 2-(4-metoxifenil)etilo; 2-(4-metoxifenil)etilo; 2-(4-fenilfenil)etilo; 2-(5-bromo-2-metoxifenil)etilo; 2-(6-cloro-1H-indol-3-il)etilo; 2,2-dimetilpropilo; 2,2-difeniletilo; 2-[2-(trifluorometoxi)fenil]etilo; 2-[3-(trifluorometil)fenil]etilo; 2-[4-(dietilcarbamoil) fenil]etilo; 2-[4-(trifluorometil)fenil]etilo; 2-benzo[1,3]dioxol-5-iletilo; 2-metilbutilo; 2-metilpropilo; 2-naftalen-1-ilpropilo; 2-fenoxipropilo; 2-fenilpropilo; 2-tiofen-2-iletilo; 3,3-dimetilbutilo; 3-fenilpropilo; 3-pirrolidin-1-ilpropilo; 4-fenilbutan-2-ilo; 4-fenilbutilo; 9H-fluoren-9-ilo; benzhidrilo; bencilo; cicloheptilo; ciclohexilo; ciclohexilmetilo; naftalen-1-ilmetilo; pentan-3-ilo; fenetilo; tiofen-2-ilmetilo; 2-fenilpropan-2-ilo; 1-fenilpropilo; [2-(4-clorofenil)-2-metilpropilo]; [4-fluoro-2-(4-fluorofenil)fenil]metilo; (4-fluoro-2-fenilfenil)metilo; [5-fluoro-2-(4-fluorofenil)fenil]metilo; (5-fluoro-2-fenilfenil)metilo; 1-(4-fluorofenil)etilo; 2-(4-clorofenil)propan-2-ilo; 2-(4-fluorofenil)propan-2-ilo; o 1-(4-clorofenil)etilo.

5. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 4 donde R^2 representa C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre fluoro, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, $-COR^{17}$, trimetilsililo, $-COXR^{18}$, arilo o Het^3);
además R^2 representa arilo o Het^4.

6. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5 donde R^2 representa
(1-bencilpirrolidin-3-ilo); (1-metilpirrol-2-il)metilo; (2,2-difluorobenzo[1,3]dioxol-5-il)metilo; (2,3-dimetilciclohexilo); (2,4-difluorofenil)metilo; (2-cloro-4-

metilsulfonilfenil)metilo; (2-clorofenil)metilo; (2-fluoro-4-metilsulfonilfenil)metilo; (2-hidroxifenil)metilo; (2-metilpropan-2-il)oxicarbonilmetilo; (3,4-diclorofenil)metilo; (3,4-difluorofenil)metilo; (3,4-dimetoxifenil)metilo; (3-carbamoil-4-fluorofenil)metilo; (3-clorofenil)metilo; (3-ciano-4-fluorofenil)metilo; (3-cianofenil)metilo; (3-metoxifenilo); (3-metil-5-fenil-1,2-oxazol-4-il)metilo; (4-amino-2-metilpirimidin-5-il)metilo; (4-carbamoilfenilo); (4-carbamoilfenil)metilo; (4-ciano-2,6-difluorofenil)metilo; (4-cianofenilo); (4-cianofenil)metilo; (4-dimetilaminofenil)metilo; (4-fluorofenil)metilo; (4-hidroxifenil)metilo; (4-metilciclohexilo); (4-metilsulfonilfenil)metilo; (5-metil-1,2-oxazol-3-il)metilo; (5-metil-2-furil)metilo; (5-metil-2-fenil-1,3-oxazol-4-il)metilo; (5-metilpirazin-2-il)metilo; [2-(trifluorometil)fenil]metilo; [3-(aminometil)-4-fluorofenil]metilo; [3-(difluorometoxi)fenil]metilo; [3-(dimetilcarbamoil)-4-fluorofenil]metilo; [3-(trifluorometil)fenil]metilo; [3,5-bis(trifluorometil)fenil]metilo; [3-[[(2,2-difluoroacetil)amino]metil]-4-fluorofenil]metilo; [4-(acetamidometil)fenil]metilo; [4-(aminometil)fenilo]; [4-(difluorometoxi)fenil]metilo; [4-(trifluorometil)fenil]metilo; [4-[[(2,2-difluoroacetil)amino]metil]fenilo]; [4-[[(2-fluoroacetil)amino]metil]fenil]metilo; [5-(2-furil)1,2-oxazol-3-il]metilo; [6-(trifluorometil)piridin-3-il]metilo; 1H-indol-3-ilmetilo; 1-piridin-4-iletilo; 2-(1H-indol-3-il)etilo; 2-(2,4-diclorofenil)etilo; 2-(2,6-diclorofenil)etilo; 2-(2-clorofenil)etilo; 2-(3,4-diclorofenil)etilo; 2-(3,4-dimetoxifenil)etilo; 2-(3-clorofenil)etilo; 2-(3-fluorofenil)etilo; 2-(4-benzoilpiperazin-1-il)etilo; 2-(4-clorofenil)etilo; 2-(4-fluorofenil)etilo; 2-(4-metoxifenil)etilo; 2-[3-(trifluorometil)fenil]etilo; 2-benzo[1,3]dioxol-5-iletilo; 2-etoxicarboniletilo; 2-furilmetilo; 2-metoxietilo; 2-piridin-2-iletilo; 2-piridin-4-iletilo; 2-tiofen-2-iletilo; 3-imidazol-1-ilpropilo; 3-metoxipropilo; 4,4,4-trifluorobutilo; 4,4-difluorobutilo; benzo[1,3]dioxol-5-ilmetilo; benzotriazol-1-ilmetilo; bencilo; butilo; ciclohexilo; etilo; metoxicarbonilmetilo; fenetilo; propan-2-ilo; propilo; piridin-3-ilmetilo; piridin-4-ilmetilo; terc-butilo; trimetilsililmetilo; (5-oxo-1-propan-2-il-pirrolidin-3-il)metilo; propan-2-ilcarbamoilmetilo; (2-fluorofenil)metilo; (3-fluorofenil)metilo; 1-feniletilo; 2-fenilpropan-ilo o 5-cianopentilo.

7. Un compuesto de acuerdo con la reivindicación 1 donde R^1 representa C_1-C_7 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre fluoro, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, -OR^8, -$COXR^{11}$, arilo o Het^1); además R^1 representa Het^2; y

R^2 representa C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre fluoro, C_2-C_6 alquenilo, C_3-C_7 cicloalquilo, $-COR^{17}$, trimetilsililo, $-COXR^{18}$, arilo o Het^3); además R^2 representa arilo o Het^4.

8. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 7 donde R^3 representa hidrógeno, C_1-C_4 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre fluoro, C_2-C_6 alquenilo, trialquilsililo, $-COXR^{27}$, arilo o Het^5).

9. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8 donde R^3 representa hidrógeno.

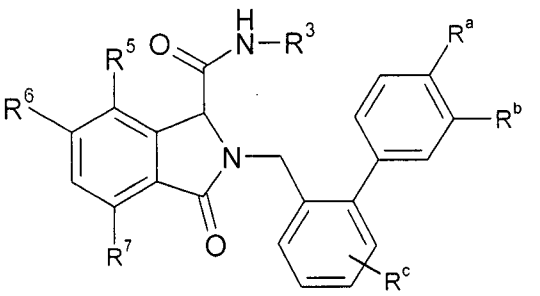
10. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9 donde R^4 representa hidrógeno.

11. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 al 10 donde R^5 a R^7 representan independientemente, cada vez que aparecen, hidrogeno, -OH, halógeno, ciano, C_{1-6} alquilo, $-OR^{36}$, $-C(O)N(R^{40a})(R^{40b})$, $-N(R^{44a})S(O)_2R^{44b}$.

12. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 11 donde arilo está, independientemente, cada vez que aparece, opcionalmente sustituido con –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, $-OR^{50}$, C_2-C_6 alquenilo, arilo, Het^8; donde R^{50} representa C_1-C_6 alquilo o fenilo.

13. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 12 donde arilo es, cada vez que aparece, fenilo.

14. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde el compuesto de fórmula I es



en la cual R^a es hidrógeno o fluoro;

R^b es hidrógeno o fluoro;

R^c es hidrógeno o fluoro;

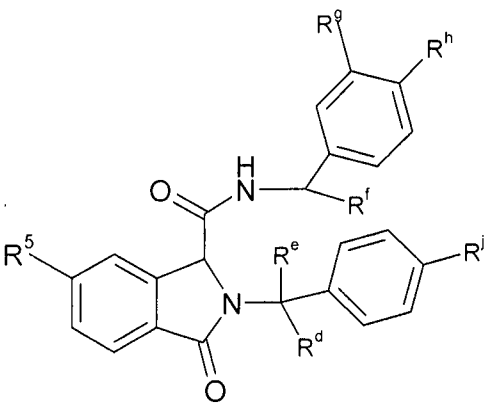
R^3 es C_{1-4} alquilo opcionalmente terminalmente sustituido con 1, 2 ó 3 fluoro;

R^5 es hidrógeno o C_{1-4} alquilo,

R^6 es hidrógeno, OH, halo o C_{1-4} alcoxi;

R^7 es hidrógeno o halo.

15. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde el compuesto de fórmula I es



en la cual

R^d es hidrógeno o C_{1-4} alquilo;

R^e es hidrógeno o C_{1-4} alquilo;

R^f es hidrógeno o C_{1-4} alquilo;

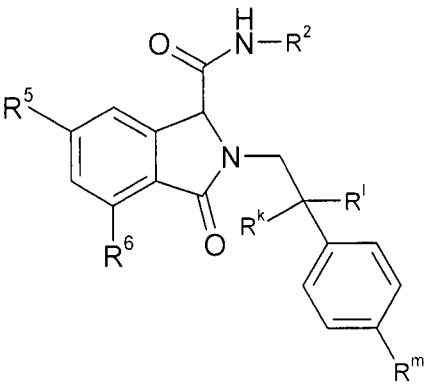
R^g es hidrógeno o halo;

R^h es hidrógeno o halo;

R^j es hidrógeno o halo;

R^5 es hidrógeno o halo.

16. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde el compuesto de fórmula I es



en la cual

R^k es hidrógeno o C_{1-4} alquilo;

R^l es hidrógeno o C_{1-4} alquilo;

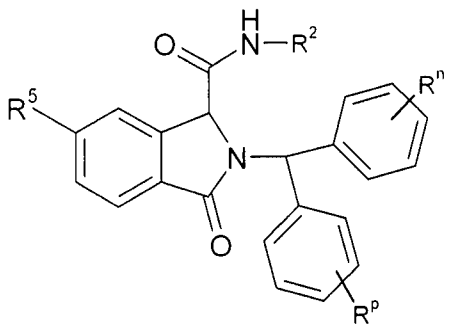
R^m es hidrógeno o halo;

R^2 es C_{3-6} alquilo;

R^5 es hidrógeno o halo;

R^6 es hidrógeno o halo.

17. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde el compuesto de fórmula I es



en la cual

R^n es hidrógeno o halo;

R^p es hidrógeno o halo;

R^2 es C_{3-6} alquilo o bencilo, opcionalmente sustituido con halo en el anillo fenilo;

R^5 es hidrógeno o halo.

18. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^1 es (2-fenilfenil)metilo, opcionalmente sustituido con uno a tres fluoro;

R^2 se selecciona entre etilo, propilo, n-butilo, terc-butilo, 4,4,4-trifluorobutilo, 4,4-difluorobutilo, 4-fluorobutilo, benzo[1,3]dioxol-5-il-metilo, (2,2-difluorobenzo[1,3]dioxol-5-il)metilo, bencilo, (2-clorofenil)metilo, (4-fluorofenil)metilo, (2-trifluorometilfenil)metilo, (3-cianofenil)metilo, (4-cianofenil)metilo, (3-ciano-4-fluorofenil)metilo, (4-carbamoilfenil)metilo, (5-metilpirazin-2-il)metilo, piridin-3-ilmetilo, (4-amino-2-metilpirimidin-5-il)metilo, [6-(trifluorometil)piridin-3-il]metilo, piridin-3-ilmetilo [6-(trifluorometil)piridin-3-il]metilo, piridin-4-ilmetilo, [4-[[(2,2-difluoroacetil)amino]metil]fenil]metilo, [4-(acetamidometil)fenil]metilo, [4-[[(2-fluoroacetil)amino]
metil]fenil]metilo, 2-feniletilo o 2-(4-fluorofenil)etilo;

R^5 a R^7 se seleccionan independientemente entre –OH, metilo, metoxi, cloro, fluoro, ciano, metilsulfonilamino, fluorometoxi, difluorometoxi, trifluorometanosulfonato;

o uno de sus enantiómeros.

19. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^1 es benzhidrilo, opcionalmente sustituido con uno o más sustituyentes seleccionados entre fluoro o cloro;

R^2 se selecciona entre etilo, propilo, butilo, terc-butilo, 4,4-difluorobutilo, 4,4,4-trifluorobutilo, bencilo, (2-cloro-4-metilsulfonilfenil)metilo, (4-metilsulfonilfenil)metilo, (2-fluoro-4-metilsulfonilfenil)metilo, (4-metilsulfonilfenil)metilo, (2-hidroxifenil)metilo, [2-(trifluorometil)fenil]metilo, (2,4-difluorofenil)metilo, (2-clorofenil)metilo o 2-(4-fluorofenil)etilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, metoxi, fluoro o cloro; o uno de sus enantiómeros.

20. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde R^1 es 4-fenilbutan-2-ilo, opcionalmente sustituido con uno o más sustituyentes seleccionados entre fluoro o cloro;

R^2 se selecciona entre (2-clorofenil)metilo, [2-(trifluorometil)fenil]metilo, bencilo, 2-feniletilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, metoxi, fluoro o cloro; o uno de sus enantiómeros.

21. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde R^1 es 3,3-dimetilbutilo;

R^2 se selecciona entre [3-(difluorometoxi)fenil]metilo, [3-(trifluorometoxi)fenil]metilo, 2-(1H-indol-3-il)etilo, 1H-indol-3-ilmetilo, (3-clorofenil)metilo, (3,4-diclorofenil)metilo, [4-(difluorometoxi)fenil]metilo, 2-(3-fluorofenil)etilo, 2-benzo[1,3]dioxol-5-iletilo, 2-[3-(trifluorometil)fenil]etilo, 2-(3,4-diclorofenil)etilo, 2-(2,4-diclorofenil)etilo, 2-(2,6-diclorofenil)etilo, 2-(4-clorofenil)etilo, 2-(3-clorofenil)etilo o 2-(2-clorofenil)etilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, metoxi, fluoro o cloro; o uno de sus enantiómeros.

22. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde R^1 es bencilo, opcionalmente sustituido con uno o más sustituyentes seleccionados entre fluoro, cloro o ciano;
R^2 se selecciona entre etilo, n-propilo, isopropilo, n-butilo, sec-butilo, terc-butilo, benzo[1,3]dioxol-5-il-metilo, bencilo, 1-feniletilo, 2-feniletilo, ciclopentilo, donde los grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre fluoro, cloro, ciano y trifluorometilo; además R^2 representa piridin-3-ilmetilo, piridin-4-ilmetilo, [3-[[(2,2-difluoroacetil)amino]metil]-4-fluorofenil]metilo, [4-(difluorometoxi) fenil]metilo, (4-dimetilaminofenil)metilo, [5-(2-furil)1,2-oxazol-3-il]metilo, [5-(2-furil)1,2-oxazol-3-il]metilo, 2-(3,4-dimetoxifenil)etilo, butan-2-ilo, ciclopentilo, (2,3-dimetilciclohexilo), (4-hidroxifenil)metilo, [2-(trifluorometil)fenil]metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, metoxi, bromo, cloro, fluoro, trimetilsililo; o uno de sus enantiómeros.

23. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^1 es (2-ciclopentilfenil)metilo;
R^2 se selecciona entre 4,4-difluorobutilo, metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre bromo, fluoro, cloro o ciano
o uno de sus enantiómeros.

24. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde R^1 es 1-feniletilo, opcionalmente sustituido con uno o más sustituyentes seleccionados entre fluoro, cloro, ciano y metoxi;

R^2 se selecciona entre etilo, propilo, terc-butilo, 4,4-difluorobutilo, 4,4,4-trifluorobutilo, 4-metilsulfonilo, bencilo, donde el grupo bencilo está opcionalmente sustituido con uno o más sustituyente seleccionados entre fluoro, cloro y ciano;
además R^2 representa piridinmetilo, ((2,2-difluoroacetil)amino)metilo, difluorometoxi, dimetilamino, 5-(2-furil)1,2-oxazol-3-il-metilo y ciclopentilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre bromo, fluoro, cloro o ciano;
o uno de sus enantiómeros.

25. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^1 es 3-hidroxi-2,2-dimetilpropilo;
R^2 se selecciona entre [3-(difluorometoxi)fenil]metilo, (3,4-diclorofenil)metilo, (3-clorofenil)metilo, [3-(trifluorometil)fenil]metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, fluoro, cloro;
o uno de sus enantiómeros.

26. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^1 es 2-(4-clorofenil)propilo;
R^2 se selecciona entre metilo, etilo, n-propilo, propan-2-ilo, butilo, (4-amino-2-metilpirimidin-5-il)metilo, (5-metilpirazin-2-il)metilo, piridin-3-ilmetilo, [6-(trifluorometil)piridin-3-il]metilo, (4-amino-2-metilpirimidin-5-il)metilo, [6-(trifluorometil)piridin-3-il]metilo, (5-metil-2-fenil-1,3-oxazol-4-il)metilo, 4,4,4-trifluorobutilo, (4-metilsulfonilfenil)metilo, bencil, (2,2-difluorobenzo[1,3]dioxol-5-il)metilo, (4-metilsulfonilfenil)metilo, butilo, 2-(1H-indol-3-il)etilo; (4-carbamoilfenil)metilo, (4-cianofenil)metilo, [3-(dimetilcarbamoil)-4-fluorofenil]metilo, [3-(dimetilcarbamoil)-4-fluorofenil]metilo, [4-(aminometil)fenilo], [4-[[(2,2-difluoroacetil)amino]metil]fenilo], (4-carbamoilfenilo), piridin-4-ilmetilo, 3-metoxipropilo, (3-ciano-4-fluorofenil)metilo, [3-[[(2,2-difluoroacetil)amino]metil]-4-fluorofenil]metilo, [3-(aminometil)-4-fluorofenil]metilo, (3-carbamoil-4-

fluorofenil)metilo, 2-piridin-4-iletilo, (1-metilpirrol-2-il)metilo, [4-(difluorometoxi)fenil]metilo, (1-bencilpirrolidin-3-ilo), 3-imidazol-1-ilpropilo, (4-dimetilaminofenil)metilo, (4-metilsulfonilfenil)metilo, 3-dimetilaminopropilo, 1-piridin-3-iletilo, (3-metoxifenilo), 1-piridin-4-iletilo, (4-cianofenilo), 3-metoxipropilo, benzo[1,3]dioxol-5-ilmetilo, (3,4-dimetoxifenil)metilo, (3-metil-5-fenil-1,2-oxazol-4-il)metilo, (5-metil-1,2-oxazol-3-il)metilo, [2-(trifluorometil)fenil]metilo, (2-clorofenil)metilo, 2-(3,4-dimetoxifenil)etilo, 2-tiofen-2-iletilo, 2-(4-metoxifenil)etilo, fenetilo, 2-metoxietilo, (4-fluorofenil)metilo, metoxicarbonilmetilo, benzotriazol-1-ilmetilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro;

o uno de sus enantiómeros.

27. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^1 es 2-(4-clorofenil)propilo;

R^2 es terc-butilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, -OH, bromo, fluoro, cloro, metilo, $-OCH_3$, $-OCH_2F$ y trimetilsililo; o uno de sus enantiómeros.

28. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^1 es 2-(4-fluorofenil)propilo;

R^2 es 4,4,4-trifluorobutilo, bencilo, terc-butilo o butilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, -OH, bromo, fluoro, cloro, metoxi, o uno de sus enantiómeros.

29. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^1 es 2,2-dimetilpropilo;

R^2 es [3-(trifluorometoxi)fenil]metilo, [3-(difluorometoxi)fenil]metilo, (3,4-diclorofenil)metilo, 2-[3-(trifluorometil)fenil]etilo, 2-(1H-indol-3-il)etilo, (3-clorofenil)metilo, [4-(difluorometoxi)fenil]metilo, [3-(trifluorometil)fenil]metilo, 2-(3-fluorofenil)etilo, 2-(2-clorofenil)etilo, 2-(3-clorofenil)etilo, 2-(2,4-diclorofenil)etilo, 2-(4-clorofenil)etilo, 2-(2,6-diclorofenil)etilo, benzo[1,3]dioxol-5-ilmetilo, o fenilmetilo;

R^3 es hidrógeno;

R^4 es hidrógeno:

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro,

o uno de sus enantiómeros.

30. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^1 es 2-fenilpropan-2-ilo;

R^2 es bencilo, 1-feniletilo, (4-fluorofenil)metilo, 4,4,4-trifluorobutilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro,

o uno de sus enantiómeros.

31. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^1 es 1-fenilpropilo;

R^2 es bencilo, (2-clorofenil)metilo, [2-(trifluorometil)fenil]metilo o (4-dimetilaminofenil)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro;

o uno de sus enantiómeros.

32. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^1 es [2-(4-clorofenil)-2-metilpropilo];

R^2 es n-butilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro o cloro;
o uno de sus enantiómeros.

33. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es (2-clorofenil)metilo;
R^1 es benzhidrilo, (2-piridin-3-ilfenil)metilo, (3,4-difluorofenil)metilo
1-(1H-indol-3-il)propan-2-ilo, 2-(4-clorofenil)propilo, (2,5-dimetilfenil)metilo,
[(1R)-1-(4-metoxifenil)etilo], 2-(1H-indol-3-il) propilo, [(1R)-1-(3-metoxifenil)etilo],
[(1S)-1-naftalen-1-iletilo], 1-fenilpropilo, 2-fenilpropilo, 3-fenilpropilo, 2-fenetilo,
4-fenilbutan-2-ilo, (2-fenilfenil)metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

34. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es (3,4-diclorofenil)metilo;
R^1 es (3-hidroxi-2,2-dimetilpropilo), 2,2-dimetilpropilo, 2-metilpropilo o 3,3-dimetilbutilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

35. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es (3-clorofenil)metilo;
R^1 es (3-hidroxi-2,2-dimetilpropilo), 2-metilpropilo, 2,2-dimetilpropilo,
3,3-dimetilbutilo, (4-hidroxifenil)metilo o (3-cianofenil)metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

36. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es (3-ciano-4-fluorofenil)metilo;
R^1 es (2-cloro-4-fluorofenil)metilo, [3,5-bis(trifluorometil)fenil]metilo, (3-ciano-4-fluorofenil)metilo, 2-feniletilo, bencilo, (3,4-difluorofenil)metilo, (2-fenilfenil)metilo o 2-(4-clorofenil)propilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

37. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es (3-cianofenil)metilo;
R^1 es (2-fenilfenil)metilo, (3-clorofenil)metilo, (3,4-difluorofenil)metilo, [3,5-bis(trifluorometil)fenil]metilo o [4-(trifluorometil)fenil]metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

38. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es (4-fluorofenil)metilo;
R^1 es [(4-clorofenil)-piridin-4-ilmetilo], [(4-fluorofenil)-piridin-3-ilmetilo], (fenilpiridin-2-ilmetilo), 2-(4-metoxifenil)etilo, (4-clorofenil)metilo (2-fenilfenil)metilo, benzhidrilo, (2-piridin-3-ilfenil)metilo, (3,4-difluorofenil)metilo, (1-fluoro-3-fenilpropan-2-ilo), (1-metilpirrol-2-il)metilo, (2-fenilfenil)metilo, 2-(4-clorofenil)propilo, 1-(4-clorofenil)etilo, 2-(4-clorofenil)propan-2-ilo, 2-(4-fluorofenil)propan-2-ilo, 2-fenilpropan-2-ilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

39. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es (4-hidroxifenil)metilo;
R^1 representa (3,4-difluorofenil)metilo, (3-clorofenil)metilo, [3,5-bis(trifluorometil)fenil]metilo o [4-(trifluorometil)fenil]metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

40. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es [2-(trifluorometil)fenil]metilo;
R^1 es (2-metoxifenil)metilo, (2-fluorofenil)metilo, benzhidrilo, 2-(4-clorofenil)etilo, [4-(piperidina-1-carbonil)fenil]metilo, 2-(4-clorofenil)propilo, (2-fenilfenil)metilo, 1-fenilpropilo, 2-fenilpropilo, 4-fenilbutan-2-ilo, 2-feniletilo, 3-fenilpropilo, 2-metilbutilo, ciclohexilmetilo, (3-fluorofenil)metilo, (2-etoxifenil)metilo, [4-(trifluorometoxi)fenil]metilo o (3,4-difluorofenil)metilo
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, metoxi o metilo; o uno de sus enantiómeros.

41. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es [3-(difluorometoxi)fenil]metilo;
R^1 is 1-feniletilo, (3-hidroxi-2,2-dimetilpropilo), 3,3-dimetilbutilo o 2.2-dimetilpropilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

42. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es [3-(trifluorometoxi)fenil]metilo;

R^1 representa 3,3-dimetilbutilo o 2,2-dimetilpropilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

43. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es [3-(trifluorometil)fenil]metilo;
R^1 es (3-hidroxi-2,2-dimetilpropilo), 2-metilpropilo, 3,3-dimetilbutilo, 2,2-dimetilpropilo o (1-metilpirrol-2-il)metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

44. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es [4-(difluorometoxi)fenil]metilo;
R^1 es 2-metilpropilo, 3,3-dimetilbutilo, 2,2-dimetilpropilo, (2-cloro-4-fluorofenil)metilo, 2-(4-clorofenil)propilo o [3,5-bis(trifluorometil)fenil]metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

45. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es [6-(trifluorometil)piridin-3-il]metilo;
R^1 es 2-(4-clorofenil)propilo o (2-fenilfenil)metilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

46. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es 2-(1H-indol-3-il)etilo;
R^1 es 2-(4-clorofenil)propilo, 2-(2-fenoxifenil)etilo, 2-[4-(dietilcarbamoil)fenil]etilo, 2-(3-fluorofenil)etilo, 2-[2-(trifluorometoxi)fenil]etilo, 2-(4-fluorofenil)etilo, 2-(3,5-dimetoxifenil)etilo, 2-(4-fenilfenil)etilo, 2-(4-fenoxifenil)etilo, 2-(2-etoxifenil)etilo o 2-benzo[1,3]dioxol-5-iletilo, 2,2-dimetilpropilo, 3,3-dimetilbutilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

47. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es 2-(2,4-diclorofenil)etilo;
R^1 es 2-metilpropilo, 3,3-dimetilbutilo o 2,2-dimetilpropilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

48. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es 2-(2,6-diclorofenil)etilo;
R^1 es 2-metilpropilo, 3,3-dimetilbutilo o 2,2-dimetilpropilo;
R^3 es hidrógeno;
R^4 es hidrógeno;
R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;
o uno de sus enantiómeros.

49. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde
R^2 es 4,4,4-trifluorobutilo;
R^1 es [2-(trifluorometil)fenil]metilo, [(1R)-1-feniletilo], benzhidrilo, 2-(4-clorofenil)propilo, (2-fenilfenil)metilo, (2-fenoxifenil)metilo, (2-fenilfenil)metilo, 2-(4-

clorofenil)etilo, 2-(4-fluorofenil)etilo, 2-(4-fluorofenil)propilo, 2-(4-clorofenil)propan-2-ilo, 2-(4-fluorofenil)propan-2-ilo o 2-fenilpropan-2-ilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, –OH, metilo, bromo, fluoro y cloro; o uno de sus enantiómeros.

50. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^2 es 4,4-difluorobutilo;

R^1 es (2-ciclopentilfenil)metilo, [2-(trifluorometil)fenil]metilo, [(1R)-1-feniletilo], (2-fenilfenil)metilo, benzhidrilo, 2-(4-clorofenil)propilo o (2-fenilfenil)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro;

o uno de sus enantiómeros.

51. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^2 es bencilo;

R^1 es bencilo, benzhidrilo, [2-(trifluorometil)fenil]metilo, (2-piridin-3-ilfenil)metilo, (4-fenoxifenil)metilo, (2,4-difluorofenil)metilo, [4-(difluorometoxi)fenil]metilo, [3-(difluorometoxi)fenil]metilo, (3-pirrol-1-ilfenil)metilo, (3-fluorofenil)metilo, (4-cianofenil)metilo, (3,5-dimetoxifenil)metilo, (2-metoxifenil)metilo, (2-etoxifenil)metilo, [4-(trifluorometil)fenil]metilo, (3,4-difluorofenil)metilo, (2,5-dimetilfenil)metilo, [3,5-bis(trifluorometil)fenil]metilo, (2-metilfenil)metilo, (2,3-difluorofenil)metilo, (2-bromofenil)metilo, [(4-fluorofenil)-piridin-3-il-metilo], [(4-clorofenil)-piridin-4-ilmetilo], (fenilpiridin-2-ilmetilo), (1-metil-5-fenil-pirazol-3-il)metilo, (5-metil-2-fenil-1,3-oxazol-4-il)metilo, (5-metil-3-fenil-1,2-oxazol-4-il)metilo, (3-fenil-1,2-oxazol-5-il)metilo, 2-(4-clorofenil)etilo, 2-(4-fluorofenil)etilo, 2-[4-(trifluorometil)fenil]etilo, 2-(5-bromo-2-metoxifenil)etilo, 2-(3-bromo-4-metoxifenil)etilo, 2-(4-fluorofenil)propilo, 2-(4-clorofenil)propilo, 4-fenilbutan-2-ilo, [2-(4-cloro-2-metilfenil)-2,2-difluoro-etilo], 2-naftalen-1-ilpropilo, (2-metil-2-fenilpropilo), 2-fenoxipropilo, 2-(4-fluorofenoxi)propilo, 2-fenilpropan-2-ilo, cicloheptilo, 2-(2-metoxifenil)etilo, 1-naftalen-1-iletilo, 2-[3-

(trifluorometil)fenil]etilo, 2-(6-cloro-1H-indol-3-il)etilo, 2-(4-clorofenil)propilo, [(1R)-1-(4-metoxifenil)etilo], [(1R)-1-(3-metoxifenil)etilo], 4-fenilbutan-2-ilo, 1-feniletilo, 2-feniletilo, 1-naftalen-2-iletilo, 2-(1-ciclohexenil)etilo, 1-(4-fluorofenil)etilo, 2-(4-fluorofenil)propan-2-ilo, 2-fenilpropan-2-ilo, 1-fenilpropilo o (2-fenilfenil)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro y cloro, -OH, metilo o metoxi; o uno de sus enantiómeros.

52. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^2 es n-butilo;

R^1 es (2-fenilfenil)metilo, (2-fenoxifenil)metilo, [2-(4-fluorofenoxi)fenil]metilo, 2-(3-fluorofenil)etilo, 2-(4-fluorofenil)etilo, 2-(4-clorofenil)etilo, 2-[4-(trifluorometil)fenil]etilo, 2-(4-clorofenil)propilo, 2-(4-fluorofenil)propilo, (2-fenilfenil)metilo, 2-(4-fenilfenil)etilo, 2-naftalen-1-ilpropilo, 2-(2-etoxifenil)etilo, 2-(2-fenoxifenil)etilo, 2-(4-fenoxifenil)etilo, 2-[2-(trifluorometoxi)fenil]etilo, 2-(3,5-dimetoxifenil)etilo, 2-benzo[1,3]dioxol-5-iletilo, (1-fluoro-3-fenil-propan-2-ilo), 2-(4-clorofenil)propilo, naftalen-1-ilmetilo, 1-naftalen-2-iletilo, (2-fenilfenil)metilo, [2-(4-clorofenil)-2-metilpropilo];

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, -OH, metilo, metoxi; o uno de sus enantiómeros.

53. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^2 es etilo;

R^1 es benzhidrilo, (2-fenilfenil)metilo o 2-(4-clorofenil)propilo

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, -OH, metilo, metoxi; o uno de sus enantiómeros.

54. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^2 es 2-feniletilo;

R^1 es (2-fenilfenil)metilo, 2-(4-metoxifenil)etilo, (4-clorofenil)metilo, 2-(4-clorofenil)etilo, 2-(3,4-diclorofenil)etilo, (3,4-difluorofenil)metilo, 2-(4-clorofenil)propilo, (2-cloro-4-fluorofenil)metilo o 4-fenilbutan-2-ilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, -OH, metilo, metoxi; o uno de sus enantiómeros.

55. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^2 es propilo;

R^1 es (2-fenilfenil)metilo, benzhidrilo o 2-(4-clorofenil)propilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, -OH, metilo, metoxi; o uno de sus enantiómeros.

56. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^2 es piridin-3-ilmetilo o piridin-4-ilmetilo;

R^1 es (2-fenilfenil)metilo, 2-(4-clorofenil)propilo, (3,4-difluorofenil)metilo, (2-cloro-4-fluorofenil)metilo o 1-(4-fluorofenil)etilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro, -OH; o uno de sus enantiómeros.

57. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^2 es terc-butilo;

R^1 es (2-fenilfenil)metilo, [2-(trifluorometil)fenil]metilo, [4-(difluorometoxi)fenil]metilo, (2-clorofenil)metilo, (2-metoxifenil)metilo, (3,4-difluorofenil)metilo, (3,4-difluorofenil)metilo, (4-fenoxifenil)metilo, [3,5-bis(trifluorometil)fenil]metilo, (4-fluoro-2-fenilfenil)metilo, (5-fluoro-2-fenilfenil)metilo, 1-feniletilo, 2-(4-clorofenil)etilo, 2-(2-

fenoxifenil)etilo, 2-[2-(trifluorometoxi)fenil]etilo, 2,2-difeniletilo, 2-(4-fluorofenil)propilo, 2-(4-clorofenil)propilo, (2-fenilfenil)metilo, 2-(4-fenilfenil)etilo, [2-(3-fluorofenil)fenil]metilo, [2-(4-fluorofenil)fenil]metilo, [2-(3,4-difluorofenil)fenil]metilo, [2-(2,4-difluorofenil)fenil]metilo, [2-(2,5-difluorofenil)fenil]metilo, [2-(2,4-diclorofenil)fenil]metilo, [2-(3,4-diclorofenil)fenil]metilo, [2-(2-clorofenil)fenil]metilo, [2-(4-clorofenil)fenil]metilo, [2-(4-metilfenil)fenil]metilo, [2-(4-fluoro-2-metilfenil)fenil]metilo, [2-(4-metoxifenil)fenil]metilo, [4-fluoro-2-(4-fluorofenil)fenil]metilo, [2-(3-cloro-4-fluorofenil)fenil]metilo, [2-(4-fluoro-2-metilfenil)fenil]metilo, [5-fluoro-2-(4-fluorofenil)fenil]metilo, benzhidrilo, [(1R)-2-(4-clorofenil)-1-(4,4,4-trifluorobutilcarbamoil)etilo], [3,5-bis(trifluorometil)fenil]metilo, 9H-fluoren-9-ilo, [2-[4-(trifluorometil)fenoxi]fenil]metilo, 2-naftalen-1-ilpropilo, [(1R)-2-(4-clorofenil)-1-metoxicarbonil-etilo], (1-metil-5-fenilpirazol-3-il)metilo o [2-(4-cloro-2-metilfenil)-2,2-difluoroetilo], (3-fenilfenil)metilo, (4-fluorofenil)metilo, (4-fenilfenil)metilo, [(4-clorofenil)-piridin-4-ilmetilo], 2-(4-fluorofenil)propilo o 2-(4-fenoxifenil)etilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 son independientemente –OH, bromo, cloro, fluoro, metilo, metoxi metilsulfonilamino, trimetilsililo, ciano, $-OCHF_2$, $-OCH_2F$, $-OSO_2CF_3$,

o uno de sus enantiómeros.

58. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13 donde

R^2 es trimetilsililmetilo;

R^1 es [3-(difluorometoxi)fenil]metilo, [4-(difluorometoxi)fenil]metilo, naftalen-1-ilmetilo, 1-naftalen-1-iletilo, 2-(4-bromofenil)etilo, (2-cloro-6-fenoxifenil)metilo o (3,4-diclorofenil)metilo;

R^3 es hidrógeno;

R^4 es hidrógeno;

R^5 a R^7 se seleccionan independientemente entre hidrógeno, bromo, fluoro, cloro;

o uno de sus enantiómeros.

59. Un compuesto seleccionado entre uno o más del grupo siguiente que consiste en:

(1R o 1S)-N-(4,4-difluorobutil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (E2);
(1S o 1R)-N-(4,4-difluorobutil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida (E1);
(1R o 1S)-N-bencil-3-oxo-2-[(1S o 1R)-1-feniletil]isoindolina-1-carboxamida (E4);
(1S o 1R)-N-bencil-3-oxo-2-[(1S o 1R)-1-feniletil]isoindolina-1-carboxamida (E3);
(1R o 1S)-N-bencil-3-oxo-2-[(1R o 1S)-1-feniletil]isoindolina-1-carboxamida (E2);
(1S o 1R)-N-bencil-3-oxo-2-[(1R o 1S)-1-feniletil]isoindolina-1-carboxamida (E1);
N-bencil-6-ciano-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-5-[(metilsulfonil)amino]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-4-metil-5-[(metilsulfonil)amino]-3-oxoisoindolina-1-carboxamida;
N-(3-clorobencil)-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-6-ciano-3-oxoisoindolina-1-carboxamida;
N-bencil-6-cloro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-bencil-2-[2-(4-clorofenil)etil]-1-hidroxi-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[(5-metil-2-fenil-1,3-oxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(1-metil-5-fenil-1H-pirazol-3-il)metil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-bromo-N-(terc-butil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(4'-fluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-5-bromo-N-(terc-butil)-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(4-fluorofenoxi)bencil]-3-oxoisoindolina-1-carboxamida;
N-(4,4-difluorobutil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-*N*-(4,4-difluorobutil)-3-oxoisoindolina-1-carboxamida;
(R o S) 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (E1);
(S o R) 2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida (E2);
2-(bifenil-2-ilmetil)-N-[(2,2-difluoro-1,3-benzodioxol-5-il)metil]-6-fluoro-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;

metanosulfonato de 2-(bifenil-2-ilmetil)-1-[(terc-butilamino)carbonil]-4-metil-3-oxo-2,3-dihidro-1H-isoindol-5-ilo;

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-(difluorometoxi)-4-metil-3-oxoisoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-(fluorometoxi)-4-metil-3-oxoisoindolina-1-carboxamida;

trifluorometanosulfonato de 2-(bifenil-2-ilmetil)-1-[(terc-butilamino)carbonil]-4-metil-3-oxo-2,3-dihidro-1H-isoindol-5-ilo;

N-(terc-butil)-2-{(1*R*)-1-(4-clorobencil)-2-oxo-2-[(4,4,4-trifluorobutil)amino]etil}-3-oxoisoindolina-1-carboxamida;

N-butil-2-[2-(4-clorofenil)etil]-N-metil-3-oxoisoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(terc-butil)-4,7-difluoro-1-metil-3-oxoisoindolina-1-carboxamida;

2-(bifenil-4-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(terc-butil)-7-hidroxi-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-2-(4-clorobencil)-7-hidroxi-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-2-(4-clorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(4-{[(difluoroacetil)-amino]metil}bencil)-3-oxoisoindolina-1-carboxamida;

N-{4-[(acetilamino)metil]bencil}-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(4-{[(fluoroacetil)-amino]metil}bencil)-3-oxoisoindolina-1-carboxamida;

N-[4-(aminometil)bencil]-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida;

(2*R*)-2-{1-[(terc-butilamino)carbonil]-3-oxo-1,3-dihidro-2H-isoindol-2-il}-3-(4-clorofenil)propanoato de metilo;

2-(bifenil-2-ilmetil)-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;

2-[2-(4-clorofenil)propil]-N-[(5-metilisoxazol-3-il)metil]-3-oxoisoindolina-1-carboxamida;

(1S o 1R)-N-butil-2-[(2R o 2S)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida (E2);

(1R o 1S)-N-butil-2-[(2S o 2R)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida (E4);

(1R o 1S)-N-butil-2-[(2R o 2S)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida (E3);

(1S o 1R)-N-butil-2-[(2S o 2R)-2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida (E1);

N-butil-2-[2-(4-clorofenil)propil]-6-fluoro-3-oxoisoindolina-1-carboxamida;

(S o R) 2-(bifenil-2-ilmetil)-N-(terc-butil)-3-oxoisoindolina-1-carboxamida;

(R o S) 2-(bifenil-2-ilmetil)-N-(terc-butil)-3-oxoisoindolina-1-carboxamida;

N-bencil-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(terc-butil)-3-oxoisoindolina-1-carboxamida;

2-(2-bromobencil)-N-terc-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;

N-bencil-2-(1-metil-1-feniletil)-3-oxoisoindolina-1-carboxamida;

N-bencil-3-oxo-2-(1-fenilpropil)isoindolina-1-carboxamida;

N-[3-(difluorometoxi)bencil]-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;

N,2-dibencil-6-bromo-3-oxoisoindolina-1-carboxamida;

6-bromo-2-(2-ciclopentilbencil)-N-(4,4-difluorobutil)-3-oxoisoindolina-1-carboxamida;

2-(2-ciclopentilbencil)-N-(4,4-difluorobutil)-6-fluoro-3-oxoisoindolina-1-carboxamida;

6-bromo-2-(2-ciclopentilbencil)-N-metil-3-oxoisoindolina-1-carboxamida;

2-(2-ciclopentilbencil)-6-fluoro-N-metil-3-oxoisoindolina-1-carboxamida;

6-cloro-2-(2-ciclopentilbencil)-N-(4,4-difluorobutil)-3-oxoisoindolina-1-carboxamida;

6-cloro-2-(2-ciclopentilbencil)-N-metil-3-oxoisoindolina-1-carboxamida;

2-(2-ciclopentilbencil)-N-(4,4-difluorobutil)-3-oxoisoindolina-1-carboxamida;

2-(2-ciclopentilbencil)-N-metil-3-oxoisoindolina-1-carboxamida;

N-bencil-6-cloro-3-oxo-2-[(1S)-1-feniletil]isoindolina-1-carboxamida;

6-cloro-N-(2-metoxietil)-3-oxo-2-[2,2,2-trifluoro-1-(3-fluorofenil)etil]isoindolina-1-carboxamida;

N-bencil-6-cloro-2-(dipiridin-3-ilmetil)-3-oxoisoindolina-1-carboxamida;

6-cloro-N-metil-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;

2-[2-(4-clorofenil)propil]-6-fluoro-N-metil-3-oxoisoindolina-1-carboxamida;

6-fluoro-N-metil-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;

6-cloro-2-[2-(4-clorofenil)propil]-N-metil-3-oxoisoindolina-1-carboxamida;

6-cloro-N-metil-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;

2-[2-(4-clorofenil)propil]-N-metil-3-oxoisoindolina-1-carboxamida;

6-cloro-N-etil-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;

N-bencil-5-[(metilsulfonil)amino]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;

N-bencil-4-metil-5-[(metilsulfonil)amino]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-bencil-5-ciano-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-bencil-5-bromo-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-bencil-6-bromo-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-[3-(difluorometoxi)bencil]-6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-(3,4-diclorobencil)-6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-(3-clorobencil)-6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
6-fluoro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida;
6-cloro-N-[3-(difluorometoxi)bencil]-2-(3- hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
6-cloro-N-(3,4-diclorobencil)-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
6-cloro-N-(3-clorobencil)-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
6-cloro-2-(3-hidroxi-2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(3,4-diclorobencil)-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-[3-(difluorometoxi)bencil]-2-(3-hidroxi-2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
2-(3-hidroxi-2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(4,4-difluorobutil)-6-fluoro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
6-cloro-N-(4,4-difluorobutil)-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
6-cloro-N-(4,4-difluorobutil)-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-(4,4-difluorobutil)-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-(terc-butil)-6-fluoro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(terc-butil)-6-cloro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
3-oxo-N-(4,4,4-trifluorobutil)-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;

6-cloro-3-oxo-N-(4,4,4-trifluorobutil)-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(terc-butil)-6-fluoro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
6-fluoro-3-oxo-2-[(1R)-1-feniletil]-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
N-(terc-butil)-6-cloro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
6-cloro-3-oxo-2-[(1R)-1-feniletil]-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
3-oxo-2-[(1R)-1-feniletil]-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
6-cloro-N-[4-(metilsulfonil)bencil]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-bencil-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-[(4-amino-2-metilpirimidin-5-il)metil]-6-cloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-[(5-metilpirazin-2-il)metil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida;
N-[(4-amino-2-metilpirimidin-5-il)metil]-2-(bifenil-2-ilmetil)-6-cloro-3-oxoisoindolina-1-carboxamida;
N-[(4-amino-2-metilpirimidin-5-il)metil]-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida;
N-butil-2-[(4-fluorofenil)(piridin-3-il)metil]-3-oxoisoindolina-1-carboxamida;
N-butil-3-oxo-2-[fenil(piridin-2-il)metil]isoindolina-1-carboxamida;
N-butil-2-[(4-clorofenil)(piridin-4-il)metil]-3-oxoisoindolina-1-carboxamida;
2-[(4-clorofenil)(piridin-4-il)metil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
6-cloro-2-(difenilmetil)-N-etil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-cloro-N-etil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-propilisoindolina-1-carboxamida;
2-(difenilmetil)-N-etil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-etil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-fluoro-3-oxo-N-propilisoindolina-1-carboxamida;
N-(4-fluorobencil)-2-[(4-fluorofenil)(piridin-3-il)metil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[(4-fluorofenil)(piridin-3-il)metil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[(5-metilpirazin-2-il)metil]-3-oxoisoindolina-1-carboxamida;
6-cloro-2-[2-(4-clorofenil)propil]-N-[(5-metilpirazin-2-il)metil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-cloro-N-[(5-metilpirazin-2-il)metil]-3-oxoisoindolina-1-carboxamida;

6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida;
6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida;
N-[(4-amino-2-metilpirimidin-5-il)metil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-3-oxo-N-{[6-(trifluorometil)piridin-3-il]metil}isoindolina-1-carboxamida;
N-bencil-6-fluoro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-[4-(metilsulfonil)bencil]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
6-fluoro-N-[4-(metilsulfonil)bencil]-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
N-bencil-6-cloro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-bencil-6-fluoro-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
6-cloro-N-[4-(metilsulfonil)bencil]-3-oxo-2-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
6-cloro-N-[2-cloro-4-(metilsulfonil)bencil]-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;
N-[2-cloro-4-(metilsulfonil)bencil]-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;
6-cloro-2-(difenilmetil)-N-[2-fluoro-4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
2-(difenilmetil)-N-[2-fluoro-4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
6-cloro-2-(difenilmetil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida;
6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-5-ciano-3-oxoisoindolina-1-carboxamida;
6-cloro-2-(difenilmetil)-3-oxo-N-propilisoindolina-1- carboxamida;
2-[2-(4-clorofenil)propil]-N-etil-6-fluoro-3-oxoisoindolina-1-carboxamida;
2-(difenilmetil)-N-etil-6-fluoro-3-oxoisoindolina-1-carboxamida;

2-[2-(4-clorofenil)propil]-N-etil-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-6-fluoro-3-oxo-N-propilisoindolina-1-carboxamida;
2-(difenilmetil)-6-fluoro-3-oxo-N-propilisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-3-oxo-N-propilisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-propilisoindolina-1-carboxamida;
2-(difenilmetil)-3-oxo-N-propilisoindolina-1-carboxamida;
2-(difenilmetil)-6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
2-(difenilmetil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
N-(terc-butil)-2-[(4-clorofenil)(piridin-4-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(4-fluorobencil)-3-oxo-2-[fenil(piridin-2-il)metil]isoindolina-1-carboxamida;
N-bencil-2-[(4-clorofenil)(piridin-4-il)metil]-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-[fenil(piridin-2-il)metil]isoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-[(5-metil-2-fenil-1,3-oxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-[(1-metil-5-fenil-1H-pirazol-3-il)metil]-3-oxoisoindolina-1-carboxamida;
N-butil-2-[(5-metil-2-fenil-1,3-oxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[(1-metil-5-fenil-1H-pirazol-3-il)metil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[(5-metil-2-fenil-1,3-oxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(bifenil-2-ilmetil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-5-hidroxi-4-metil-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-5-hidroxi-4-metil-3-oxo-N-propilisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-butil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-etil-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(2',4'-diclorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-2-[(3',4'-diclorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(2'-clorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(3'-cloro-4'-fluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(4'-clorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(4'-fluoro-2-metilbifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(2',4'-difluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(2',5'-difluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(3'-fluorobifenil-2-il)metil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-butil-3-oxo-2-(2-(fenoxibencil)isoindolina-1-carboxamida;
N-[3-(difluorometoxi)bencil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
2-(3,3-dimetilbutil)-3-oxo-N-[3-(trifluorometoxi)bencil]isoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometoxi)bencil]isoindolina-1-carboxamida;
N-[3-(difluorometoxi)bencil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
6-cloro-2-(difenilmetil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
6-cloro-2-(difenilmetil)-N-(2-hidroxibencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-6-cloro-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-6-cloro-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-cloro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-6-cloro-N-(3-cianobencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(bifenil-2-ilmetil)-6-cloro-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-6-cloro-3-oxoisoindolina-1-carboxamida;
6-cloro-2-[2-(4-clorofenil)propil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
6-cloro-2-[2-(4-clorofenil)propil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-6-cloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-bencil-6-cloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-4,5-dimetoxi-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida;
2-[1-(1,5-dimetil-1H-pirazol-4-il)etil]-5,7-dimetoxi-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
5,7-dimetoxi-2-(2-metoxibencil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
2-(2-fluorobencil)-5,7-dimetoxi-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(terc-butil)-5,7-dimetoxi-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida;
3-oxo-2-(2-fenoxibencil)-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[(2,2-difluoro-1,3-benzodioxol-5-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(3,4-diclorobencil)-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-(1H-indol-3-ilmetil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-3-oxo-N-{2-[3-(trifluorometil)fenil]etil}isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-6-fluoro-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(bifenil-2-ilmetil)-6-fluoro-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)etil]-N-[(2,2-difluoro-1,3-benzodioxol-5-il)metil]-6-fluoro-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)etil]-6-fluoro-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)etil]-6-fluoro-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-clorofenil)etil]-6-fluoro-3-oxoisoindolina-1-carboxamida;
6-fluoro-2-[2-(4-fluorofenil)etil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
N-bencil-6-fluoro-2-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-6-fluoro-2-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
6-fluoro-2-[2-(4-fluorofenil)propil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
N-bencil-6-fluoro-2-[2-(4-fluorofenil)propil]- 3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-6-fluoro-2-[2-(4-fluorofenil)propil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-1-metil-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;

2-[2-(4-clorofenil)propil]-4,7-difluoro-1-metil-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;

N-butil-2-[2-(4-clorofenil)propil]-1-metil-3-oxoisoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(terc-butil)-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida;

N-bencil-2-(difenilmetil)-5-metoxi-3-oxoisoindolina-1-carboxamida;

2-(difenilmetil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;

N-(terc-butil)-2-[2-(4-clorofenil)propil]-1-metil-3-oxoisoindolina-1-carboxamida;

N-butil-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(terc-butil)-5-metoxi-4-metil-3-oxoisoindolina-1-carboxamida;

dimetilcarbamato de 2-(bifenil-2-ilmetil)-1-[(terc-butilamino)carbonil]-4-metil-3-oxo-2,3-dihidro-1H-isoindol-5-ilo;

2-(bifenil-2-ilmetil)-5-hidroxi-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;

5-hidroxi-2-[2-(4-metoxifenil)etil]-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;

2-(4-clorobencil)-5-hidroxi-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;

N-(4-fluorobencil)-5-hidroxi-2-[2-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;

2-[2-(3,4-diclorofenil)etil]-N-(4-fluorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida;

2-(4-clorobencil)-N-(4-fluorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida;

2-(bifenil-2-ilmetil)-N-(4-fluorobencil)-5-hidroxi-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-2-[2-(3,4-diclorofenil)etil]-5-hidroxi-3-oxoisoindolina-1-carboxamida;

N-(3,4-diclorobencil)-2-isobutil-3-oxoisoindolina-1-carboxamida;

N-[2-(1H-indol-3-il)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida;

N-(3-clorobencil)-2-isobutil-3-oxoisoindolina-1-carboxamida;

N-[4-(difluorometoxi)bencil]-2-isobutil-3-oxoisoindolina-1-carboxamida;

2-isobutil-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida;

N-(1H-indol-3-ilmetil)-2-isobutil-3-oxoisoindolina-1-carboxamida;

N-[2-(1,3-benzodioxol-5-il)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida;

N-[2-(3-fluorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida;

2-isobutil-3-oxo-N-{2-[3-(trifluorometil)fenil]etil}isoindolina-1-carboxamida;

N-[2-(3,4-diclorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida;

N-[2-(4-clorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida;

N-[2-(3-clorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida;

N-[2-(2-clorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida;

N-[2-(2,4-diclorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida;
N-[2-(2,6-diclorofenil)etil]-2-isobutil-3-oxoisoindolina-1-carboxamida;
2-(3,3-dimetilbutil)-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
N-(3-clorobencil)-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
N-(3,4-diclorobencil)-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
2-(3,3-dimetilbutil)-N-(1H-indol-3-ilmetil)-3-oxoisoindolina-1-carboxamida;
N-[4-(difluorometoxi)bencil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
2-(3,3-dimetilbutil)-N-[2-(3-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-[2-(1,3-benzodioxol-5-il)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
N-[2-(3-cianofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
2-(3,3-dimetilbutil)-3-oxo-N-{2-[3-(trifluorometil)fenil]etil}isoindolina-1-carboxamida;
N-[2-(3-clorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
N-[2-(3,4-diclorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
N-[2-(4-clorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
N-[2-(2-clorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
N-[2-(2,4-diclorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
N-(3-clorobencil)-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-[4-(difluorometoxi)bencil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-[2-(1,3-benzodioxol-5-il)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-[2-(3-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-[2-(3-cianofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-[2-(2-clorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-[2-(3-clorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-[2-(2,4-diclorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)etil]-N-etil-3-oxo-N-(2-piridin-2-iletil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)etil]-3-(1,3-dihidro-2H-isoindol-2-ilcarbonil)isoindolin-1-ona;
2-[2-(4-clorofenil)etil]-N-metil-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-bencil-2-[2-(4-clorofenil)etil]-N-etil-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-clorofenil)etil]-N-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-{2-[4-(trifluorometil)fenil]etil}isoindolina-1-carboxamida;

N-butil-3-oxo-2-{2-[4-(trifluorometil)fenil]etil}isoindolina-1-carboxamida;
N-bencil-3-oxo-2-{2-[4-(trifluorometil)fenil]etil}isoindolina-1-carboxamida;
N-(terc-butil)-5-hidroxi-2-[2-(1H-indol-3-il)etil]-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-fluorofenil)propil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(2,2-difeniletil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(difenilmetil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(9H-fluoren-9-il)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5-hidroxi-4-metil-3-oxo-2-{2-[4-(trifluorometil)fenoxi]bencil}isoindolina-1-carboxamida;
2-(bifenil-3-ilmetil)-N-(terc-butil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(4-fluorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-fluorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-fluorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-[2-(1H-indol-3-il)etil]-3-oxo-2-[4-(piperidin-1-ilcarbonil)bencil]isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(2,4-difluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(4-ciano-2,6-difluorobencil)-3-oxoisoindolina-1-carboxamida;
N-(2,4-difluorobencil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;
N-(2-clorobencil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;
2-(difenilmetil)-N-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
2-(difenilmetil)-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-(2,4-difluorobencil)-3-oxo-2-(2-piridin-3-ilbencil)isoindolina-1-carboxamida;
N-(2-clorobencil)-3-oxo-2-(2-piridin-3-ilbencil)isoindolina-1-carboxamida;
N-[2-(4-fluorofenil)etil]-3-oxo-2-(2-piridin-3-ilbencil)isoindolina-1-carboxamida;
N-bencil-3-oxo-2-(2-piridin-3-ilbencil)isoindolina-1-carboxamida;

N-(4-fluorobencil)-3-oxo-2-(2-piridin-3-ilbencil)isoindolina-1-carboxamida;
N-butil-5-metoxi-2-(2-metil-2-fenilpropil)-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-butil)-5-metoxi-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(4-fluorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(4-clorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5-metoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-fluorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-5-metoxi-3-oxoisoindolina-1-carboxamida;
N-bencil-5-metoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida;
N-bencil-5-metoxi-2-(2-metil-2-fenilpropil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(bifenil-2-ilmetil)-5-metoxi-3-oxoisoindolina-1-carboxamida;
N-butil-5,6-dimetoxi-2-(2-metil-2-fenilpropil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-clorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida;
N-butil-5,6-dimetoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(4-fluorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-butil)-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(4-clorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5,6-dimetoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida;
N-bencil-5,6-dimetoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida;
N-bencil-5,6-dimetoxi-2-(2-metil-2-fenilpropil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-fluorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(bifenil-2-ilmetil)-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(difenilmetil)-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-clorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-1-metil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-butil-1-metil-3-oxoisoindolina-1-carboxamida;
N-bencil-N-({2-[2-(4-clorofenil)etil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de etilo;
2-[2-(4-clorofenil)etil]-N-metil-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)etil]-N,N-dietil-3-oxoisoindolina-1-carboxamida;
N-bencil-N-butil-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida;

N-[2-(2,6-diclorofenil)etil]-2-(3,3-dimetilbutil)-3-oxoisoindolina-1-carboxamida;
N-[2-(4-clorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-[2-(2,6-diclorofenil)etil]-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-butil-5-metoxi-2-[2-(1-naftil)propil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-fluorofenil)propil]-5-metoxi-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5,6-dimetoxi-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(4'-fluoro-2'-metilbifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(4'-metilbifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(4'-metoxibifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[(4'-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;
N-({2-[(3',4'-difluorobifenil-2-il)metil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo;
N-({2-[(4'-fluoro-2'-metilbifenil-2-il)metil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo;
N-({2-[(4'-fluorobifenil-2-il)metil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo;
N-({2-[(4'-metilbifenil-2-il)metil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo;
2-[(3',4'-difluorobifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
2-[(4'-fluoro-2'-metilbifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
2-[(4'-metoxibifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
2-[(4'-fluorobifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
2-[(4'-metilbifenil-2-il)metil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(4-clorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5-hidroxi-2-[2-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-7-hidroxi-2-[2-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-3-oxoisoindolina-1-carboxamida;
2-[2-(3,4-diclorofenil)etil]-5-hidroxi-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;

N-(3,4-difluorobencil)-2-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida;
N-(3-clorobencil)-2-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida;
2-(4-hidroxibencil)-3-oxo-N-[4-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-[3,5-bis(trifluorometil)bencil]-2-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida;
N-(3-clorobencil)-2-(3-cianobencil)-3-oxoisoindolina-1-carboxamida;
N-[3,5-bis(trifluorometil)bencil]-2-(3-cianobencil)-3-oxoisoindolina-1-carboxamida;
2-(3-cianobencil)-N-(3,4-difluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(3-cianobencil)-3-oxo-N-[4-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-[4-(aminocarbonil)bencil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-[4-(aminocarbonil)bencil]-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida;
2-(3,4-difluorobencil)-N-{4-[(dimetilamino)metil]bencil}-3-oxoisoindolina-1-carboxamida;
2-(3-clorobencil)-N-{4-[(dimetilamino)metil]bencil}-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-{4-[(dimetilamino)metil]bencil}-3-oxoisoindolina-1-carboxamida;
2-(3,4-difluorobencil)-N-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida;
2-(3-clorobencil)-N-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-(4-hidroxibencil)-3-oxoisoindolina-1-carboxamida;
2-(3-clorobencil)-N-(3-cianobencil)-3-oxoisoindolina-1-carboxamida;
N-(3-cianobencil)-2-(3,4-difluorobencil)-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-(3-cianobencil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-hidroxi-3-oxoisoindolina-1-carboxamida;
N-{4-[(dimetilamino)metil]bencil}-3-oxo-2-[4-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(4-hidroxibencil)-3-oxo-2-[4-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(3-cianobencil)-3-oxo-2-[4-(trifluorometil)bencil]isoindolina-1-carboxamida;
2-(bifenil-3-ilmetil)-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida;
2-(bifenil-4-ilmetil)-N-(4-cianobencil)-3-oxoisoindolina-1-carboxamida;
N-butil-3-oxo-2-[2-(2-fenoxifenil)etil]isoindolina-1-carboxamida;
N-butil-2-(2-{4-[(dietilamino)carbonil]fenil}etil)-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(3-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-butil-3-oxo-2-{2-[2-(trifluorometoxi)fenil]etil}isoindolina-1-carboxamida;

2-(2-bifenil-4-iletil)-N-butil-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(3,5-dimetoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
N-butil-3-oxo-2-[2-(4-fenoxifenil)etil]isoindolina-1-carboxamida;
N-butil-2-[2-(2-etoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
2-[2-(1,3-benzodioxol-5-il)etil]-N-butil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-[2-(2-fenoxifenil)etil]isoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-{2-[2-(trifluorometoxi)fenil]etil}isoindolina-1-carboxamida;
2-(2-bifenil-4-iletil)-N-(terc-butil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(3,5-dimetoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-[2-(4-fenoxifenil)etil]isoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(2-etoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
2-[2-(1,3-benzodioxol-5-il)etil]-N-(terc-butil)-3-oxoisoindolina-1-carboxamida;
N-[2-(1H-indol-3-il)etil]-3-oxo-2-[2-(2-fenoxifenil)etil]isoindolina-1-carboxamida;
2-(2-{4-[(dietilamino)carbonil]fenil}etil)-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
2-[2-(3-fluorofenil)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
N-[2-(1H-indol-3-il)etil]-3-oxo-2-{2-[2-(trifluorometoxi)fenil]etil}isoindolina-1-carboxamida;
2-[2-(4-fluorofenil)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
2-[2-(3,5-dimetoxifenil)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
2-(2-bifenil-4-iletil)-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
N-[2-(1H-indol-3-il)etil]-3-oxo-2-[2-(4-fenoxifenil)etil]isoindolina-1-carboxamida;
2-[2-(2-etoxifenil)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
2-[2-(1,3-benzodioxol-5-il)etil]-N-[2-(1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
(1R)-2-[(1S)-1-(4-fluorofenil)etil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-2-[2-(dimetilamino)-2-feniletil]-3-oxoisoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-2-(2,2-difeniletil)-3-oxoisoindolina-1-carboxamida;
2-(1-bencil-2-fluoroetil)-N-[(5-metilisoxazol-3-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(2-cloro-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(3,4-difluorobencil)-N-(4-fluorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;

2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida;
2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
2-(3,4-difluorobencil)-5-hidroxi-3-oxo-4-fenil-N-(2-feniletil)isoindolina-1-carboxamida;
N-(2-clorobencil)-2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(terc-butil)-2-(2-clorobencil)-5-hidroxi-3-oxo-4-(trimetilsilil)isoindolina-1-carboxamida;
N-(terc-butil)-2-(2-clorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(terc-butil)-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-(terc-butil)-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-{3-[(dimetilamino)carbonil]-4-fluorobencil}-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-(4-cianofenil)-3-oxoisoindolina-1-carboxamida;
2-(1-bencil-2-fluoroetil)-N-butil-3-oxoisoindolina-1-carboxamida;
2-(1-bencil-2-fluoroetil)-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(1-bencil-2-fluoroetil)-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida;
N-[4-(aminometil)fenil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(4-{[(difluoroacetil)amino]metil}fenil)-3-oxoisoindolina-1-carboxamida;
N-[4-(aminocarbonil)fenil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-(fluorometoxi)-4-metil-3-oxoisoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-3-oxo-2-(4-fenilbutil)isoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-2-(2-hidroxi-2-feniletil)-3-oxoisoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-3-oxo-2-[2-(1H-pirazol-1-il)bencil]isoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-3-oxo-2-(4-fenoxibencil)isoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-3-oxo-2-[(1-fenil-1H-pirazol-4-il)metil]isoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-2-[1-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;

2-(2-cloro-4-fluorobencil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
N-[4-(dimetilamino)bencil]-3-oxo-2-(1-fenilpropil)isoindolina-1-carboxamida;
N-[4-(metilsulfonil)bencil]-3-oxo-2-[2-(1H-pirazol-1-il)bencil]isoindolina-1-carboxamida;
2-(2-hidroxi-2-feniletil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
2-(2,2-difeniletil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
2-(difenilmetil)-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida;
N-[4-(metilsulfonil)bencil]-3-oxo-2-(1,2,3,4-tetrahidronaftalen-1-il)isoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida;
2-[1-(4-fluorofenil)etil]-3-oxo-N-(piridin-4-ilmetil)isoindolina-1-carboxamida;
(1S)-2-[(2R)-2-(4-clorofenil)propil]-N-(3-metoxipropil)-1-metil-3-oxoisoindolina-1-carboxamida;
(1R)-2-[(2R)-2-(4-clorofenil)propil]-N-(3-metoxipropil)-1-metil-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(3-metoxipropil)-1-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-hidroxi-3-oxo-4-(trimetilsilil)isoindolina-1-carboxamida;
N-(terc-butil)-2-(3,4-difluorobencil)-5-hidroxi-3-oxo-4-(trimetilsilil)isoindolina-1-carboxamida;
N-(terc-butil)-2-(3,4-difluorobencil)-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(3,4-difluorobencil)-5-hidroxi-3-oxo-4-fenilisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)propil]-5-hidroxi-4-metil-3-oxoisoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N,2-bis(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-(3-ciano-4-fluorobencil)-3-oxo-2-(2-feniletil)isoindolina-1-carboxamida;
N-(3-ciano-4-fluorobencil)-2-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-bencil-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-(3-ciano-4-fluorobencil)-2-(3,4-difluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(3-ciano-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;

2-(2-cloro-4-fluorobencil)-N-(3-{[(difluoroacetil)amino]metil}-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(3-{[(difluoroacetil)amino]metil}-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-[3-(aminometil)-4-fluorobencil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-[3-(aminocarbonil)-4-fluorobencil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-[3-(aminocarbonil)-4-fluorobencil]-2-(2-cloro-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-(4-fenilbutil)isoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-(1,2,3,4-tetrahidronaftalen-1-il)isoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-(4-fenoxibencil)isoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-[2-(1H-pirazol-1-il)bencil]isoindolina-1-carboxamida;
N-(terc-butil)-2-(2,2-difeniletil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(difenilmetil)-3-oxoisoindolina-1-carboxamida;
N-(1,3-benzodioxol-5-ilmetil)-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-N-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(1,3-benzodioxol-5-ilmetil)-2-(2-cloro-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-N-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-3-oxo-N-(2-piridin-4-iletil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-(2-piridin-4-iletil)isoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida;
N-(1,3-benzodioxol-5-ilmetil)-2-[3,5-bis(trifluorometil)bencil]-3-oxoisoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida;
N-(1-bencilpirrolidin-3-il)-2-(2-cloro-4-fluorobencil)-3-oxoisoindolina-1-carboxamida;

N-(1-bencilpirrolidin-3-il)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-N-{[5-(2-furil)isoxazol-3-il]metil}-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-{[5-(2-furil)isoxazol-3-il]metil}-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-{[5-(2-furil)isoxazol-3-il]metil}-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[3-(1H-imidazol-1-il)propil]-3-oxoisoindolina-1-carboxamida;
2-[3,5-bis(trifluorometil)bencil]-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida;
N-(1-bencilpirrolidin-3-il)-2-[3,5-bis(trifluorometil)bencil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-[(1-fenil-1H-tetrazol-5-il)metil]isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[3-(dimetilamino)propil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[2-(dimetilamino)etil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida
N-[2-(4-benzoilpiperazin-1-il)etil]-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-(1-piridin-3-iletil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(3-metoxifenil)-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-(1-piridin-4-iletil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(4-cianofenil)-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(3-metoxipropil)-3-oxoisoindolina-1-carboxamida;
N-(1,3-benzodioxol-5-ilmetil)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(3,4-dimetoxibencil)-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[(3-metil-5-fenilisoxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida;
N-butil-2-[2-(4-clorofenil)propil]-7-fluoro-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)propil]-7-fluoro-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-[2-(fenilsulfonil)etil]isoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-fluorofenoxi)propil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-(2-fenoxipropil)isoindolina-1-carboxamida;

N-bencil-2-[(5-metilisoxazol-3-il)metil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[4-(metilsulfonil)bencil]-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-[2-(fenilsulfonil)etil]isoindolina-1-carboxamida;
N-bencil-3-oxo-2-(2-fenoxietil)isoindolina-1-carboxamida;
N-bencil-3-oxo-2-(2-fenoxipropil)isoindolina-1-carboxamida;
N-bencil-2-[2-(4-fluorofenoxi)propil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[(1-bencil-1H-pirazol-4-il)metil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[(5-metil-3-fenilisoxazol-4-il)metil]-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-[(3-fenilisoxazol-5-il)metil]isoindolina-1-carboxamida;
N-(terc-butil)-5,6-dicloro-2-(4-cianobencil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5,6-dicloro-2-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5,6-dicloro-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5,6-dicloro-2-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5-fluoro-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida;
N-(4-fluorobencil)-3-oxo-2-(2-piridin-4-iletil)isoindolina-1-carboxamida;
2-[(1-metil-1H-pirrol-2-il)metil]-3-oxo-N-[3-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-(2-furilmetil)-3-oxo-2-(2-fenilpropil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)etil]-N-[(5-metil-2-furil)metil]-3-oxoisoindolina-1-carboxamida;
N-(4-fluorobencil)-2-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida;
N-(2-clorobencil)-2-[2-(1H-indol-3-il)-1-metiletil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5,6-dicloro-2-[2-(4-cloro-2-metilfenil)-2,2-difluoroetil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-5,6-dicloro-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-cloro-2-metilfenil)-2,2-difluoroetil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-cloro-2-metilfenil)-2,2-difluoroetil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
2-[3-(difluorometoxi)bencil]-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida;
N-(2-clorobencil)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
2-[4-(difluorometoxi)bencil]-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida;
N-(2-clorobencil)-2-(2,5-dimetilbencil)-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;

N-(2-clorobencil)-2-[(1R)-1-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
N-(2-clorobencil)-2-[(1R)-1-(3-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
N-(2-clorobencil)-2-[(1S)-1-(1-naftil)etil]-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-(4-fenoxibencil)isoindolina-1-carboxamida;
N-(2-clorobencil)-3-oxo-2-(3-fenilpropil)isoindolina-1-carboxamida;
N-(2-clorobencil)-3-oxo-2-(2-feniletil)isoindolina-1-carboxamida;
N-(2-clorobencil)-3-oxo-2-(1-fenilpropil)isoindolina-1-carboxamida;
N-(2-clorobencil)-2-(1-metil-3-fenilpropil)-3-oxoisoindolina-1-carboxamida;
N-(2-clorobencil)-3-oxo-2-(2-fenilpropil)isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(2-clorobencil)-3-oxoisoindolina-1-carboxamida;
3-oxo-2-(1-fenilpropil)-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
3-oxo-2-(2-fenilpropil)-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
2-(1-metil-3-fenilpropil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
3-oxo-2-(2-feniletil)-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-bencil-2-[2-(5-bromo-2-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
3-oxo-2-(3-fenilpropil)-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-bencil-2-[2-(3-bromo-4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
2-(2-metilbutil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-bencil-2-(2,4-difluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(ciclohexilmetil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
2-(3-fluorobencil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
2-(2-etoxibencil)-3-oxo-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
3-oxo-2-[4-(trifluorometoxi)bencil]-N-[2-(trifluorometil)bencil]isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[2-(3,4-dimetoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-[2-(2-tienil)etil]isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-[2-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(2-metoxietil)-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[4-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[3-(difluorometoxi)bencil]-3-oxoisoindolina-1-carboxamida;

N-butil-2-(1-naftilmetil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-cicloheptil-3-oxoisoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-[2-(4-bromofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(1-etilpropil)-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-[3-(1H-pirrol-1-il)bencil]isoindolina-1-carboxamida;
N-bencil-2-(3-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(2-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(2-etoxibencil)-3-oxoisoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-3-oxo-2-(2-fenilpropil)isoindolina-1-carboxamida;
N-bencil-2-(4-cianobencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(3,5-dimetoxibencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[1-(1-naftil)etil]-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-[4-(trifluorometil)bencil]isoindolina-1-carboxamida;
N-({2-[3,5-bis(trifluorometil)bencil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)-beta-alaninato de etilo;
2-(1-naftilmetil)-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida;
N-({2-[2-(3,4-diclorofenil)etil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)-beta-alaninato de etilo;
4-({1-[(bencilamino)carbonil]-3-oxo-1,3-dihidro-2H-isoindol-2-il}metil)benzoato de metilo;
3-oxo-2-[3-(trifluorometil)bencil]-N-[(trimetilsilil)metil]isoindolina-1-carboxamida;
2-[1-(1-naftil)etil]-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida;
3-oxo-2-[4-(trifluorometil)bencil]-N-[(trimetilsilil)metil]isoindolina-1-carboxamida;
2-[2-(4-bromofenil)etil]-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida;
2-(2-cloro-6-fenoxibencil)-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida;
2-(3,4-diclorobencil)-3-oxo-N-[(trimetilsilil)metil]isoindolina-1-carboxamida;
N-bencil-2-(1-bencilpirrolidin-3-il)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(1-bencilpirrolidin-3-il)-4,5-dimetoxi-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(3,4-difluorobencil)-4,5-dimetoxi-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(4-clorofenil)propil]-4,5-dimetoxi-3-oxoisoindolina-1-carboxamida;
N-bencil-4,5-dimetoxi-2-(1-metil-3-fenilpropil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[(1-metil-1H-pirrol-2-il)metil]-3-oxoisoindolina-1-carboxamida;

N-bencil-3-oxo-2-(1-fenil-2-pirrolidin-1-iletil)isoindolina-1-carboxamida;
N-bencil-2-[2-(4-metoxifenil)-2-oxoetil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[(1R)-1-(4-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(3,4-difluorobencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[(1R)-1-(3-metoxifenil)etil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(2,5-dimetilbencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(1-metil-3-fenilpropil)-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-{2-[3-(trifluorometil)fenil]etil}isoindolina-1-carboxamida;
N-bencil-2-[3,5-bis(trifluorometil)bencil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[2-(6-cloro-1H-indol-3-il)etil]-3-oxoisoindolina-1-carboxamida;
N,2-dibencil-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(ciclohexilmetil)-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida;
2-(1,3-benzodioxol-5-ilmetil)-N-ciclohexil-3-oxoisoindolina-1-carboxamida;
2-(2-metoxibencil)-N-(4-metilciclohexil)-3-oxoisoindolina-1-carboxamida;
N-{[3-oxo-2-(3-pirrolidin-1-ilpropil)-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
N-(terc-butil)-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(2-bromobencil)-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)etil]-N-ciclohexil-3-oxoisoindolina-1-carboxamida;
N-(2,3-dimetilciclohexil)-3-oxo-2-(2-tienilmetil)isoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida;
2-(2-clorobencil)-N-(4-metilciclohexil)-3-oxoisoindolina-1-carboxamida;
N-butil-2-(2-ciclohex-1-en-1-iletil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[(2R)-2-hidroxi-1,2-difeniletil]-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-butil-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-isopropil-3-oxoisoindolina-1-carboxamida;
N-{[2-(2-bromobencil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
2-[2-(4-clorofenil)propil]-N-isopropil-3-oxoisoindolina-1-carboxamida;
N-{[3-oxo-2-(2-feniletil)-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de metilo;
N-(terc-butil)-2-[1-(2-naftil)etil]-3-oxoisoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-[1-(2-naftil)etil]-3-oxoisoindolina-1-carboxamida;

2-[2-(3,4-dietoxifenil)etil]-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
2-bencil-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-[4-(dimetilamino)bencil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(3-metoxibencil)-3-oxoisoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-N-ciclopentil-3-oxoisoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-3-oxo-N-(piridin-3-ilmetil)isoindolina-1-carboxamida;
2-(2,5-dimetoxibencil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
N-(sec-butil)-2-[2-(4-clorofenil)etil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(2,3-difluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(2-cloro-4-fluorobencil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)etil]-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(2-metilbencil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(ciclohexilmetil)-3-oxoisoindolina-1-carboxamida;
2-(1-metil-3-fenilpropil)-3-oxo-N-(2-feniletil)isoindolina-1-carboxamida;
N-bencil-2-ciclohexil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(2-ciclohex-1-en-1-iletil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;
N-{[2-(ciclohexilmetil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-(2-ciclohex-1-en-1-iletil)-3-oxoisoindolina-1-carboxamida;
N-{[2-(bifenil-2-ilmetil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
N-bencil-2-(2,2-dimetilpropil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(3-metilbutil)-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-[2-(2-tienil)etil]isoindolina-1-carboxamida;
N-(1H-1,2,3-benzotriazol-1-ilmetil)-3-oxo-2-(2-feniletil)isoindolina-1-carboxamida;
N-bencil-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(2-metilbencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(2-metoxibencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-3-oxo-2-(2-feniletil)isoindolina-1-carboxamida;
N-bencil-2-[1-(2-naftil)etil]-3-oxoisoindolina-1-carboxamida;

N-({2-[2-(4-clorofenil)propil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de metilo;

N-({2-[1-(2-naftil)etil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de terc-butilo;

N-(1H-1,2,3-benzotriazol-1-ilmetil)-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;

N-butil-2-[1-(2-naftil)etil]-3-oxoisoindolina-1-carboxamida;

N-bencil-2-(2-bromobencil)-3-oxoisoindolina-1-carboxamida;

N-bencil-2-(2-ciclohex-1-en-1-iletil)-3-oxoisoindolina-1-carboxamida;

N-bencil-2-(bifenil-2-ilmetil)-3-oxoisoindolina-1-carboxamida;

N-butil-2-[2-(4-clorofenil)propil]-3-oxoisoindolina-1-carboxamida;

N-butil-2-[2-(4-clorofenil)-2-metilpropil]-3-oxo-1H-isoindol-1-carboxamida;

N-(terc-butil)-2-[(4,4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;

(1R o 1S)-N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;

(1S o 1R)-N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;

2-[2-(4-clorofenil)-2-metilpropil]-N-[(1-isopropil-5-oxopirrolidin-3-il)metil]-3-oxoisoindolina-1-carboxamida;

2-[2-(4-clorofenil)propil]-N-[(1-isopropil-5-oxopirrolidin-3-il)metil]-3-oxoisoindolina-1-carboxamida;

1H-isoindol-1-carboxamida, 2-[2-(4-clorofenil)propil]-2,3-dihidro-N-[2-[(1-metiletil)amino]-2-oxoetil]-3-oxo-;

N-(terc-butil)-2-[(4',5-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-2-[(5-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-2-[(4-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-2-[(4-fluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;

(1R o 1S)-N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;

(1S o 1R)-N-(terc-butil)-2-[(3',4'-difluorobifenil-2-il)metil]-3-oxoisoindolina-1-carboxamida;

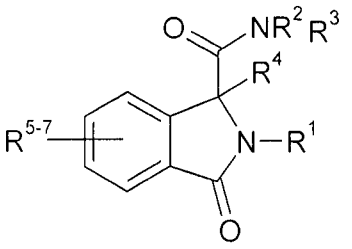
2-[2-(4-clorofenil)propil]-N-[(1-isopropil-5-oxopirrolidin-3-il)metil]-3-oxoisoindolina-1-carboxamida;

1H-isoindol-1-carboxamida, 2-[2-(4-clorofenil)propil]-2,3-dihidro-N-[2-[(1-metiletil)amino]-2-oxoetil]-3-oxo-;
2-(2,2-dimetilpropil)-6-fluoro-3-oxo-N-(1-feniletil)isoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-6-fluoro-N-(3-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-6-fluoro-N-(2-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-(3-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(2,2-dimetilpropil)-N-(2-fluorobencil)-3-oxoisoindolina-1-carboxamida;
2-(1-metil-1-feniletil)-3-oxo-N-(1-feniletil)isoindolina-1-carboxamida;
6-fluoro-3-oxo-N,2-bis(1-feniletil)isoindolina-1-carboxamida;
N-(1-metil-1-feniletil)-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;
3-oxo-N,2-bis(1-feniletil)isoindolina-1-carboxamida;
N-(3-fluorobencil)-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;
N-(2-fluorobencil)-3-oxo-2-(1-feniletil)isoindolina-1-carboxamida;
(1R o 1S)-2-[(2S o 2R)-2-(4-clorofenil)propil]-3-oxo-N-propilisoindolina-1-carboxamida;
(1S o 1R)-2-[(2R o 2S)-2-(4-clorofenil)propil]-3-oxo-N-propilisoindolina-1-carboxamida;
(1R o 1S)-2-[(2R o 2S)-2-(4-clorofenil)propil]-3-oxo-N-propilisoindolina-1-carboxamida;
(R o S) 2-(bifenil-2-ilmetil)-6-cloro-N-etil-3-oxoisoindolina-1-carboxamida;
(S o R) 2-(bifenil-2-ilmetil)-6-cloro-N-etil-3-oxoisoindolina-1-carboxamida;
N-(4-fluorobencil)-2-[1-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
2-[1-(4-clorofenil)etil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-2-[1-(4-fluorofenil)etil]-3-oxoisoindolina-1-carboxamida;
2-[1-(4-clorofenil)-1-metiletil]-N-(4-fluorobencil)-3-oxoisoindolina-1-carboxamida;
N-bencil-6-fluoro-2-[1-(4-fluorofenil)-1-metiletil]-3-oxoisoindolina-1-carboxamida;
2-[1-(4-clorofenil)-1-metiletil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
N-(4-fluorobencil)-2-[1-(4-fluorofenil)-1-metiletil]-3-oxoisoindolina-1-carboxamida;
N-bencil-6-fluoro-2-(1-metil-1-feniletil)-3-oxoisoindolina-1-carboxamida;
2-[1-(4-fluorofenil)-1-metiletil]-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
N-(4-fluorobencil)-2-(1-metil-1-feniletil)-3-oxoisoindolina-1-carboxamida;
2-(1-metil-1-feniletil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-(5-cianopentilo)-6-fluoro-3-oxoisoindolina-1-carboxamida;
N-bencil-6-bromo-3-oxo-2-(1-fenilpropil)isoindolina-1-carboxamida
N-bencil-2-[2-(4-clorofenil)propil]-4-fluoro-3-oxoisoindolina-1-carboxamida;

2-[2-(4-clorofenil)propil]-N-(4,4-difluorobutil)-4-fluoro-3-oxoisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-4-fluoro-3-oxo-N-propilisoindolina-1-carboxamida;
2-[2-(4-clorofenil)propil]-N-etil-4-fluoro-3-oxoisoindolina-1-carboxamida;
N-bencil-2-(bifenil-2-ilmetil)-4-fluoro-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-(4,4-difluorobutil)-4-fluoro-3-oxoisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-4-fluoro-3-oxo-N-propilisoindolina-1-carboxamida;
2-(bifenil-2-ilmetil)-N-etil-4-fluoro-3-oxoisoindolina-1-carboxamida;
N-bencil-4-fluoro-3-oxo-2-[(1R)-1-feniletil]isoindolina-1-carboxamida;
o una de sus sales farmacéuticamente aceptables;

o uno de sus enantiómeros.

60. Un compuesto de fórmula I:



I

o una de sus sales farmacéuticamente aceptables, donde

$\mathbf{R}^1$ representa C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, oxo, $-OR^8$, $-COR^9$, $-SR^{10}$, $-COXR^{11}$, $-N(R^{12a})(R^{12b})$, $-N(R^{13a})C(O)OR^{13b}$, $-OC(O)N(R^{14a})(R^{14b})$, $-SO_2R^{15}$, arilo o Het^1); además R^1 representa arilo o Het^2;

R^8 a R^{11}, R^{13a}, R^{13b}, R^{15} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^9 (donde los grupos C_1-C_6 alquilo, arilo y Het^9 están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{10});

R^{12a} y R^{12b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{11} (donde los grupos C_1-C_6 alquilo, arilo y Het^{11} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{12}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{14a} y R^{14b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{13} (donde los grupos C_1-C_6 alquilo, arilo y Het^{13} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{14}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^2 representa C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, $-OR^{16}$, $-COR^{17}$, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, ciano, trialquilsililo, $–COXR^{18}$, arilo o Het^3); además R^2 representa $-(CH_2)_kN(R^{19a})(R^{19b})$, $-(CH_2)_kNR^{20a}C(O)N(R^{20b})(R^{20c})$, $-(CH_2)_nNR^{21a}SO_2R^{21b}$, $-(CH_2)_nSO_2R^{22}$, $-(CH_2)_kN(R^{23a})C(O)OR^{23b}$, $-OC(O)N(R^{24a})(R^{24b})$, C_3-C_8 cicloalquilo, arilo o Het^4;

R^{16} a R^{18}, R^{21}, R^{22}, R^{23a}, R^{23b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{15} (donde los grupos C_1-C_6 alquilo, arilo y Het^{15} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{16});

R^{19a} y R^{19b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{19} (donde los grupos C_1-C_6 alquilo, arilo y Het^{19} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{20}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{20a}, R^{20b} y R^{20c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{21} (donde los grupos C_1-C_6 alquilo, arilo y Het^{21} están opcionalmente

sustituidos con uno o más sustituyentes selecionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{22});
R^{20b} y R^{20c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^3 representa hidrógeno, C_1-C_{12} alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, $-OR^{25}$, $-COR^{26}$, C_2-C_6 alquenilo, C_3-C_8 cicloalquilo, trialquilsililo, $-COXR^{27}$, arilo o Het^5); además R^3 representa $-(CH_2)_kN(R^{28a})(R^{28b})$, $-(CH_2)_kN(R^{29a})C(O)N(R^{29b})(R^{29c})$, $-(CH_2)_nNR^{30a}SO_2R^{30b}$, $-(CH_2)_nSO_2R^{31}$, $-(CH_2)_kN(R^{32a})C(O)OR^{32b}$, $-OC(O)N(R^{33a})(R^{33b})$, C_3-C_8 cicloalquilo, arilo o Het^6;

R^{25} a R^{27}, R^{30}, R^{31}, R^{32a}, R^{32b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{23} (donde los grupos C_1-C_6 alquilo, arilo y Het^{23} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{24});

R^{28a} y R^{28b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{25} (donde los grupos C_1-C_6 alquilo, arilo y Het^{25} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{26}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{33a} y R^{33b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{27} (donde los grupos C_1-C_6 alquilo, arilo y Het^{27} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{28}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{29a}, R^{29b} y R^{29c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{29} (donde los grupos C_1-C_6 alquilo, arilo y Het^{29} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro,

C_1-C_6 alquilo, arilo y Het^{30}); R^{29b} y R^{29c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^4 representa hidrógeno, –OH, arilo, C_1-C_6 alquilo (donde el grupo alquilo está opcionalmente sustituido con uno o más grupos seleccionados entre halógeno, hidroxi, C_2-C_4 alquenilo, trialquilsililo), $-OR^{34}$, $-(CH_2)_mR^{35}$;

R^{34} representa independientemente, cada vez que aparece, hidrógeno, C_1-C_6 alquilo, arilo o Het^{31} (donde los grupos C_1-C_6 alquilo, arilo y Het^{31} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{32});

R^{35} representa independientemente arilo o Het^{33}(donde los grupos arilo y Het^{33} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{34});

R^5 a R^7 representan independientemente, cada vez que aparecen, hidrogeno, -OH, halógeno, ciano, nitro, C_{1-6} alquilo, $-OR^{36}$, $-N(R^{37a})(R^{37b})$, $-C(O)R^{38}$, $-C(O)OR^{39}$, $-C(O)N(R^{40a})(R^{40b})$, $-NC(O)OR^{41}$, $-OC(O)N(R^{42a})(R^{42b})$, $-N(R^{43a})C(O)R^{43b}$, $-N(R^{44a})S(O)_2R^{44b}$, $-S(O)_2R^{45}$, $-OS(O)_2R^{46}$, $-(CH_2)_nN(R^{47a})(R^{47b})$, $-(CH_2)_nNR^{48a}C(O)N(R^{48b})(R^{48c})$, $-(CH_2)_nNR^{49a}SO_2R^{49b}$, trialquilsililo, arilo o Het^7;

R^{36}, R^{38}, R^{39}, R^{41}, R^{43}, R^{44a}, R^{44b}, R^{45}, R^{46}, R^{49a} y R^{49b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{35} (donde los grupos C_1-C_6 alquilo, arilo y Het^{35} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{36});

R^{37a} y R^{37b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{37} (donde los grupos C_1-C_6 alquilo, arilo y Het^{37} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{38}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{40a} y R^{40b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{39} (donde los grupos C_1-C_6 alquilo, arilo y Het^{39} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{40}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{42a} y R^{42b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{41} (donde los grupos C_1-C_6 alquilo, arilo y Het^{41} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{42}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{47a} y R^{47b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{43} (donde los grupos C_1-C_6 alquilo, arilo y Het^{43} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{44}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{48a}, R^{48b} y R^{48c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{45} (donde los grupos C_1-C_6 alquilo, arilo y Het^{45} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{46}) R^{48b} y R^{48c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

arilo está, cada vez que aparece, opcionalmente sustituido con –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, C_3-C_8 cicloalquilo, C_2-C_6 alquenilo, arilo, Het^8, $-OR^{50}$, $-(CH_2)_mR^{51}$, $-SR^{52}$, $-C(O)R^{53}$, $-COXR^{54}$, $-N(R^{55a})(R^{55b})$, $-SO_2R^{56}$, $-OS(O)_2R^{57}$, $-(CH_2)_mN(R^{58a})(R^{58b})$, $-CH_2)_mNR^{59a}C(O)N(R^{59b})(R^{59c})$, $-C(O)OR^{60}$, $-C(O)N(R^{61a})(R^{61b})$, $-N(R^{62a}C(O)R^{62b}$, $-N(R^{63a})C(O)OR^{63b}$, $-OC(O)N(R^{64a})(R^{64b})$, $-N(R^{65a})S(O)_2R^{65b}$ y $OC(O)R^{66}$;

R^{50} a R^{54}, R^{56}, R^{57}, R^{60}, R^{62a}, R^{62b}, R^{63a}, R^{63b}, R^{65a}, R^{65b} y R^{66} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{47} (donde los grupos C_1-C_6 alquilo, arilo y Het^{47} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{48});

R^{51} representa independientemente arilo o Het^{49} (donde los grupos arilo y Het^{49} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{50});

R^{55a} y R^{55b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{51} (donde los grupos C_1-C_6 alquilo, arilo y Het^{51} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{52}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{58a} y R^{58b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{53} (donde los grupos C_1-C_6 alquilo, arilo y Het^{53} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{54}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{59a}, R^{59b} y R^{59c} representan independientemente, cada vez que aparecen, hidrogeno, C_1-C_6 alquilo, arilo o Het^{55} (donde los grupos C_1-C_6 alquilo, arilo y Het^{55} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{56});
R^{59b} y R^{59c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{61a} y R^{61b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{57} (donde los grupos C_1-C_6 alquilo, arilo y Het^{57} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{58});

o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{64a} y R^{64b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{59} (donde los grupos C_1-C_6 alquilo, arilo y Het^{59} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{60});

Het^1 a Het^{60} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde los grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro, C_{1-6} alquilo, C_{2-6} alquenilo, arilo, otro Het, $-OR^{67}$, $-(CH_2)_mR^{68}$, $-SR^{69}$, $-COXR^{70}$, $-N(R^{71a})(R^{71b})$, $-SO_2R^{72}$, $-(CH_2)_mN(R^{73a})(R^{73b})$, $-(CH_2)_mNR^{74a}C(O)N(R^{74b})(R^{74c})$, $-C(O)R^{75}$, $-C(O)OR^{76}$, $-C(O)N(R^{77a})(R^{77b})$, $-N(R^{78a})C(O)R^{78b}$, $-N(R^{79a})S(O)_2R^{79b}$, $OC(O)R^{80}$, $-NC(O)OR^{81}$, $-OC(O)N(R^{82a})(R^{82b})$;

R^{67}, R^{69}, R^{70}, R^{72}, R^{75}, R^{76}, R^{78a}, R^{78b}, R^{79a}, R^{79b}, R^{80} o R^{81} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{61} (donde los grupos C_1-C_6 alquilo, arilo y Het^{61} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{62});

R^{68} representa independientemente arilo o Het^{63}(donde los grupos arilo y Het^{63} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{64});

R^{71a} y R^{71b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{65} (donde los grupos C_1-C_6 alquilo, arilo y Het^{65} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{66}), o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{73a} y R^{73b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{67} (donde los grupos C_1-C_6 alquilo, arilo y Het^{67} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{68});
o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{74a} y R^{74b} y R^{74c} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{69} (donde los grupos C_1-C_6 alquilo, arilo y Het^{69} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{70});
R^{74b} y R^{74c} pueden juntos representar C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{77a} y R^{77b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{71} (donde los grupos C_1-C_6 alquilo, arilo y Het^{71} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{72});
o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

R^{82a} y R^{82b} representan independientemente, cada vez que aparecen, hidrógeno, C_1-C_6 alquilo, arilo o Het^{73} (donde los grupos C_1-C_6 alquilo, arilo y Het^{73} están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre –OH, halógeno, ciano, nitro, C_1-C_6 alquilo, arilo y Het^{74}) o juntos representan C_3-C_6 alquileno, opcionalmente interrumpido por un átomo de O;

Het^{61} a Het^{74} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde los grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro y C_{1-6} alquilo;

X representa un átomo de nitrógeno u oxígeno;

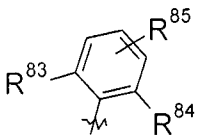
m es un número entero entre 0 y 10;

n es un número entero entre 0 y 4;

k es un número entero entre 1 y 5;

siempre que:

a) R^2 o R^3 no representan un fragmento de fórmula



donde

R^{83} y R^{84} representan independientemente, cada vez que aparecen, halógeno, C_1-C_{12} alquilo, C_1-C_{12} alcoxi, C_1-C_{12} haloalquilo, C_1-C_{12} haloalcoxi, ciano, $-SR^{86}$, $-N(R^{87a})R^{87b}$, C_2-C_6 alquinilo, arilo o Het^{75};

R^{85} representa hidrógeno, un grupo C_1-C_{12} alquilo o un grupo C_1-C_{12} alcoxi (donde los grupos C_1-C_{12} alquilo y C_1-C_{12} alcoxi están opcionalmente sustituidos con uno o más grupos seleccionados entre halógeno, C_2-C_6 alquenilo, C_2-C_6 alquinilo, ciano, oxo, arilo, Het^{76}, $-OR^{88}$, $-SR^{89}$, $-COXR^{90}$, $-N(R^{91a})R^{91b}$ y $-SO_2R^{92}$);

Het^{75} a Het^{76} representan independientemente, cada vez que aparecen, grupos heterocíclicos de cinco a doce miembros que contienen uno o más heteroátomos seleccionados entre oxígeno, nitrógeno y/o azufre, donde esos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre -OH, oxo, halo, ciano, nitro, C_{1-6} alquilo, C_{1-6} alcoxi, arilo, ariloxi, $-N(R^{93a})R^{93b}$, $-C(O)R^{93c}$, $-C(O)OR^{93d}$, $-C(O)N(R^{93e})R^{93f}$, $-N(R^{93g})C(O)R^{93h}$ y $-N(R^{93i})S(O)_2R^{93j}$, $OC(O)R^{93k}$ y otro Het;

R^{86} a R^{93} representan independientemente, cada vez que aparecen, hidrógeno o C_{1-6} alquilo; y

c) el compuesto no es:

2-(2-etoxietil)-N-isopropil-3-oxoisoindolina-1-carboxamida;

N-(terc-butil)-3-oxo-2-(3-pirrolidin-1-ilpropil)isoindolina-1-carboxamida;

N-(terc-butil)-3-oxo-2-(tetrahidrofuran-2-ilmetil)isoindolina-1-carboxamida;
2-[1-(hidroximetil)butil]-N-isopropil-3-oxoisoindolina-1-carboxamida;
N-isopropil-2-(3-metilbutil)-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-ciclohexil-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-(3-metilbutil)-3-oxoisoindolina-1-carboxamida;
N-{[2-(3-metilbutil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de metilo;
N-({2-[1-(hidroximetil)butil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de terc-butilo;
N-{[2-(3-metilbutil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
N-(terc-butil)-2-[1-(metoximetil)propil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[2-(dietilamino)etil]-3-oxoisoindolina-1-carboxamida;
N-(terc-butil)-2-[1-(hidroximetil)butil]-3-oxoisoindolina-1-carboxamida;
N-{[3-oxo-2-(2-tienilmetil)-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de terc-butilo;
N-({2-[2-(metiltio)etil]-3-oxo-2,3-dihidro-1H-isoindol-1-il}carbonil)glicinato de terc-butilo;
N-{[2-(ciclopropilmetil)-3-oxo-2,3-dihidro-1H-isoindol-1-il]carbonil}glicinato de metilo;
o
2-(2,2-dimetilpropil)-3-oxo-N-(4,4,4-trifluorobutil)isoindolina-1-carboxamida.
para usar en terapia

61. El uso de un compuesto de fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 60, en la fabricación de un medicamento para el tratamiento de las arritmias.

62. El uso de un compuesto de fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 60, en la fabricación de un medicamento para el tratamiento de las arritmias auriculares o ventriculares.

63. Una composición farmacéutica que comprende como principio activo una cantidad terapéuticamente eficaz de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 60 en asociación con uno o más diluyentes, excipientes y/o portadores inertes, farmacéuticamente aceptables.

64. La composición farmacéutica de acuerdo con la reivindicación 63, para usar en el tratamiento de las arritmias.

65. Un método de tratamiento de arritmias, que comprende administrar a un mamífero, incluido el ser humano que necesite dicho tratamiento, una cantidad terapéuticamente eficaz de los compuestos de fórmula I, de acuerdo con cualquiera de las reivindicaciones 1 a 60.

66. Un agente para el tratamiento de arritmias, que comprende como principio activo un compuesto de fórmula I, de acuerdo con cualquiera de las reivindicaciones 1 a 60.

67. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 60 para usar en el tratamiento de arritmias.

68. Un proceso para preparar un compuesto de fórmula I según se describe aquí.

PATENT COOPERATION TREATY PCT/SE2007/000683

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA AB
Global Intellectual Property
S-151 85 Södertälje
SUÈDE

Date of mailing *(day/month/year)* 28 November 2008 (28.11.2008)	
Applicant's or agent's file reference 102418-1 WO	IMPORTANT NOTIFICATION
International application No. PCT/SE2007/000683	International filing date *(day/month/year)* 12 July 2007 (12.07.2007)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
STRANDLUND, Gert AstraZeneca R & D Mölndal S-431 83 Mölndal Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
STRANDLUND, Gert Ättehögsvägen 19 S-437 33 Lindome Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☐ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 70 80	Authorized officer Ulhaq Faizan e-mail ptl1.pct@wipo.int Telephone No. +41 22 338 74 11

Form PCT/IB/306 (July 2008) I/DVGID0BS0

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional Nº
PCT/SE2007/000683

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

IPC: ver hoja extra

De acuerdo con la Clasificación Internacional de Patentes (CIP) o según la clasificación nacional y la CPI

B. SECTORES COMPRENDIDOS POR LA BÚSQUEDA

Documentación mínima consultada (sistema de clasificación, seguido de los símbolos de clasificación)
IPC: C07D, A61K, A61P

Otra documentación consultada, además de la documentación mínima, en la medida en que tales documentos formen parte de los sectores comprendidos por la búsqueda
SE,DK,FI,NO clases como arriba

Bases de datos electrónicas consultadas durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda utilizados)
EPO-INTERNAL, WPI DATA, PAJ, CHEMICAL RESUMEN

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones Nº
X	ILYN, A.P. et al., "Synthesis of novel carbomoyl-substituted derivatives of isoindole and benzo[f][1,4]oxazepine using a modified Ugi reaction; Izvestiya Vysshikh Uchebnykh Zavedenii", Khimiya i Khimicheskaya Teknologiya, 2006, vol. 49, no.5, página 13 - página 19; página 15, tabla 1	1-13,22
	--	
X	LEY S.V. et al., "A polymer-supported [1,2,3]oxazaphospholidine for the conversion of isothiocyanates to isocyanides and their subsequent use in an Ugi reaction", Bioorganic & Medicinal Chemistry Letters, 2002, vol. 12, no. 14, página 1813 - página 1816, ISSN 0960-894X, entrada 7-18, tabla 3, resumen	1-13
	--	

☒ En la continuación del recuadro C se relacionan otros documentos.

☒ Los documentos de familias de patentes se indican en el anexo.

* Categorías especiales de documentos citados:

"A" documento que define el estado general de la técnica no considerado como particularmente relevante

"E" documento anterior aunque publicado en la fecha de presentación internacional o en fecha posterior

"L" documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada)

"O" documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro medio

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada

"T" documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad, que no pertenece al estado de la técnica pertinente pero que se cita por permitir la comprensión del principio o teoría que constituye la base de la invención

"X" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado

"Y" documento particularmente relevante; la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros documentos de la misma naturaleza, resultando dicha combinación evidente para un experto en la materia

"&" documento que forma parte de la misma familia de patentes

Fecha en que se ha concluido la búsqueda internacional	Fecha de expedición del Informe de Búsqueda Internacional
10 de Octubre de 2007	15-10-2007
Nombre y dirección postal de la Administración encargada de la Búsqueda Internacional Oficina Sueca de Patentes Box 5055, S-102 42 STOCKHOLM Fax No. + 46 8 666 02 86	**Funcionario autorizado** Anna Sjölund/Eö Teléfono No. +46 8 782 25 00

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional Nº
PCT/SE2007/000683

C (Continuación). DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones Nº
A	HANUSCH-KOMPA, C et al.,"Multi-component reactions 13: Synthesis of gamma-lactams as part of a multi-ring system via Ugi-4-center-3-component reaction"; Tetrahedron Letters, 1998, vol. 39, no. 18, página 2725 - página 2728, tabla 2, esquema 2	1-3,5,7-11
	--	
A	WO 2005054195 A1 (AVENTIS PHARMA DEUTSCHLAND GMBH), 16 de Junio de 2005 (16.06.2005)	1-68
	--	
A	WO 03101450 A1 (AVENTIS PHARMA DEUTSCHLAND GMBH), 11 de Diciembre de 2003 (11.12.2003)	1-68
	--	
A	EP 0273401 A1 (KYOWA HAKKO KOGYO KABUSHIKI KAISHA), 6 de Julio de 1988 (06.07.1988)	1-68
	--	
A	WO 0140231 A1 (BRISTOL-MYERS SQUIBB COMPANY), 7 de Junio de 2001 (07.06.2001)	1-68
	--	
A	WO 0224655 A1 (MERCK & CO., INC.), 28 de Marzo de 2002 (28.03.2002)	1-68
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A	WO 2005025674 A1 (AVENTIS PHARMA DEUTSCHLAND GMBH), 24 de Marzo de 2005 (24.03.2005)	1-68
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P,X	DEBDAB M. et al., "Ionic-Liquid-Supported Synthesis of Amines and Derivatives", Synthesis, 2006, vol. 23, página 4046 - página 4042, ejemplos 12, 13	1-12
	--	

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional Nº
PCT/SE2007/000683

C (Continuación). DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones Nº
f,X	TRIFILENKOV, A. S. et al., "One-pot tandem complexity-generating reaction based om Ugi four component condensation and intramolecular cyclization", Tetrahedron Letters, 2007, vol. 48, no. 18, página 2563 - página 2567, ISSN 0040-4039, página 2565	1-9,12-13

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional N°
PCT/SE2007/000683

Recuadro II **Observaciones cuando se estime que algunas reivindicaciones no pueden ser objeto de búsqueda (continuación del punto 2 de la primera hoja)**

Este informe de búsqueda internacional no se ha realizado en relación a ciertas reivindicaciones por los siguientes motivos:

1. ☒ Las reivindicaciones n^{os}: 65
se refieren a un objeto con respecto al cual esta Administración no está obligada a proceder a la búsqueda, a saber:

La reivindicación 65 se relaciona con un método de tratamiento del cuerpo humano o animal mediante cirugía o terapia, así como con

.../...

2. ☐ Las reivindicaciones n^{os}:
se refieren a elementos de la solicitud nacional que no cumplen con los requisitos establecidos, de tal modo que no pueda efectuarse una búsqueda provechosa, concretamente:

3. ☐ Las reivindicaciones n^{os}:
son reivindicaciones dependientes y no están redactadas de conformidad con los párrafos segundo y tercero de la Regla 6.4(a)..

Recuadro III **Observaciones cuando falta unidad de incención (continuación del punto 3 de la primera hoja)**

La Administración encargada de la búsqueda internacional ha detectado varias invenciones en la presente solicitud nacional, a saber:

1. ☐ Dado que todas las tasas adicionales requeridas han sido satisfechas por el solicitante dentro del plazo, el presente informe de búsqueda de tipo internacional comprende todas las reivindicaciones que pueden ser objeto de búsqueda.

2. ☐ Dado que todas las reivindicaciones que pueden ser objeto de búsqueda podrían serlo sin realizar un esfuerzo que justifique tasas adicionales, esta Administración no requirió el pago de tasas adicionales.

3. ☐ Dada que tan sólo una parte de las tasas adicionales requeridas ha sido satisfecha dentro del plazo por el solicitante, el presente informe de búsqueda de tipo internacional comprende solamente aquellas reivindicaciones respecto de las cuales han sido satisfechas las tasas, concretamente las reivindicaciones n^{os}:

4 ☐ Ninguna de las tasas adicionales requeridas ha sido satisfecha por el solicitante dentre de plazo, En consecuencia, el presente informe de búsqueda de tipo internacional se limita a la invención mencionada en primer término en las reivindicaciones, cubierta por las reivindicaciones n^{os}:

Indicación en cuanto a la protesta

☐ Se acompañó a las tasas adicionales la protesta del solicitante y, en su caso, el pago de una tasa de protesta.

☐ Se acompañó a las tasas adicionales la protesta del solicitante, pero la tasa de protesta aplicable no se pagó en el plazo estabecido para ello.

☐ El pago de las tasas adicionales no ha sido acompañado de ninguna protesta.

Recuadro II.1

métodos de diagnósticos / Regla 39.1(iv). Sin embargo, una búsqueda ha sido realizada para esta reivindicación. La búsqueda se ha basado en los efectos alegados de los compuestos.

Clasificación de patente internacional (IPC)

C07D 209/46 (2006.01)
A61K 31/40 (2006.01)
A61K 31/4035 (2006.01)
A61K 31/41 (2006.01)
A61K 31/435 (2006.01)
A61K 31/495 (2006.01)
A61P 9/04 (2006.01)
A61P 9/06 (2006.01)
C07D 401/00 (2006.01)
C07D 403/00 (2006.01)
C07D 413/00 (2006.01)

Descargue los documentos de su patente en www.prv.se
Los documentos de patente citados se pueden descargar en www.prvf.se mediante los vínculos siguientes:

- En English/Searches and advisory services/Cited documents (servicio en inglés) o
- e-tjänster/anförda document (servicio en sueco).

Use el número de solicitud como número de usuario.
La contraseña es **NXPLFMMZPN**.

Las copias en papel se pueden ordenar a un costo de 50 SEK por copia a PVR InterPat (número de teléfono 08-782 28 85).

La bibliografía citada, si la hay, se adjuntará impresa.

INFORME DE BÚSQUEDA INTERNACIONAL
Información sobre miembros de la familia de patentes

01/09/2007

Solicitud internacional N°
PCT/SE2007/000683

WO	2005054195	A1	16/06/2005	AR	046733	A	21/12/2005
				AU	2004295056	A	16/06/2005
				BR	PI0417147	A	06/03/2007
				CA	2548020	A	16/06/2005
				CN	1886374	A	27/12/2006
				DE	10356717	A	07/07/2005
				EP	1692105	A	23/08/2006
				JP	2007516243	T	21/06/2007
				KR	20060111558	A	27/10/2006
				NO	20063058	A	30/06/2006
				US	20050124681	A	09/06/2005
WO	03101450	A1	11/12/2003	AT	324889	T	15/06/2006
				AU	2003240677	A	00/00/0000
				BR	0311556	A	12/04/2005
				CA	2488373	A	11/12/2003
				CN	1290833	C	20/12/2006
				CN	1658869	A	24/08/2005
				DE	60305042	D,T	24/05/2007
				DK	1528923	T	04/09/2006
				EP	1528923	A,B	11/05/2005
				SE	1528923	T3	
				ES	2261939	T	16/11/2006
				FR	2840302	A,B	05/12/2003
				HK	1076383	A	11/05/2007
				HR	20041151	A	30/06/2005
				IL	165520	D	00/00/0000
				JP	2005533034	T	04/11/2005
				MA	27308	A	02/05/2005
				MX	PA04011931	A	31/03/2005
				NO	20045660	A	27/12/2004
				PL	372188	A	11/07/2005
				PT	1528923	T	31/08/2006
				RU	2004138789	A	27/06/2005
				SI	1528923	T	31/08/2006
				US	7078428	B	18/07/2006
				US	20040048916	A	11/03/2004
				US	20060148880	A	06/07/2006
				YU	104804	A	15/12/2006
				ZA	200409094	A	12/07/2005
EP	0273401	A1	06/07/1988	CA	1284647	A,C	04/06/1991
				DE	3782636	A,T	17/12/1992
				JP	1949566	C	10/07/1995
				JP	6070011	B	07/09/1994
				JP	63264457	A	01/11/1988
				US	4849441	A	18/07/1989

INFORME DE BÚSQUEDA INTERNACIONAL
Información sobre miembros de la familia de patentes
01/09/2007

Solicitud internacional N°
PCT/SE2007/000683

WO	0140231	A1	07/06/2001	AR	029457	A	02/07/2003
				AU	781862	B	16/06/2005
				AU	1812701	A	12/06/2001
				BR	0016166	A	24/06/2003
				CA	2393809	A	07/06/2001
				CN	1407985	A,T	02/04/2003
				CZ	20021949	A	12/03/2003
				EP	1237891	A	11/09/2002
				HU	0301834	A	29/09/2003
				IL	149473	D	00/00/0000
				JP	2004507442	T	11/03/2004
				MX	PA02005533	A	31/10/2002
				NO	323588	B	11/06/2007
				NO	20022649	A	06/06/2002
				NZ	518663	A	26/11/2004
				PL	364926	A	27/12/2004
				RU	2296766	C	10/04/2007
				RU	2002118622	A	10/01/2004
				US	6706720	B	16/03/2004
				US	7157451	B	02/01/2007
				US	20030022890	A	30/01/2003
				US	20040063687	A	01/04/2004
				US	20070099899	A	03/05/2007
				ZA	200203407	A	25/09/2003
WO	0224655	A1	28/03/2002	AU	1296902	A	02/04/2002
				CA	2421819	A	28/03/2002
				EP	1322619	A	02/07/2003
				US	6870055	B	22/03/2005
				US	20040044030	A	04/03/2004
WO	2005025674	A1	24/03/2005	AU	2004271697	A	24/03/2005
				BR	PI0414203	A	31/10/2006
				CA	2538009	A	24/03/2005
				DE	10341233	A	24/03/2005
				EP	1670551	A	21/06/2006
				JP	2007505036	T	08/03/2007
				MX	PA06002103	A	31/05/2006
				US	20050054673	A	10/03/2005

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000683

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEMICAL ABSTRACT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ILYN, A. P. et al., "Synthesis of novel carbomoyl-substituted derivatives of isoindole and benzo[f][1,4]oxazepine using a modified Ugi reaction; Izvestiya Vysshikh Uchebnykh Zavedenii", Khimiya i Khimicheskaya Teknologiya, 2006, vol. 49, no. 5, page 13 - page 19; page 15, table 1	1-13,22
	--	
X	LEY S. V. et al., "A polymer-supported [1,2,3]oxazaphospholidine for the conversion of isothiocyanates to isocyanides and their subsequent use in an Ugi reaction", Bioorganic & Medicinal Chemistry Letters, 2002, vol. 12, no. 14, page 1813 - page 1816, ISSN 0960-894X, entry 7-18, table 3, abstract	1-13
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2007	15 -10- 2007
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/Eö Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000683

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HANUSCH-KOMPA, C et al., "Multi-component reactions 13: Synthesis of gamma-lactams as part of a multi-ring system via Ugi-4-center-3-component reaction"; Tetrahedron Letters, 1998, vol. 39, no. 18, page 2725 - page 2728, table 2, scheme 2	1-3,5,7-11
A	WO 2005054195 A1 (AVENTIS PHARMA DEUTSCHLAND GMBH), 16 June 2005 (16.06.2005)	1-68
A	WO 03101450 A1 (AVENTIS PHARMA DEUTSCHLAND GMBH), 11 December 2003 (11.12.2003)	1-68
A	EP 0273401 A1 (KYOWA HAKKO KOGYO KABUSHIKI KAISHA), 6 July 1988 (06.07.1988)	1-68
A	WO 0140231 A1 (BRISTOL-MYERS SQUIBB COMPANY), 7 June 2001 (07.06.2001)	1-68
A	WO 0224655 A1 (MERCK & CO., INC.), 28 March 2002 (28.03.2002)	1-68
A	WO 2005025674 A1 (AVENTIS PHARMA DEUTSCHLAN GMBH), 24 March 2005 (24.03.2005)	1-68
P,X	DEBDAB M. et al., "Ionic-Liquid-Supported Synthesis of Amines and Derivatives", Synthesis, 2006, vol. 23, page 4046 - page 4052, examples 12, 13	1-12

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000683

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TRIFILENKOV, A. S. et al., "One-pot tandem complexity-generating reaction based om Ugi four component condensation and intramolecular cyclization", Tetrahedron Letters, 2007, vol. 48, no. 18, page 2563 - page 2567, ISSN 0040-4039, page 2565 -- --------	1-9,12-13

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000683

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 65
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 65 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000683

International patent classification (IPC)

C07D 209/46 (2006.01)
A61K 31/40 (2006.01)
A61K 31/4035 (2006.01)
A61K 31/41 (2006.01)
A61K 31/435 (2006.01)
A61K 31/495 (2006.01)
A61P 9/04 (2006.01)
A61P 9/06 (2006.01)
C07D 401/00 (2006.01)
C07D 403/00 (2006.01)
C07D 413/00 (2006.01)

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- In English/Searches and advisory services/Cited documents (service in English) or
- e-tjänster/anförda dokument (service in Swedish).

Use the application number as username.
The password is **NXPLFMMZPN**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-001709- -00000-0000

Fecha: 2009-01-09 15:59:32 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 589

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Claudia M Nava Ortiz.
Firma Responsable

Fecha_____

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