PCT

Industria y Comercio
SUPERINTENDENCIA
República de Colombia
Ministerio de Comercio, Industria y Turismo

PROPIEDAD INDUSTRIAL

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

11-3062

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-003062- -00000-0000
Fecha: 2011-01-13 14:22:09 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 429

21. EXPEDIENTE No. _____

54. TITULO: **DERIVADOS DE BENZAZEPINA Y SU USO COMO ANTAGONISTAS DE HISTAMINA H3**

52. CLASIFICACION INTERNACIONAL: **C07D 223/16, C07D 401/06, C07D 401/12, C07D 401/14, C07D 403/12, C07D 405/12, C07D 405/14, C07D 409/12, C07D 409/14, C07D 413/12, C07D 417/12, A61K 31/55, A61P 25/18**

71. SOLICITANTE: **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

DOMICILIO: **1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045, JAPON**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., _____

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-003062- -00000-0000

Fecha: 2011-01-13 14:22:09 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
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FORMULARIO UNICO DE SOLIC...
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

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

[X] Capítulo I [ ] Capítulo II

(2) **SOLICITANTE (71)**	Nombre: **TAKEDA PHARMACEUTICAL COMPANY LIMITED** Dirección: **1-1, Doshomachi 4-chome Chuo-ku, Osaka-shi Osaka 541-0045 JAPON** Nacionalidad o Domicilio: **Osaka - JAPON** Lugar de Constitución: **JAPON** Teléfono: Fax: E-mail:	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual Número
(3) **REPRESENTANTE O APODERADO**	Nombre: **MARGARITA CASTELLANOS A.** Dirección: **CALLE 94A No. 7A-09** Teléfono: **756 0770** Fax: **755 0158** E-mail: info@castellanosyco.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual Número **39'779.654** TPA **70.819**
(4) **INVENTOR (ES) (72)**	**VER ANEXO # 1**	

(5) **PCT (86)**

Solicitud Internacional No. **PCT/GB2009/001774** Fecha **17/07/2009**

Publicación Internacional No. **WO 2010/007382 A8** Fecha **21/01/2010**

(6) **Título (54)** **DERIVADOS DE BENZAZEPINA Y SU USO COMO ANTAGONISTAS DE HISTAMINA H3**

(7) **Clasificación Internacional (51)** C07D 223/16, C07D 401/06, C07D 401/12, C07D 401/14, C07D 403/12, C07D 405/12, C07D 405/14, C07D 409/12, C07D 409/14, C07D 413/12, C07D 417/12, A61K 31/55, A61P 25/18

(8) **Prioridad** SI [X] NO [ ]

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GB	18/07/2008	0813254,0
GB	26/03/2009	0905231,7

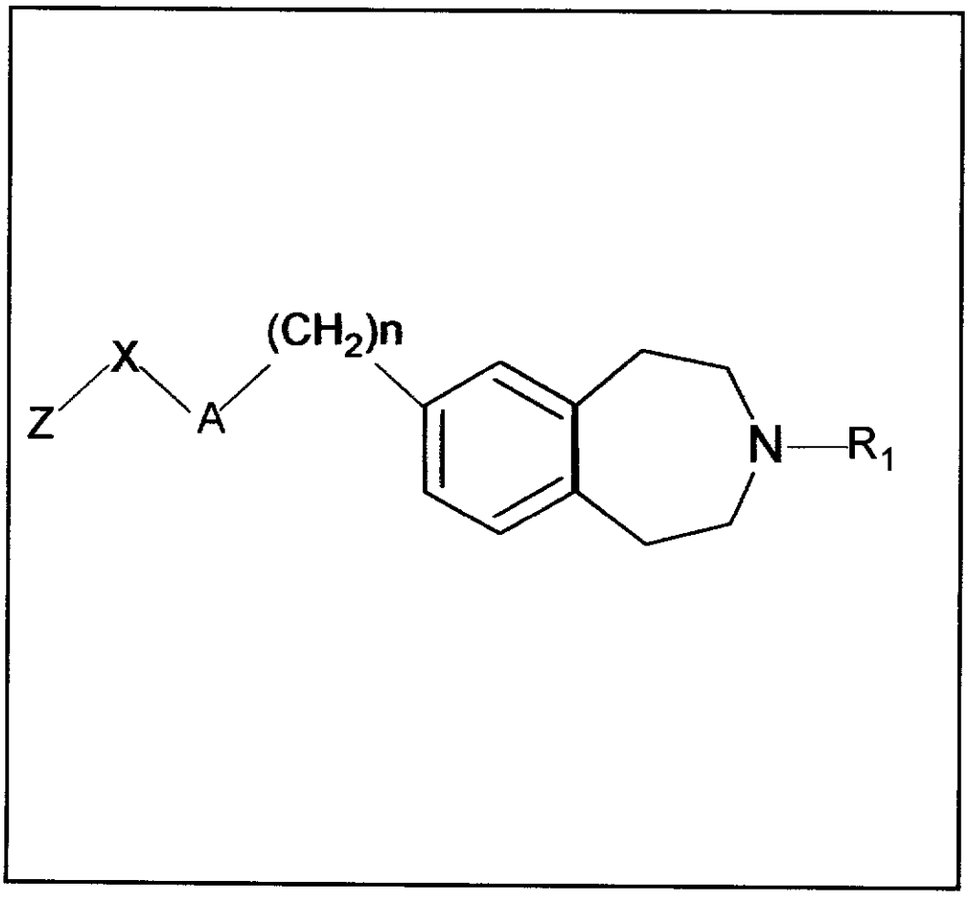
(9) **Comprobante de pago No.** **10-107,694 y 10-107,697**
11-001951 y 11-001952 Fecha **Diciembre 17 de 2010**
Enero 12 de 2010

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

(10) **Anexos**

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] 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).
- [ ] 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.
- [X] Arte final 12x12
- [ ] 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.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros **Tarjeta Propietario y Extracto para la Publicación** , Forma PCT/IB/306 (notificación de un cambio)

(11) **FIGURA CARACTERISTICA:**



(12) **Solicito la concesión de la patente,**

NOMBRE: **MARGARITA CASTELLANOS ABONDANO**

FIRMA:

C.C. No. 39'779.654 Usaquén - TPA 70.819 C.S.J.

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - P2115

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176000-2

RECIBO OFICIAL DE CAJA : 10 - 107,694
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***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	VR. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062764797	397640245	17/12/2010	7,392,000.00

***** 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	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

2115

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 001951

Bogotá D.C., 12 de 2011 - 08:48:19

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	387633676	11/01/2011	8.380.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	17.000.00	17.000.00
				$17.000.00

SON: **DIECISIETE MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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000007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 107,697
FECHA : DICIEMPRE 17 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 429

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754397	387660245	17/12/2010	1,392,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS	650,000.00
		TOTAL : $	650,000.00

SON: SEISCIENTOS CINCUENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO

000003

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 001952

Bogotá D.C., 12 de 2011 - 08:48:19

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	387633676	11/01/2011	8.380.000.00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	25.000.00	25.000.00
				$25.000.00

SON: **VEINTICINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-003062- -00000-0000
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PCT

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C07D 401/06 (2006.01) *C07D 409/14* (2006.01)
C07D 401/12 (2006.01) *C07D 413/12* (2006.01)
C07D 401/14 (2006.01) *C07D 417/12* (2006.01)
C07D 403/12 (2006.01) *A61K 31/55* (2006.01)
C07D 405/12 (2006.01) *A61P 25/18* (2006.01)
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0905231.7	26 March 2009 (26.03.2009)	GB

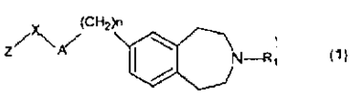
(71) Applicant *(for all designated States except US)*: **TAKEDA PHARMACEUTICAL COMPANY LIMITED.** [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **POONI, Parminder, Kaur** [GB/GB]; Takeda Cambridge Ltd, 418 Cambridge Science Park, Cambridge CB4 0PA (GB). **MERCHANT, Kevin, John** [GB/GB]; Takeda Cambridge Ltd, 418 Cambridge Science Park, Cambridge CB4 0PA (GB). **KERR, Catrina** [GB/GB]; Takeda Cambridge Ltd, 418 Cambridge Science Park, Cambridge CB4 0PA (GB). **CROSBY, Stuart, Richard** [GB/GB]; Takeda Cambridge Ltd, 418 Cambridge Science Park, Cambridge CB4 0PA (GB). **OKAWA, Tomohiro** [JP/JP]; Takeda Pharmaceutical Company Limited, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 5328686 (JP). **SASAKI, Mitsuru** [JP/JP]; Takeda Pharmaceutical Company Limited, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 5328686 (JP). **GOTOU, Mika** [JP/JP]; Takeda Pharmaceutical Company Limited, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 5328686 (JP). **SHOWELL, Graham, Andrew** [GB/GB]; Takeda Cambridge Ltd, 418 Cambridge Science Park,

[Continued on next page]

(54) Title: BENZAZEPINE DERIVATIVES AND THEIR USE AS HSTAMINE H3 ANTAGONISTS



(1)

(57) Abstract: A compound having the formula (1) wherein: R1 is a group selected from C_{3-8} cycloalkyl, C_{1-6} alkyl, C_{1-6} alkylene-C_{3-8} cycloalkyl, each of which groups may optionally be substituted with C_{1-6} alkyl, halogen, haloC_{1-6} alkyl or OR15, or R1 is heterocyclyl, optionally substituted with C_{1-6} alkyl, haloC_{1-6} alkyl or OR15; n is 0, 1, 2, 3 or 4, the alkylene group -$(CH_2)_n$- formed thereby being optionally substituted with a group selected from C_{1-4} alkyl, C_{3-8} cycloalkyl and arylsulfonyl; A is a group selected from -N(R2)CO-, -CON(R2)-, -OC(O)-, -C(O)O-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, - C(=CR2R3)-, -C_{3-8} cycloalkylene-, -C(R2)(haloC_{1-6} alkyl)-, C_{1-4} alkylene and -C(OR3)(haloC_{1-6} alkyl)-; R2 and R3 are each independently selected from H, C_{1-6} alkyl, and C_{3-8} cycloalkyl, or, when A is -N(R2)CO- and X is absent, R2 may form, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group, which may optionally be substituted; X is absent or is C_{1-4} alkylene or C_{2-4} alkenylene, each of which may optionally be substituted with one or more C_{1-4} alkyl groups, OR16, halogen or haloC_{1-6} alkyl; Z is selected from aryl, heteroaryl, C_{3-8} cycloalkyl, and heterocyclyl, each of which may optionally be substituted by a group selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl, or, when X is present, Z may be H, or, when X is absent and A is -C(R2)(OR3)- or -N(R2)CO-, Z may be H, or, when A is -N(R2)CO- and X is absent, Z may form, together with the adjacent nitrogen atom and R2, an N-containing heterocyclyl group which may optionally be substituted, wherein, when A is -CO-, Z is linked to X or A via a carbon atom and wherein, when A is -N(R2)CO- and Z is H, R1 is C_{3-8} cycloalkyl; and Y represents a bond, C_{1-6} alkylene, CO, NR14, COC_{2-6} alkenylene, O, SO_2 or NHCOC_{1-6} alkylene; wherein said cycloalkyl, aryl, heteroaryl and heterocyclyl groups Z may be optionally substituted by one or more substituents which may be the same or different, and which are selected from halogen, haloC_{1-6} alkyl, hydroxy, cyano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alkyl-NR5R6, -C_{1-8} cycloalkyl-NR5R6, - CONR12R13, -NR12COR13, -NR5SO_2R6, -OCONR5R6, -NR5CO_2R6, -NR4CONR5R6 or -SO_2NR5R6- SHR8, -alkyl-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, -alkyl-SO_2R9, -alkyl-CONHR9, -alkyl-SONHR9, -alkyl-COR10, -CO-alkyl-R10, -O-alkyl-R11 (wherein R4, R5 and R6 independently represent hydrogen, C_{1-6} alkyl, -C_{3-8} cycloalkyl, -C_{1-6} alkylene-C_{3-8} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein R8 represents C_{1-6} alkyl, wherein R9 represents C_{1-6} alkyl or aryl, wherein R10 represents aryl, wherein R11 represents C_{3-8} cycloalkyl or aryl, R12, R13, R14, R15 and R16 each independently represent H or C_{1-6} alkyl, and wherein -NR5R6 and -NR12R13 may represent a nitrogen containing heterocyclyl group); wherein said R4, R5, R6 R8, R9, R11 and R11 groups may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl; and wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8}cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen, haloC_{1-6} alkyl and C_{1-6}alkyl; and wherein, when A is C_{1-4} alkylene, said

[Continued on next page]

WO 2010/007382 A8

Cambridge CB4 0PA (GB). **TEALL, Martin, Richard** [GB/GB]; Takeda Cambridge Ltd, 418 Cambridge Science Park, Cambridge CB4 0PA (GB).

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, 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, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(48) **Date of publication of this corrected version**:
18 March 2010

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cycloalkyl, aryl, heteroaryl or heterocyclyl group Z (such as a heterocyclyl group Z) is substituted at least with hydroxy, CF_3, or =O; and wherein, when A is CON(R2) n is 1; or a pharmaceutically acceptable salt or ester thereof, provided that: when A is -CO-, R1 is CH_3, C_{4-8} cycloalkyl-substituted C_{1-6} alkylene or n-butyl, n is 0 and X is $-CH_2CH_2-$, Z is not N-benzyl substituted 4-piperidinyl, N-(3-fluorobenzyl)-substituted 4-piperidinyl or N-acetyl substituted 4-piperidinyl; when A is -OC(O)-, R1 is cyclobutyl, n is 0 and X is $-CH_2CH_2-$, Z is not H; when A is -OC(O)-, R1 is n-propyl, n is 0 and X is $-CH_2-$, Z is not H; and when A is -CO-, R1 is CH_3, n is 0 and X is CH_2, Z is not H.

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C07D 401/12 (2006.01)	*C07D 413/12* (2006.01)
C07D 401/14 (2006.01)	*C07D 417/12* (2006.01)
C07D 403/12 (2006.01)	*A61K 31/55* (2006.01)
C07D 405/12 (2006.01)	*A61P 25/18* (2006.01)
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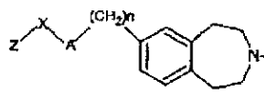
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(54) Title: BENZAZEPINE DERIVATIVES AND THEIR USE AS HISTAMINE H3 ANTAGONISTS



(1)

(57) Abstract: A compound having the formula (1) wherein: R1 is a group selected from C_{3-8} cycloalkyl, C_{1-6} alkyl, C_{1-6} alkylene-C_{3-8} cycloalkyl, each of which groups may optionally be substituted with C_{1-6} alkyl, halogen, haloC_{1-6} alkyl or OR15, or R1 is heterocyclyl, optionally substituted with C_{1-6} alkyl, haloC_{1-6} alkyl or OR15; n is 0, 1, 2, 3 or 4, the alkylene group $-(CH_2)_n-$ formed thereby being optionally substituted with a group selected from C_{1-4} alkyl, C_{3-8} cycloalkyl and arylsulfonyl; A is a group selected from -N(R2)CO-, -CON(R2)-, -OC(O)-, -C(O)O-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, - C(=CR2R3)-, -C_{3-8} cycloalkylene-, -C(R2)(haloC_{1-4} alkyl)-, C_{1-4} alkylene and -C(OR3)(haloC_{1-6} alkyl)-; R2 and R3 are each independently selected from H, C_{1-6} alkyl, and C_{3-8} cycloalkyl, or, when A is -N(R2)CO- and X is absent, R2 may form, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group, which may optionally be substituted; X is absent or is C_{1-4} alkylene or C_{2-4} alkenylene, each of which may optionally be substituted with one or more C_{1-4} alkyl groups, OR16, halogen or haloC_{1-6} alkyl; Z is selected from aryl, heteroaryl, C_{3-8} cycloalkyl, and heterocyclyl, each of which may optionally be substituted by a group selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl, or, when X is present, Z may be H, or, when X is absent and A is -C(R2)(OR3)- or -N(R2)CO-, Z may be H, or, when A is -N(R2)CO- and X is absent, Z may form, together with the adjacent nitrogen atom and R2, an N-containing heterocyclyl group which may optionally be substituted, wherein, when A is -CO-, Z is linked to X or A via a carbon atom and wherein, when A is -N(R2)CO- and Z is H, R1 is C_{3-8} cycloalkyl; and Y represents a bond, C_{1-6} alkylene, CO, NR14, COC_{2-6} alkenylene, O, SO_2 or $NHCOC_{1-6}$ alkylene; wherein said cycloalkyl, aryl, heteroaryl and heterocyclyl groups Z may be optionally substituted by one or more substituents which may be the same or different, and which are selected from halogen, haloC_{1-6} alkyl, hydroxy, cyano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alkyl-NR5R6, -C_{3-8} cycloalkyl-NR5R6, - CONR12R13, -NR12COR13, -NR5SO_2R6, -OCONR5R6, -NR5CO_2R6, -NR4CONR5R6 or -SO_2NR5R6- SHR8, -alkyl-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, -alkyl-SO_2R9, -alkyl-CONHR9, -alkyl-SONHR9, -alkyl-COR10, -CO-alkyl-R10, -O-alkyl-R11 (wherein R4, R5 and R6 independently represent hydrogen, C_{1-6} alkyl, -C_{3-8} cycloalkyl, -C_{1-6} alkylene-C_{3-8} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein R8 represents C_{1-6} alkyl, wherein R9 represents C_{1-6} alkyl or aryl, wherein R10 represents aryl, wherein R11 represents C_{3-8} cycloalkyl or aryl, R12, R13, R14, R15 and R16 each independently represent H or C_{1-6} alkyl, and wherein -NR5R6 and -NR12R13 may represent a nitrogen containing heterocyclyl group); wherein said R4, R5, R6 R8, R9, R11 and R11 groups may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl; and wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8}cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen, haloC_{1-6} alkyl and C_{1-6}alkyl; and wherein, when A is C_{1-4} alkylene, said cycloalkyl, aryl, heteroaryl or heterocyclyl group Z (such as a heterocyclyl group Z) is substituted at least with hydroxy, CF

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3, or =0; and wherein, when A is CON(R2) n is 1; or a pharmaceutically acceptable salt or ester thereof, provided that: when A is -CO-, R1 is CH_3, C_{3-8} cycloalkyl-substituted C_{1-6} alkylene or n-butyl, n is 0 and X is $-CH_2CH_2-$, Z is not N-benzyl substituted 4-piperidinyl, N-(3-fluorobenzyl)-substituted 4-piperidinyl or N-acetyl substituted 4-piperidinyl; when A is -OC(O)-, R1 is cyclobutyl, n is 0 and X is $-CH_2CH_2-$, Z is not H; when A is -OC(O)-, R1 is n-propyl, n is 0 and X is $-CH_2-$, Z is not H; and when A is -CO-, R1 is CH_3, n is 0 and X is CH_2, Z is not H.

BENZAZEPINE DERIVATIVES AND THEIR USE AS HSTAMINE H3 ANTAGONISTS

The present invention relates to compounds and their uses, and in particular to compounds having a benzazepine scaffold and their therapeutic use in the treatment or prevention of conditions having an association with the histamine H3 receptor.

The H3 receptor was first identified pharmacologically in 1983 as an autoreceptor that regulates the production of histamine (**1**). The receptor was later cloned in 1999 (**2**). It is a constitutively active G protein-coupled receptor that is expressed predominantly in the central nervous system (CNS) and modulates a variety of CNS functions both centrally and peripherally. It is expressed on the presynaptic terminals of CNS neurones and acts as a negative modulator of release of neurotransmitters such as histamine, acetylcholine, norepinephrine, serotonin and dopamine (**3**). Consequently, the ability of the H3 receptor to regulate the release of a wide range of neurotransmitters has fuelled research into the development of antagonists / inverse agonists which have potential in behavioural and physiological conditions, for example CNS disorders such as narcolepsy, disorders of wakefulness, cognition or attention, pain and in suppression of food intake.

Histaminergic neurones are located in the tuberomammillary nucleus of the posterior hypothalamus and project their axons into brain regions including the hypothalamus, thalamus, cerebral cortex, amygdala, and septum. Activity of histaminergic neurons is closely linked with the sleep / wake cycle and numerous reports in the literature have established that the H3 receptor plays a role in cognition and sleep / wake related processes, based on studies with known H3 receptor antagonists and their effects in animal models (**4**, **5**, **6**). H3 antagonist compound A-349821 is currently in preclinical development and has been shown to demonstrate cognition-enhancing effects in the rat (**7**).

The histaminergic system is one of the targets of leptin signalling in the hypothalamus. Known H3 antagonist clobenpropit increases histamine release in the hypothalamus of mice and has the effect of reducing energy intake in both lean and obese mice (**8**). The role of the H3 receptor in obesity has been further substantiated through studies with antagonists thioperamide and ciproxifan and more recently with non-imidazole compounds (**10**).

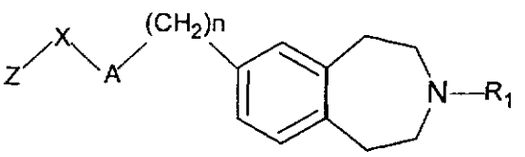
The non-selective antagonist thioperamide has an antinociceptive effect in a number of acute pain models (**11**). H3 antagonists have been suggested for the treatment of neuropathic pain (**12**). In addition GSK207040 and GSK334429 are selective non-imidazole H3 antagonist compounds that display high affinity for both rat and human H3 receptors. Both compounds reduced tactile allodynia in the rat, suggesting H3 antagonists have therapeutic potential in the treatment of neuropathic pain (**13**).

In an attempt to identify compounds with improved drug-like properties, non-imidazole compounds have been at the forefront of research, for example A-349821 (**7**) and GSK207040 / GSK334429 (**13**). ABT-239 is currently being investigated for use in attention deficit hyperactivity disorder, Alzheimer's Disease and schizophrenia (**14**).

WO05/123723, WO06/018260 and WO05/058837 disclose H3 antagonist benzazepine derivatives claimed to be useful in the treatment of neurological and psychiatric disorders. WO05/058328 discloses dopamine D3 receptor benzazepine derivatives claimed to be useful in the treatment of CNS disorders such as schizophrenia and depression. WO02/40471 also discloses benzazepine derivatives useful as modulators of the dopamine D3 receptor. US2003/0158177 discloses melanin-concentrating hormone antagonists claimed to be useful in the treatment of obesity.

There exists a clinical need to generate further classes of H3 antagonist and/or inverse agonist compounds that demonstrate improved drug-like properties (9).

In accordance with a first aspect of the present invention, there is provided a compound having the Formula 1:



Formula 1

wherein:

R1 is a group selected from C_{3-8} cycloalkyl, C_{1-6} alkyl, and C_{3-8} cycloalkyl-substituted C_{1-6} alkylene, each of which groups may optionally be substituted with C_{1-6} alkyl (such as methyl), halogen (such as F), haloC_{1-6} alkyl (such as CH_2F) or OR15, or R1 is heterocyclyl, optionally substituted with C_{1-6} alkyl (such as methyl), haloC_{1-6} alkyl (such as CH_2F) or OR15;

n is 0, 1, 2, 3 or 4, the alkylene group $-(CH_2)_n-$ formed thereby being optionally substituted with a group selected from C_{1-4} alkyl, C_{3-8} cycloalkyl and arylsulfonyl;

A is a group selected from -N(R2)CO-, -OC(O)-, -C(O)O-, -CON(R2)-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cycloalkylene-, -C(R2)(haloC_{1-6} alkyl)-, C_{1-4} alkylene and -C(OR3)(haloC_{1-6} alkyl)-;

R2 and R3 are each independently selected from H, C_{1-6} alkyl (which may be straight- or branched-chain), and C_{3-8} cycloalkyl, or, when A is -N(R2)CO- and X is absent, R2 may form, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group, which may optionally be substituted;

X is absent or is C_{1-4} alkylene or C_{2-4} alkenylene, optionally substituted with one or more C_{1-4} alkyl groups, OR16, halogen (such as F), or haloC_{1-6} alkyl (such as CF_3);

Z is selected from aryl, heteroaryl, C_{3-8} cycloalkyl, and heterocyclyl, each of which may optionally be substituted by a group selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl, or, when X is present, Z may be H, or, when X is absent and A is -C(R2)(OR3)- or -N(R2)CO-, Z may be H, or, when A is -N(R2)CO- and X is absent, Z may form, together with the adjacent nitrogen atom and R2, an N-containing

heterocyclyl group which may optionally be substituted, wherein, when A is -CO-, Z is linked to X or A via a carbon atom and wherein, when A is –N(R2)CO- and Z is H, R1 is C_{3-8} cycloalkyl; and

Y represents a bond, C_{1-6} alkylene, CO, COC_{2-6} alkenylene, O, SO_2, NR14, or $NHCOC_{1-6}$ alkylene;

wherein said cycloalkyl, aryl, heteroaryl and heterocyclyl groups Z may be optionally substituted by one or more substituents which may be the same or different, and which are selected from halogen, haloC_{1-6} alkyl, such as halomethyl, hydroxy, cyano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alkyl-NR5R6, -C_{3-8} cycloalkyl-NR5R6, -CONR12R13, -NR12COR13, -NR5SO_2R6, -OCONR5R6, -NR5CO_2R6, -NR4CONR5R6 or -SO_2NR5R6-SHR8, -C_{1-6} alkyl-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, -C_{1-6} alkyl-SO_2R9, -C_{1-6} alkyl-CONHR9, -C_{1-6} alkyl-SONHR9, -C_{1-6} alkyl-COR10, -CO-C_{1-6} alkyl-R10, -O-C_{1-6} alkyl-R11 (wherein R4, R5 and R6 independently represent hydrogen, C_{1-6} alkyl, -C_{3-8} cycloalkyl, -C_{1-6} alkylene-C_{3-8} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein R8 represents -C_{1-6} alkyl, wherein R9 represents C_{1-6} alkyl or aryl, wherein R10 represents aryl, wherein R11 represents C_{3-8} cycloalkyl or aryl, R12, R13, R14, R15 and R16 each independently represent H or C_{1-6} alkyl, and wherein -NR5R6 and -NR12R13 may represent a nitrogen containing heterocyclyl group); wherein said R4, R5, R6, R8, R9, R10 and R11 groups may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl;

wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen, haloC_{1-6} alkyl (such as halomethyl) and C_{1-6} alkyl;

wherein, when A is C_{1-4} alkylene, said cycloalkyl, aryl, heteroaryl or heterocyclyl group Z (such as a heterocyclyl group Z) is substituted at least with hydroxy, CF_3 or =O;

and wherein, when A is CON(R2), n is 1;

or a pharmaceutically acceptable salt or ester thereof,

provided that: when A is -CO-, R1 is CH_3, C_{3-8} cycloalkyl-substituted C_{1-6} alkylene or n-butyl, n is 0 and X is -CH_2CH_2-, Z is not N-benzyl substituted 4-piperidinyl, N-(3-fluorobenzyl)-substituted 4-piperidinyl or N-acetyl substituted 4-piperidinyl;

when A is -OC(O)-, R1 is cyclobutyl, n is 0 and X is -CH_2CH_2-, Z is not H;

when A is -OC(O)-, R1 is n-propyl, n is 0 and X is -CH_2-, Z is not H; and

when A is –CO-, R1 is CH_3, n is 0 and X is CH_2, Z is not H.

The compounds of the invention have been found to modulate the histamine H3 receptor. In particular, the compounds possess antagonist or inverse agonist properties at this receptor. Based on the high affinity for the receptor, the compounds may have the potential to display useful selectivity for the H3 receptor. Compounds of the invention where n is at least 1, particularly those in which A is -CON(R2)-, and particularly those in which

n is 1, have been found to display blood brain barrier permeability properties rendering them potentially suitable for the treatment of CNS disorders.

The term 'C_{x-y} alkyl' as used herein refers to a linear or branched saturated hydrocarbon group containing from x to y carbon atoms. For example, C_{1-6} alkyl refers to a linear or branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of C_{1-6} alkyl groups include methyl, ethyl, n-propyl, isopropyl, n- butyl, isobutyl, sec-butyl, tert butyl, n-pentyl, isopentyl, neopentyl and hexyl.

The term 'C_{x-y} alkylene' as used herein refers to a divalent hydrocarbon group obtained by removing one hydrogen atom from 'C_{x-y} alkyl' above. Examples of C_{1-6} alkylene groups include methylene, ethylene and propylene.

The term 'C_{x-y} alkenyl' as used herein refers to a linear or branched hydrocarbon group containing one or more carbon-carbon double bonds and having from x to y carbon atoms. Examples of such groups include ethenyl, propenyl, butenyl, pentenyl and hexenyl.

The term 'C_{x-y} alkenylene' as used herein refers to a divalent hydrocarbon group obtained by removing one hydrogen atom from 'C_{x-y} alkenyl' above. Examples of C_{2-6} alkenylene groups include vinylene and propenylene.

The term 'C_{x-y} alkoxy' as used herein refers to an -O-C_{x-y} alkyl group wherein C_{x-y} alkyl is as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

The term 'C_{x-y} cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of x to y carbon atoms. For example, C_{3-8} cycloalkyl refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of C_{3-8} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term 'C_{x-y} cycloalkylene' as used herein refers to a divalent hydrocarbon group obtained by removing one hydrogen atom from 'C_{x-y} cycloalkyl' above. Examples of C_{3-8} cycloalkylene groups include cyclopropylene and cyclobutylene.

The term 'halogen' as used herein refers to a fluorine, chlorine, bromine or iodine atom, unless otherwise specified.

The term 'haloC_{1-6} alkyl' as used herein refers to a C_{1-6} alkyl group as defined herein wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include fluoroethyl, trifluoromethyl and trifluoroethyl.

The term 'aryl' as used herein refers to a C_{6-12} monocyclic or bicyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthyl and tetrahydronaphthalenyl.

The term 'heteroaryl' as used herein refers to a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring which monocyclic or bicyclic ring contains 1 to 4 heteroatoms selected from oxygen,

nitrogen and sulphur. Examples of such monocyclic aromatic rings include thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl and the like. Examples of such bicyclic aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indolizinyl, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and imidazopyridyl.

The term 'heterocyclyl' refers to a 4-7 membered monocyclic ring or a fused 8-12 membered bicyclic ring which may be saturated or partially unsaturated, which monocyclic or bicyclic ring contains 1 to 4 heteroatoms selected from oxygen, nitrogen, silicon or sulphur. Examples of such monocyclic rings include pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl and azepanyl. Examples of such bicyclic rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1H-3-benzazepine and tetrahydroisoquinolinyl.

The term 'N-containing-heterocyclyl' refers to a ring containing at least one nitrogen atom and selected from among the 'heterocyclyl' groups mentioned above. Preferred examples of such rings include pyrrolidinyl, azetidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl.

'Pharmaceutically acceptable salts' of compounds of Formula I of the present invention include salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids. Salts with acids may, in particular, be employed in some instances. The compound of Formula I of the present invention may be in either hydrate or non-hydrate form.

'Pharmaceutically acceptable esters' of compounds of Formula I are derivatives in which one or more carboxyl (i.e. -C(O)OH) groups of the said compounds are modified by reaction with an alcoholic moiety W-OH so as to yield -C(O)OW groups, wherein W may be C_{1-18} alkyl (e.g. C_{1-6} alkyl), aryl, heteroaryl, C_{3-8} cycloalkyl or combinations thereof.

General methods for the preparation of salts and esters are well known to the person skilled in the art. Pharmaceutical acceptability of salts and esters will depend on a variety of factors, including formulation processing characteristics and *in vivo* behaviour, and the skilled person would readily be able to assess such factors having regard to the present disclosure.

Where compounds of the invention exist in different enantiomeric and/or diastereoisomeric forms (including geometric isomerism about a double bond), these compounds may be prepared as isomeric mixtures or racemates, although the invention relates to all such enantiomers or isomers, whether present in an optically pure form or as mixtures with other isomers. Individual enantiomers or isomers may be obtained by methods known in the art, such as optical resolution of products or intermediates (for example chiral chromatographic

separation (e.g. chiral HPLC)), or an enantiomeric synthesis approach. Similarly, where compounds of the invention may exist as alternative tautomeric forms (e.g. keto/enol, amide/imidic acid), the invention relates to the individual tautomers in isolation, and to mixtures of the tautomers in all proportions.

In particular embodiments of the first aspect of the invention, when A is NHCO, R1 is cyclobutyl, ethyl, n-propyl or isobutyl, n is 0 and X is absent, Z is not 1-[[5-chloro-2(2-methylpropoxy)phenyl]methyl]-5-methyl-1H-pyrazol-3-yl, and/or, when A is C_2 alkylene, R1 is CH_3, n is 0 and X is absent, Z is not N-(4-carboxycyclohexyl)-substituted imidazolidinonyl.

In certain embodiments of the first aspect of the invention: R1 is a group selected from C_{3-8} cycloalkyl, C_{1-6} alkyl, and C_{3-8} cycloalkyl-substituted C_{1-6} alkylene, each of which groups may optionally be substituted with halogen (such as F), haloC_{1-6} alkyl (such as CF_3) or OR2;

n is 0, 1, 2, 3 or 4, the alkylene group -$(CH_2)_n$ formed thereby being optionally substituted with a group selected from C_{1-4} alkyl and C_{3-8} cycloalkyl;

A is a group selected from -N(R2)CO-, -OC(O)-, -C(O)O-, -CON(R2)-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cycloalkylene-, -C(R2)(haloC_{1-6} alkyl)- and -C(OR3)(haloC_{1-6} alkyl)-;

R2 and R3 are each independently selected from H, C_{1-6} alkyl (which may be straight- or branched-chain), and C_{3-8} cycloalkyl, or, when A is -N(R2)CO- and X is absent, R2 may form, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group, which may optionally be substituted;

X is absent or is C_{1-4} alkylene or C_{2-4} alkenylene, optionally substituted with one or more C_{1-4} alkyl groups, OR2, halogen (such as F) or haloC_{1-6} alkyl (such as CF_3);

Z is selected from aryl, heteroaryl, C_{3-8} cycloalkyl, and heterocyclyl, each of which may optionally be substituted by a group selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl, or, when X is present, Z may be H, or, when A is -N(R2)CO- and X is absent, Z may form, together with the adjacent nitrogen atom and R2, an N-containing heterocyclyl group which may optionally be substituted, provided that, when A is -CO-, Z is linked to X or A via a carbon atom; and

Y represents a bond, C_{1-6} alkylene, CO, CONH, COC_{2-6} alkenylene, O, SO_2 or $NHCOC_{1-6}$ alkylene;

wherein said alkylene, cycloalkyl, aryl, heteroaryl and heterocyclyl groups of Z may be optionally substituted by one or more substituents which may be the same or different, and which are selected from halogen, haloC_{1-6} alkyl, such as halomethyl, hydroxy, cyano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alkyl-NR5R6, -C_{3-8} cycloalkyl-NR5R6, -CONR5R6, -NR5CR6, -NR5SO_2R6, -OCONR5R6 , -NR5CO_2R6, -NR4CONR5R6 or -SO_2NR5R6-SHR8, C_{1-6} alkyl-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, C_{1-6} alkyl-SO_2R9, C_{1-6} alkyl-CONHR9, C_{1-6} alkyl-SONHR9, C_{1-6} alkyl-COR10, -CO-C_{1-6} alkyl-R10, -O-C_{1-6} alkyl-R11 (wherein R4, R5 and R6 independently represent hydrogen, C_{1-6} alkyl, -C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein R8 represents C_{1-6} alkyl, wherein R9 represents C_{1-6} alkyl or aryl, wherein R10 represents

aryl, wherein R11 represents C_{3-8} cycloalkyl or aryl, and wherein -NR5R6 may represent a nitrogen containing heterocyclyl group); wherein said R4, R5, R6, R8, R9, R10 and R11 groups may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl;

and wherein the provisos to the first aspect apply.

In additional embodiments of the first aspect of the invention, R1 is a group selected from C_{3-8} cycloalkyl, C_{1-6} alkyl, and C_{3-8} cycloalkyl-substituted C_{1-6} alkylene, each of which groups may optionally be substituted with halogen (such as F), haloC_{1-6} alkyl (such as CF_3) or OR2;

n is 0, 1, 2, 3 or 4, the alkylene group $-(CH_2)_n-$ formed thereby being optionally substituted with a group selected from C_{1-4} alkyl and C_{3-8} cycloalkyl;

A is a group selected from -N(R2)CO-, -OC(O)-, -C(O)O-, -CON(R2)-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cycloalkylene-, -C(R2)(haloC_{1-6} alkyl)-, C_{1-4} alkylene and -C(OR3)(haloC_{1-6} alkyl)-;

R2 and R3 are each independently selected from H, C_{1-6} alkyl (which may be straight- or branched-chain), and C_{3-8} cycloalkyl, or, when A is -N(R2)CO- and X is absent, R2 may form, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group, which may optionally be substituted;

X is absent or is C_{1-4} alkylene or C_{2-4} alkenylene, optionally substituted with one or more C_{1-4} alkyl groups, OR2, halogen (such as F), or haloC_{1-6} alkyl (such as CF_3);

Z is selected from aryl, heteroaryl, C_{3-8} cycloalkyl, and heterocyclyl, each of which may optionally be substituted by a group selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl, or, when X is present, Z may be H, or, when X is absent and A is -C(R2)(OR3)- or -N(R2)CO-, Z may be H, or, when A is -N(R2)CO- and X is absent, Z may form, together with the adjacent nitrogen atom and R2, an N-containing heterocyclyl group which may optionally be substituted, provided that, when A is -CO-, Z is linked to X or A via a carbon atom; and

Y represents a bond, C_{1-6} alkylene, CO, CONH, COC_{2-6} alkenylene, O, SO_2 or $NHCOC_{1-6}$ alkylene;

wherein said cycloalkyl, aryl, heteroaryl and heterocyclyl groups of Z may be optionally substituted by one or more substituents which may be the same or different, and which are selected from halogen, haloC_{1-6} alkyl, such as halomethyl, hydroxy, cyano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alkyl-NR5R6, -C_{3-8} cycloalkyl-NR5R6, -CONR5R6, -NR5CR6, -NR5SO_2R6, -OCONR5R6 , -NR5CO_2R6, -NR4CONR5R6 or -SO_2NR5R6-SHR8, C_{1-6} alkyl-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, C_{1-6} alkyl-SO_2R9, C_{1-6} alkyl-CONHR9, C_{1-6} alkyl-SONHR9, C_{1-6} alkyl-COR10, -CO-C_{1-6} alkyl-R10, -O-C_{1-6} alkyl-R11 (wherein R4, R5 and R6 independently represent hydrogen, C_{1-6} alkyl, -C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein R8 represents C_{1-6} alkyl, wherein R9 represents C_{1-6} alkyl or aryl, wherein R10 represents aryl, wherein R11 represents C_{3-8} cycloalkyl or aryl, and wherein -NR5R6 may represent a nitrogen containing heterocyclyl group); wherein said R4, R5, R6, R8, R9, R10 and R11 groups may be optionally substituted by

one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl;

wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen, haloC_{1-6} (alkyl such as halomethyl) and C_{1-6} alkyl;

and wherein, when A is C_{1-4} alkylene, said cycloalkyl, aryl, heteroaryl or heterocyclyl group Z (such as a heterocyclyl group Z) is substituted at least with hydroxy;

and wherein the provisos to the first aspect apply.

In certain compounds of the invention in which Z is selected from aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl, -C_{3-8} cycloalkyl-Y-C_{3-8} cycloalkyl, -C_{3-8} cycloalkyl-Y-aryl, -C_{3-8} cycloalkyl-Y-heteroaryl, -C_{3-8} cycloalkyl-Y-heterocyclyl, -aryl-Y-C_{3-8} cycloalkyl, -aryl-Y-aryl, -aryl-Y-heteroaryl, -aryl-Y-heterocyclyl, -heteroaryl-Y-C_{3-8} cycloalkyl, -heteroaryl-Y-aryl, -heteroaryl-Y-heteroaryl, -heteroaryl-Y-heterocyclyl, -heterocyclyl-Y-C_{3-8} cycloalkyl, -heterocyclyl-Y-aryl, -heterocyclyl-Y-heteroaryl, and -heterocyclyl-Y-heterocyclyl, Z may be linked to A or X via a carbon atom (that is, a carbon atom of the group Z). When A is -CO-, such that Z is linked to A or X via a carbon atom, this means that Z is linked to A or X via a carbon atom of Z.

In certain embodiments of the invention, Y represents a bond or C_{1-6} alkylene (e.g. methylene).

In certain embodiments of the invention, when A is -CO-, n is 0, R1 is C_{1-6} alkyl (such as CH_3), and X is present (and may be C_{1-4} alkyl, such as -CH_2CH_2-), Z is not a -heterocyclyl-Y-aryl- group containing a piperidinyl moiety. In particular embodiments within this group, Z is not -heterocyclyl-Y-aryl-.

In particular embodiments, Z may be H when A is -CONH-(or -CON(R2)-) or -NHCO-(or -N(R2)CO-).

In other embodiments, for example when A is -NHCO- (or -N(R2)CO-), and n is 0, Z may be any of the aryl, cycloalkyl, heterocyclyl or heteroaryl-containing moieties defined above, particularly moieties containing a combination of two or more such groups. Such groups of Z are, in certain instances, not substituted with halogen and/or alkoxy (such as butyloxy). In certain instances, when Z comprises said two or more such groups, one or none of the aryl, cycloalkyl, heterocyclyl or heteroaryl groups of Z is further substituted. In certain embodiments, Z is not aryl-Y-heteroaryl, particularly not aryl-CH_2-heteroaryl.

In particular compounds of the invention, A is selected from -N(R2)CO-, -OC(O)-, -C(O)O-, -CON(R2)-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cycloalkylene-, CO-, C_{1-4} alkylene, -C(R2)(haloC_{1-6} alkyl)- and -C(OR3)(haloC_{1-6} alkyl)-.

In those embodiments in which A is -N(R2)CO- and X is absent, with R2 forming, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group, possible substituents on the N-containing heterocyclyl group include halogen and carbamoyl.

In certain compounds of the invention, R1 is C_{1-6} alkyl (such as C_{1-3} alkyl), C_{3-8} cycloalkyl (such as C_{3-7} cycloalkyl) or heterocyclyl (preferably tetrahydrofuranyl). Particular C_{1-6} alkyl or C_{3-8} cycloalkyl groups of R1 include methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl and cyclopentyl.

Alternatively, R1 may be C_{1-6} alkyl (such as C_{1-3} alkyl) substituted with C_{3-8} cycloalkyl (such as C_{3-7} cycloalkyl). In such embodiments, R1 may, for example, be cyclopropylethyl or cyclopropylmethyl.

In any event, C_{1-6} alkyl, C_{3-8} cycloalkylene-C_{1-6} alkyl and C_{3-8} cycloalkyl for R1 may be further substituted with one or more (e.g. 1 to 3) groups selected from hydroxy, C_{1-6} alkoxy (such as methoxy), C_{1-6} alkyl (such as methyl), halogen (such as F or Cl) and haloC_{1-6} alkyl, e.g. halomethyl (such as CH_2F), particularly selected from F and CH_2F.

In particular embodiments of the invention R1 is C_{3-8} cycloalkyl substituted with hydroxy or methoxy.

In certain embodiments of the invention, n is 0, 1 or 2.

In particular embodiments n is 0.

In particular embodiments n is 1.

In certain embodiments of the invention, A is -N(R2)CO-, -OC(O)-, -CON(R2)-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)- or -C(=CR2R3)-.

In particular embodiments of the invention, A is -C(R2)(OR3)-, C_{1-4}alkylene, -N(R2)CO-, or -CON(R2)-.

In certain embodiments of the invention, A is -C(R2)(OR3)-.

In certain embodiments of the invention, A is –CON(R2)-.

In particular embodiments of the invention, n is 0 and A is -N(R2)CO- (such as -NHCO-) in particular -N(R2)CO-. In other embodiments, n is 0 and A is -C(R2)(OR3)- (such as -C(R2)OH-).

In other particular embodiments of the invention, n is 1 and A is -N(R2)CO- (such as -NHCO-) or -CON(R2)- (such as -CONH-), in particular –CON(R2)-. In other embodiments, n is 1 and A is -C(R2)(OR3)- (such as -C(R2)OH-).

In certain compounds of the invention, R2 and R3 are each independently H or C_{1-6} alkyl, such as methyl. In particular embodiments, R2 is H. In particular embodiments, R3 is H.

In certain embodiments of the invention, A is -NHCO-, -N(Me)CO-, -OC(O)-, -CONH-, -CO-, -CH(OH)-, -CH(OMe)-, -C(=N-O-Me)-, -C(=N-O-H)-, $-CH_2-$ or $-C(=CH_2)-$.

In certain compounds of the invention, where A is -C(R2)(haloC_{1-6} alkyl)- or -C(OR3)(haloC_{1-6} alkyl), the group (haloC_{1-6} alkyl) may be a fluorinated alkyl, such as CF_3.

In certain embodiments of the invention, X is absent or is C_{1-4} alkylene (e.g., methylene, ethylene) or C_{2-4} alkenylene (e.g., vinylene), each of which may optionally be substituted with a C_{1-4} alkyl group (e.g., methyl).

In particular embodiments, X is a C_{1-4} alkylene group, (preferably straight chain), optionally having one or more (e.g. 1 to 3) methyl or ethyl substituents. In certain compounds, X is methylene or ethylene.

In certain embodiments of the invention, when A is -N(R2)CO- and X is absent, R2 may form, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group (e.g., azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl) which may optionally be substituted by one to three halogen atoms (e.g., F) or carbamoyl groups.

In certain compounds of the present invention, Z is aryl, heteroaryl, C_{3-8} cycloalkyl or heterocyclyl, each of which may be substituted with one or more (e.g. 1 to 3) substituents selected from C_{1-6} alkyl (such as methyl, ethyl or isopropyl), C_{1-6} cycloalkyl (such as cyclobutyl), halogen (such as Cl, Br or F), haloC_{1-6} alkyl (such as halomethyl (e.g. trifluoromethyl)), cyano, amino, C_{1-6} alkoxy (such as methoxy), carbonyl (such as C_{1-6} alkyl-carbonyl (e.g. acetyl), carboxyl, C_{1-6} alkoxy-carbonyl (e.g. methoxycarbonyl)), amido (such as carbamoyl, C_{1-6} alkyl-carbamoyl (e.g. methylcarbamoyl)), heterocyclyl-amino (e.g. cyclobutylamino, cyclopropylamino), aryl (such as phenyl), and heteroaryl (such as triazolyl, thiazolyl, pyrazolyl, thiophenyl, pyrrolidinyl, morpholinyl or pyridinyl).

In embodiments in which Z is, or comprises, heteroaryl, said heteroaryl may be selected from thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indolizinyl, indazolyl, purinyl, pyrrolopyridinyl, fluropyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and imidazopyridyl. In particular, said heteroaryl may be selected from pyrazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, indolyl, indazolyl, benzimidazolyl, benzothiazolyl, imidazopyridyl, imidazolyl, isoxazolyl, thienyl, oxazolyl, thiazolyl, furyl, imidazopyridyl and pyrrolyl groups.

In embodiments in which Z is, or comprises, aryl, said aryl may in particular be a phenyl, naphthyl, or tetrahydronaphthalenyl group, in particular a phenyl group.

In embodiments in which Z is, or comprises, heterocyclyl, said heterocyclyl may be selected from pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl, indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1H-3-benzazepinyl and tetrahydroisoquinolinyl. In particular, said heterocyclyl may be selected from piperidinyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, dioxanyl, tetrahydrothiopyranyl, tetrahydrothiophenyl, morpholinyl and tetrahydropyranyl groups.

In embodiments in which Z is, or comprises, C_{3-8} cycloalkyl, said C_{3-8} cycloalkyl may in particular be selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups, more particularly from cyclobutyl, cyclopentyl and cyclohexyl groups.

In particular embodiments, Z is aryl (preferably phenyl), heteroaryl (preferably pyrazolyl, pyridyl, indolyl, indazolyl, benzimidazolyl, benzothiazolyl, imidazopyridyl, imidazolyl, isoxazolyl, thienyl, oxazolyl, thiazolyl, furyl, pyridazinyl, pyrimidyl, pyrazinyl or pyrrolyl), C_{3-8} cycloalkyl (preferably cyclobutyl, cyclopentyl or cyclohexyl) or heterocyclyl (preferably piperidinyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, tetrahydrothiophenyl, piperazinyl, tetrahydrothiopyranyl, dioxanyl or tetrahydropyranyl),

each of which may optionally be substituted by

(1) a group selected from -Y-aryl, -Y-heteroaryl, Y-heterocyclyl, and -Y-C_{3-8} cycloalkyl,

wherein Y represents a bond, O, NR14 or C_{1-6} alkylene (preferably methylene), and said aryl is phenyl, said heteroaryl is selected from triazolyl, thiazolyl, thienyl and pyrazolyl, said heterocyclyl is selected from morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrrolidinyl, and said C_{3-8} cycloalkyl is selected from cyclobutyl or cyclopropyl; or

(2) one to three substituents selected from

C_{1-6} alkyl (preferably methyl, ethyl or isopropyl), C_{3-8} cycloalkyl (preferably cyclobutyl) halogen (preferably F, Cl or Br), haloC_{1-6} alkyl (preferably trifluoromethyl), cyano, hydroxy, amino, C_{1-6} alkoxy (preferably methoxy, ethoxy or isopropoxy), C_{1-6} alkyl-carbonyl (preferably acetyl), carboxyl, C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl), carbamoyl, hydroxy-substituted C_{1-6} alkyl-carbonyl, C_{3-8} cycloalkyl-carbonyl, C_{1-6} alkyl-carbamoyl (preferably methylcarbamoyl), C_{1-6} alkylamino (preferably methylamino), and =O,

wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen, haloC_{1-6} alkyl (such as halomethyl) and C_{1-6} alkyl.

In certain embodiments Y is a bond or C_{1-6} alkylene; in particular embodiments, Y is a bond.

In certain compounds of the present invention, Z is H when X is present.

In certain embodiments of the first aspect of the invention, A is -N(R2)CO- or -CON(R2)-, and n is 0, 1 or 2. In certain such embodiments, R2 is H. In particular embodiments, A is -CON(R2)-.

In alternative embodiments of the first aspect of the invention, A is -OC(O)- or -C(O)O-, and n is 0, 1 or 2.

In other embodiments of the first aspect of the invention, A is -C(R2)(OR3)- or -CO-, and n is 0, 1 or 2. In certain such embodiments, R2 and/or R3 are H or C_{1-6} alkyl, such as methyl.

Particular embodiments of the first aspect of the invention include compounds wherein: R1 is C_{1-6} alkyl (preferably methyl, ethyl, isopropyl or isobutyl), C_{3-8} cycloalkyl-C_{1-6} alkylene- (preferably cyclopropylmethyl), or C_{3-8} cycloalkyl (preferably cyclobutyl or cyclopentyl), each of which may optionally be substituted by hydroxy, C_{1-6} alkoxy, or one or two halogens (preferably F), or R1 is heterocyclyl (preferably tetrahydrofuranyl), optionally substituted by hydroxy, C_{1-6} alkoxy, or C_{1-6} alkyl (such as methyl);

n is 0, 1 or 2;

A is -N(R2)CO-, -OC(O)-, -CON(R2)-, -CO-, -C(R2)(OR3)-, C_{1-4} alkylene, -C(=N-O-R3)- or -C(=CHR3)-;

R2 and R3 are each independently H or C_{1-6} alkyl (preferably methyl);

or, when A is -N(R2)CO- and X is absent, R2 may form, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group (optionally azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, and preferably azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl) which may optionally be substituted by one to three halogen atoms (preferably F), alkyl carbonyl or carbamoyl groups;

X is absent or is C_{1-4} alkylene (preferably methylene or ethylene) or C_{2-4} alkenylene (preferably vinylene), each of which may optionally be substituted with a C_{1-4} alkyl group (preferably methyl); and

Z is aryl (preferably phenyl), heteroaryl (preferably pyrazolyl, pyridyl (such as 3-pyridyl), indolyl, indazolyl, benzimidazolyl, benzothiazolyl, imidazopyridyl, imidazolyl, isoxazolyl, thienyl, oxazolyl, thiazolyl, furyl, pyridazinyl, pyrimidyl, pyrazinyl or pyrrolyl), C_{3-8} cycloalkyl (preferably cyclobutyl, cyclopentyl or cyclohexyl) or heterocyclyl (preferably piperidinyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, tetrahydrothiophenyl, piperazinyl, tetrahydrothiopyranyl, dioxanyl, or tetrahydropyranyl),

each of which may optionally be substituted by

(1) a group selected from -Y-aryl, -Y-heteroaryl, Y-heterocyclyl, and -Y-C_{3-8} cycloalkyl,

wherein Y represents a bond, O, NR14, or C_{1-6} alkylene (preferably methylene), and said aryl is selected from phenyl, said heteroaryl is selected from triazolyl, thiazolyl, thienyl and pyrazolyl, said heterocyclyl is selected from morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrrolidinyl, and said C_{3-8} cycloalkyl is selected from cyclobutyl and cyclopropyl; or

(2) one to three substituents selected from

C_{1-6} alkyl (preferably methyl, ethyl or isopropyl), halogen (preferably F, Cl or Br), haloC_{1-6} alkyl (preferably trifluoromethyl), cyano, hydroxy, amino, C_{1-6} alkoxy (preferably methoxy, ethoxy or isopropoxy), C_{1-6} alkyl-carbonyl (preferably acetyl), hydoxy-substituted C_{1-6} alkyl-carbonyl, C_{3-8} cycloalkyl-carbonyl, carboxyl, C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl), carbamoyl, C_{1-6} alkyl-carbamoyl (preferably methylcarbamoyl), C_{1-6} alkylamino (such as methylamino), and =O; or

Z may be H when X is present, or Z may be H when X is absent and A is -C(R2)(OR3)- or -N(R2)CO-,

wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8}cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen, haloC_{1-6} alkyl such as halomethyl and C_{1-6} alkyl,

wherein, when A is C_{1-4} alkylene, said cycloalkyl, aryl, heteroaryl or heterocyclyl group Z (such as a heterocyclyl group Z) is substituted at least with hydroxy, CF_3 or =O;

and wherein, when A is CON(R2), n is 1.

Particular embodiments of the first aspect of the invention include compounds wherein: R1 is C_{1-6} alkyl (preferably methyl, ethyl) or C_{3-8} cycloalkyl (preferably cyclobutyl or cyclopentyl);

n is 1;

A is -C(R2)(OR3)-;

R2 and R3 are each independently H or C_{1-6} alkyl (preferably methyl);

X is absent or is C_{1-4} alkylene (preferably methylene);

Z is heteroaryl (preferably pyridyl), or heterocyclyl (preferably piperidinyl, or tetrahydropyranyl),

each of which may optionally be substituted by one to three substituents selected from

C_{1-6} alkyl (preferably methyl, ethyl or isopropyl), halogen (preferably Cl or Br), haloC_{1-6} alkyl (preferably trifluoromethyl), cyano, hydroxy, amino, C_{1-6} alkoxy (preferably methoxy), C_{1-6} alkyl-carbonyl (preferably acetyl or propionyl), hydroxy-substituted C_{1-6} alkyl-carbonyl, carboxyl, C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl), C_{3-8} cycloalkyl-carbonyl, carbamoyl, C_{1-6} alkyl-carbamoyl (preferably methylcarbamoyl).

Further embodiments of the first aspect of the invention include compounds wherein: R1 is C_{1-6} alkyl (preferably methyl or ethyl) or C_{3-8} cycloalkyl (preferably cyclobutyl or cyclopentyl);

n is 0;

A is C_{1-4} alkylene (preferably methylene);

R2 and R3 are each independently H or C_{1-6} alkyl (preferably methyl);

X is absent or is C_{1-4} alkylene (preferably methylene);

Z is heteroaryl (preferably pyridyl or pyrrolopyridinyl), or heterocyclyl (preferably piperidinyl, pyrrolidinyl or tetrahydropyranyl),

each of which may optionally be substituted by one to three substituents selected from

C_{1-6} alkyl (preferably methyl, ethyl or isopropyl), halogen (preferably Cl or Br), haloC_{1-6} alkyl (preferably trifluoromethyl), cyano, hydroxy, amino, C_{1-6} alkoxy (preferably methoxy), C_{1-6} alkyl-carbonyl (preferably acetyl or propionyl), hydroxy-substituted C_{1-6} alkyl-carbonyl, carboxyl, C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl), C_{3-8} cycloalkyl-carbonyl, carbamoyl, C_{1-6} alkyl-carbamoyl (preferably methylcarbamoyl).

wherein said heteroaryl or heterocyclyl group Z (such as a heterocyclyl group Z) is substituted at least with hydroxy, CF_3 or =O.

In particular compounds defined according to the preceding two paragraphs, R1 is C_{3-8} cycloalkyl (preferably cyclobutyl). In certain embodiments, Z is heterocyclyl (such as piperidinyl, pyrrolidinyl or tetrahydropyranyl), which may be substituted with one to three (preferably 1 or 2) of the carbonyl-containing substituents defined in the said paragraphs.

Alternative particular embodiments of the first aspect of the invention include compounds wherein: R1 is C_{1-6} alkyl (preferably methyl or ethyl), C_{3-8} cycloalkyl (preferably cyclobutyl or cyclopentyl), optionally substituted with halogen (such as F) or C_{1-6} alkoxy (such as methoxy), or R1 is heterocyclyl (preferably tetrahydrofuranyl), optionally substituted with C_{1-6} alkyl;

n is 1;

A is –CON(R2)- or -N(R2)CO-;

R2 is selected from H and C_{1-6} alkyl (preferably methyl or isobutyl);

X is absent or is C_{1-4} alkylene (preferably methylene, ethylene, propylene, isopropylene, t-butylene or isobutylene), which may be optionally substituted with one or more C_{1-4} alkyl (such as methyl) or hydroxy groups;

Z is aryl (preferably phenyl), heteroaryl (preferably pyrazolyl, pyridyl (such as 3-pyridyl), pyrrolyl, isoxazolyl, pyridazinyl, pyrimidyl, pyrazinyl, thiazolyl, oxazolyl or furyl), C_{3-8} cycloalkyl (preferably cyclohexyl) or heterocyclyl (preferably piperidinyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, tetrahydrothiophenyl, tetrahydropyridyl, piperazinyl, tetrahydrothiopyranyl, dioxanyl or tetrahydropyranyl),

each of which may optionally be substituted by

(1) a group selected from -Y-aryl, -Y-heteroaryl, Y-heterocyclyl, and -Y-C_{3-8} cycloalkyl,

wherein Y represents a bond, O, NR14 (such as NH), or C_{1-6} alkylene (preferably methylene), and said aryl is selected from phenyl, said heteroaryl is selected from triazolyl, thiazolyl, thienyl and pyrazolyl, said heterocyclyl is selected from morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrrolidinyl, and said C_{3-8} cycloalkyl is selected from cyclobutyl and cyclopropyl; or

(2) one to three substituents selected from

C_{1-6} alkyl (preferably methyl, ethyl or isopropyl), halogen (preferably F, Cl or Br), haloC_{1-6} alkyl (preferably trifluoromethyl), cyano, amino, C_{1-6} alkylamino (such as methylamino), N,N-C_{1-6} dialkylamino (such as hydroxpropyl(methyl)amino) C_{1-6} alkoxy (preferably methoxy, ethoxy or isopropoxy), C_{1-6} alkyl-carbonyl (preferably acetyl), carboxyl, C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl), carbamoyl, C_{1-6} alkyl-carbamoyl (preferably methylcarbamoyl), hydroxy C_{1-6} alkyl and =O; or

Z may be H when X is present,

wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen (such as F), haloC_{1-6} alkyl (such as halomethyl) and C_{1-6} alkyl.

In particular compounds defined according to the preceding paragraph, R1 is C_{3-8} cycloalkyl (preferably cyclobutyl). In certain compounds, A is -CON(R2)-. In certain embodiments, Z is heteroaryl (such as pyridazinyl or pyridyl), which may be substituted with one to three (preferably 1 or 2) substituents selected from -Y-heterocyclyl (such as morpholinyl or pyrrolidinyl), C_{1-6} alkoxy (such as methoxy) and C_{1-6} alkylamino (such as methylamino).

In accordance with a second aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to the first aspect of the invention, together with one or more pharmaceutically acceptable excipients.

Pharmaceutical compositions of this invention comprise any of the compounds of the first aspect of the present invention, or pharmaceutically acceptable salts and esters thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention are those conventionally employed in the field of pharmaceutical formulation, and include, but are not limited to, sugars, sugar alcohols, starches, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycerine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulphate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene- polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, rectally, nasally, buccally, vaginally or via an implanted reservoir. Oral administration is preferred. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as that described in Ph. Helv, or a similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, powders, granules, and aqueous suspensions and solutions. These dosage forms are prepared according to techniques well-known in the art of pharmaceutical formulation. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavouring and/or colouring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilising or dispersing agents known in the art.

The compounds of the present invention may be administered in a dose of around 1 to around 20,000 μg/kg per dose, depending on the condition to be treated or prevented, and the characteristics of the subject being administered with the compound. In many instances, the dose may be around 1 to around 1500 μg/kg per dose. The dosing regimen for a given compound could readily be determined by the skilled person having access to this disclosure.

In one particular embodiment, the pharmaceutical composition of the invention additionally comprises one or more additional active pharmaceutical ingredients. These additional active ingredients may be agents known to the skilled person to be useful in the treatment or prevention of the diseases mentioned in the present disclosure.

In a third aspect, the present invention provides a compound according to the first aspect of the invention, or a composition according to the second aspect, for use in therapy.

In a fourth aspect, the invention provides a compound according to the first aspect of the invention, or a composition according to the second aspect, for use in the treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, wherein the provisos to the first aspect do not apply.

In certain embodiments of the fourth aspect, the first, second, third, and/or fourth provisos to the first aspect do apply.

A number of conditions whose development or symptoms are linked to histamine H3 receptor activity are known to the skilled person.

In a fifth aspect, the invention also provides a method of treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, the method comprising the administration, to a subject in need of such treatment or prevention, of a therapeutically effective amount of a compound according to the first aspect of the invention, or a composition according to the second aspect, wherein the provisos to the first aspect do not apply.

In certain embodiments of the fifth aspect, the first, second, third, and/or fourth provisos to the first aspect do apply.

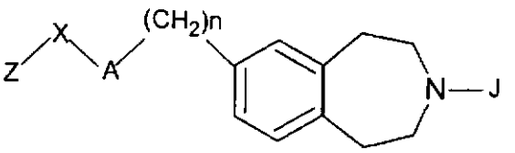
A compound according to the fourth aspect, or a method according to the fifth aspect, wherein the condition is a disorder of the central nervous system.

In certain embodiments, the condition to be treated may be selected from sleep disorders (such as narcolepsy), cognitive disorders (such as dementia), attentional disorders (such as attention deficit hyperactivity disorder), neurodegenerative disorders (such as AD), schizophrenia, epilepsy, pain (such as neuropathic pain) and obesity.

In preferred embodiments the condition may be selected from schizophrenia, Alzheimer's Disease (AD) and dementia. In an alternative embodiment, the condition may be selected from narcolepsy, pain and obesity.

In particular embodiments, the condition may be selected from narcolepsy, neuropathic pain and obesity.

In a sixth aspect, the present invention provides an intermediate compound having the formula:



wherein n, A, X and Z have the same meaning as in Formula 1 above, or Z-X-A- together represents C_{1-6} alkylsulfonyloxy, nitro, halogen (such as Br), carbaldehyde O-C_{1-6} alkyl oxime, amino, amino attached to an amino protecting group or arylsulfonyl, and wherein J is an amino protecting group or H, provided that Z is linked to X or A via a carbon atom when Z contains a piperazinyl moiety, and provided that:

when A is -OC(O)-, J is H, n is 0 and X is -CH_2CH_2-, Z is not H;

when A is -OC(O)-, J is tert-butoxycarbonyl, n is 0 and X is -CH_2-, Z is not H;

when A is -NHCO-, J is tert-butoxycarbonyl, n is 0 and X is -isopropyl, Z is not H; and

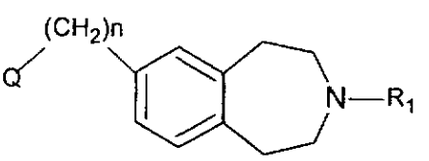
when A is -NHCO-, J is tert-butoxycarbonyl or H, n is 0 and X is -CH_2- or -CH_2CH_2-, Z is not pyrrolidin-2-yl substituted with oxo, phenylpropyl and acetic acid substituents.

In particular embodiments of the sixth aspect, A, X znd Z have the same meaning as in Formula I above. In certain embodiments of the sixth aspect, Z is linked to X or A via a carbon atom (i.e. regardless of whether Z contains a piperazinyl moiety).

In certain embodiments of the sixth aspect, when A is -NHCO, J is H, n is 0 and X is absent, Z is not 1-[[5-chloro-2(2-methylpropoxy)phenyl]methyl]-5-methyl-1H-pyrazol-3-yl.

A preferred amino protecting group is *tert*-butoxycarbonyl (Boc), although many other protecting groups will be known to those skilled in the art. The methods of addition and removal of such protecting groups are those which would conventionally be used in relation to the particular molecule-type or group being protected, for example the methods described in standard works of reference in synthetic methodology, such as Kocienski (2004) *Protecting Groups*. 4th Edn. Georg Thieme Verlag.

In a seventh aspect, the present invention also provides an intermediate compound having the formula:



wherein n and R1 have the same meaning as in Formula I above, and wherein Q is selected from cyano, amino, amino attached to an amino protecting group (such as t-butyloxycarbonyl), arylsulfonyl (such as phenylsulfonyl) and halogen (such as Br).

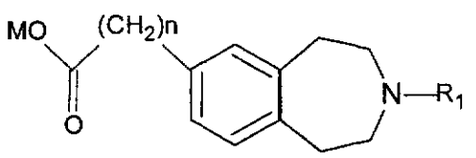
In a related eighth aspect, the invention also provides the use of an intermediate compound according to the sixth or seventh aspects in the synthesis of a compound according to the first aspect, wherein the provisos specified in the sixth aspect do not apply. In certain embodiments of the eighth aspect, one or more of the provisos specified in the sixth aspect do apply.

It will be appreciated by the skilled person that, following removal of the protecting group (where present) on the intermediate, the nitrogen of the azepine ring becomes available for nucleophilic attack on a suitable R1-containing reagent (for example, in an alkylation or reductive amination reaction).

In a ninth aspect, the present invention provides the use of a compound according to the first aspect of the invention in the preparation of a medicament for the treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, wherein the provisos to the first aspect do not apply.

Exemplary conditions of relevance to the ninth aspect are mentioned above.

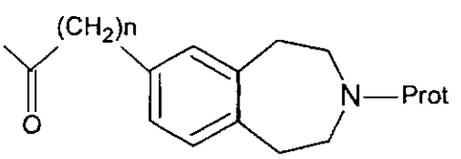
In a tenth aspect, the present invention also provides a method of synthesis of a compound according to the first aspect, wherein A is -N(R2)CO-, the method comprising the reaction of an intermediate having the formula:



with an amine (Z-X)(R2)NH in the presence of a catalyst, wherein n, Z, X, R1 and R2 have the same meaning as given in relation to the first aspect, and wherein M represents H or a monovalent metal cation.

In certain embodiments of the tenth aspect, M is a monovalent metal cation, such as Li. The catalyst may be thionyl chloride, such that the reaction proceeds via the creation of an acyl chloride intermediate. The acyl chloride may, if necessary, be isolated before introduction of (Z-X)(R2)NH.

In an eleventh aspect, the present invention provides a method of synthesis of a compound according to the first aspect, wherein A is -CO- or -C(R2)(OR3)- and X is present, the method comprising the reaction of a protected intermediate:



with an aldehyde Z-CHO in the presence of a catalyst, followed by deprotection of the protected amine and substitution thereof with R1 and, optionally, by catalytic hydrogenation, wherein n, Z, X, R1, R2 and R3 have the same meaning as given in relation to the first aspect, and wherein Prot represents an amine protecting group.

The catalyst may be, for example, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU). In compounds in which X is alkenylene, the catalytic hydrogenation step may be omitted. Such a step (e.g. using H_2 gas in the presence of $Pt(IV)O_2$) saturates the double bond which results from the reaction between Z-CHO and the protected intermediate. Suitable amine protecting groups are described above.

The invention will now be described in more detail by way of example only.

1. Synthetic Methodologies

The methods used for synthesis of the compounds of the invention are illustrated by the general schemes below and the preparative examples that follow. All compounds and intermediates were characterised at least by liquid chromatography-mass spectroscopy (LCMS). The starting materials and reagents used in preparing these compounds are available from commercial suppliers. These general schemes are merely illustrative of methods by which the compounds of this invention can be synthesised, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

Nuclear magnetic resonance (NMR) spectra were recorded at 400MHz,; the chemical shifts (δ) are reported in parts per million.

Mass spectra were recorded using an LCMS system (ZQ mass spec detector).

Compounds were purified using normal phase chromatography on silica or alumina, or by reverse phase chromatographic methods.

Room temperature in the following schemes means the temperature ranging from 20°C to 25°C.

The desired compounds of Formula 1 can be prepared as outlined in **Schemes 1-16,** as follows:

List of Abbreviations:

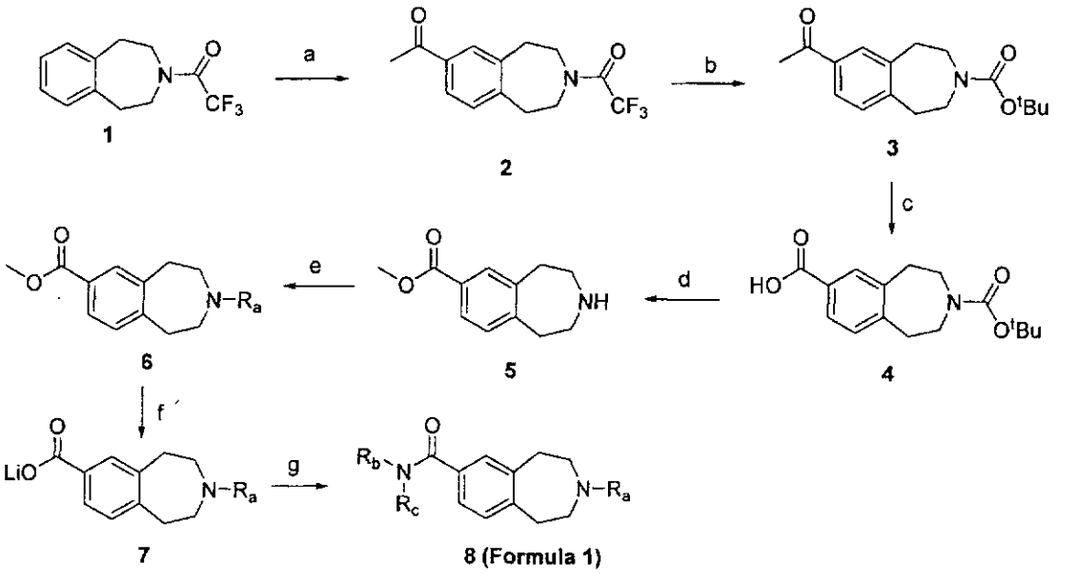
Ac	Acetyl
AcOH	Acetic Acid
$(Boc)_2O$	Boc Anhydride
DCM	Dichloromethane
DMSO	Dimethyl Sulfoxide
DMF	Dimethyl Formamide
EtOAc	Ethyl Acetate
EtOH	Ethanol
HCl	Hydrochloric Acid
H_2SO_4	Sulfuric acid
IPE	Di-isopropyl Ether
KOH	Potassium Hydroxide
LCMS	Liquid Chromatography Mass Spectrum

$MgSO_4$	Magnesium Sulfate
MS	Mass Spectrum
MeOD	Deuterated Methanol
MeOH	Methanol
Min	Minute
NaOH	Sodium hydroxide
NMR	Nuclear Magnetic Resonance
RT	Room Temperature
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

In the following schemes, R_a represents R1, R_b and R_c independently represent R2 or R3, or R_b and R_c represent X-Z, and R_d represents X-Z, wherein R1, R2, R3, X and Z are as defined above.

1.1 Scheme 1

This scheme can be used for synthesising **example compounds 1-115 and example compounds 158-174**



Reagents and conditions: a) MeCOCl, $AlCl_3$, CH_2Cl_2; b)i. K_2CO_3, H_2O, MeOH; ii. K_2CO_3, Boc_2O, dioxane; c)aq NaOH, Br_2; d) $SOCl_2$, MeOH; e) R_aI, K_2CO_3, DMA; or R_aCO or R_aHCO, AcOH, $Na(OAc)_3BH$, DCM; f) LiOH, THF, H_2O g)i. $SOCl_2$, MeOH; ii. R_bR_cNH

1.1.1 The *benzazepine intermediate* (**1**) can be prepared by methods outlined in WO 2005/058328 and WO 2005/094834. The alkanoyl benzazepine (**2**) can be prepared from the corresponding (**1**) by Friedel-Crafts acylation as outlined in US 2005/20616. Removal of the trifluoroacetyl group of (**2**) under basic conditions followed by protection of the benzazepine nitrogen as a t-butyl carbamate using standard conditions well known in the art (for example, Bioorg.Med.Chem 13 (2005) 1901-1911) gave intermediate (**3**). Modification of the acyl group using standard literature conditions (for example US2003/207863) gave the carboxylic acid

intermediate (4). The carboxylic acid of (4) can be converted to a methyl ester using well known conditions. These conditions may also remove the t-butyl oxy carbonyl protecting group. The t-butyl oxy carbonyl protecting group can also be removed using other standard conditions well known in the art such as treatment with trifluoroacetic acid. Alkylation of the benzazepine nitrogen can be done using well known standard conditions of reductive amination or by use of alkyl halides. Further modifications using standard conditions well known in the art for saponification of the ester, conversion of the resulting acid into the acid chloride with subsequent amide formation furnishes compounds of formula 1.

1.1.2 Intermediate 2

To a solution of 1-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (15.5g, 63.7mmol) (1) and acetyl chloride (10eq, 50g, 637mmol) in dichloromethane (300ml) was added aluminium chloride (34g, 255mmol) portion-wise. The reaction was allowed to stir at room temperature for 1 hour. The reaction was quenched by pouring into a mixture of ice and saturated sodium hydrogen carbonate solution. Further solid sodium hydrogen carbonate was then added until the aqueous solution became basic. The reaction mixture was then filtered through celite and diluted with dichloromethane. The combined organics were then dried over sodium sulphate and concentrated *in vacuo* to give 1-(7-acetyl-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (2) as a dark pink solid in 60mmol.

MS ES^+: 286

1H NMR (400 MHz, DMSO-d6): δ 7.72 - 7.82 (m, 2H), 7.29 - 7.39 (m, 1H), 3.72 (br. s., 4H), 3.02 - 3.16 (m, 4H), 2.56 (s, 3H)

1.1.3 Intermediate 3

To a suspension of 1-(7-acetyl-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (2) (10g, 35mmol) in methanol (496ml) was added water (164ml) and saturated potassium carbonate solution (164ml) and the reaction allowed to stir at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water. The aqueous layer was washed with ethyl acetate and the combined organics washed with brine and dried over magnesium sulphate. The residue was azeotroped with toluene and the material used directly.

MS ES^+: 190

1H NMR (400 MHz, DMSO-d6): δ 7.64 - 7.70 (m, 2H), 7.20 - 7.26 (m, 1H), 2.86 - 2.93 (m, 4H), 2.73 - 2.80 (m, 4H), 2.53 (s, 3H)).

To a solution of 1-(2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethanone (10.44g, 35mmol) in dioxane (93ml) and water (35ml) was added Boc anhydride (7.64g, 35mmol) and potassium carbonate (4.84g, 35mmol) and the reaction allowed to stir at room temperature for 48 hours. The reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate and aqueous saturated sodium hydrogen carbonate solution. The combined organics were washed with brine and dried over magnesium sulphate. The crude oil was crystallised over night

to give *tert*-butyl 7-acetyl-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (**3**) as a cream solid in 16.8mmol.

MS ES^+: 189, ES: 216

1H NMR (400 MHz, DMSO-d6) δ 7.66 - 7.74 (m, 2H), 7.21 - 7.30 (m, 1H), 3.37 - 3.48 (m, 4H), 2.83 - 2.93 (m, 4H), 2.50 (s, 3H), 1.36 (s, 9H)

1.1.4 Intermediate 4

To a solution of *tert*-butyl 7-acetyl-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (**3**) (2g, 6.9mmol) in dioxane (23ml) was added an aqueous solution of sodium hydroxide (2.2g, 55.2mmol in 32ml of water) drop wise. The reaction mixture was then cooled to 0° C and bromine (1.06ml, 20.7mmol) added drop wise. The reaction was allowed to stir at 0° C for 1 hour. The reaction was carefully quenched with acetone and the reaction reduced *in vacuo*. The remaining aqueous layer was washed with ethyl acetate and then acidified with 5N hydrochloride acid. The aqueous layer was then extracted with ethyl acetate and the combined organics washed with brine and dried over magnesium sulphate to give 3(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid (**4**) as a pale yellow solid in quantitative yield.

MS ES^+: 192

1H NMR (400 MHz, DMSO-d6) δ 7.60 - 7.80 (m, 2H), 7.16 - 7.32 (m, 1H), 3.41 - 3.52 (m, 4H), 2.84 - 2.97 (m, 4H), 1.34 - 1.47 (m, 9H)

1.1.5 Intermediate 5

Thionyl chloride (60mL, 825mmol) was added dropwise to a stirred solution of methanol (1L) at -20°C and the reaction warmed to room temperature. To this solution 3-(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid 25g, 85.8mmol) (**4**) was added portion-wise to give an orange solution. The reaction mixture was concentrated in vacuo and azeotroped with toluene to give methyl 2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**5**) as a pale brown solid in quantitative yield.

MS ES^+: 206 1H NMR (400 MHz, DMSO-d6):δ 9.46 (br. s., 2H), 7.71 - 7.87 (m, 2H), 7.32 - 7.42 (m, 1H), 3.85 (s, 3H), 3.19 (br. s., 8H)

1.1.6 Synthesis of intermediate 6

Method A

Alkylation:

To a solution of methyl 2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**5**) (7.58g, 31.4mmol) in dimethylacetamide (75mL) was added potassium carbonate (10.8g, 78.5mmol) and iodoethane (2.63mL, 32.9mmol) and the reaction stirred at room temperature for 18 hours. The reaction mixture was diluted with

ethyl acetate and washed with saturated aqueous potassium carbonate and brine, dried over magnesium sulphate and reduced *in* vacuo. Purification by silica chromatography using methanol/dichloromethane mixtures with added ammonia afforded methyl 3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**6**) in12.9mmol.

MS ES^+: 234 ^1H NMR (400 MHz, DMSO-d_6): δ 7.66 - 7.75 (m, 2H), 7.21 - 7.32 (m, 1H), 3.83 (s, 3H), 2.87 - 2.97 (m, 4H), 2.43 - 2.60 (m, 6H), 0.97 - 1.05 (m, 3H)

Method B

Reductive amination:

To a solution of methyl 2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**5**) (20g, 82.7mmol) in dichloromethane (200mL) was added cyclobutanone (9.27mL, 124.1mmol), acetic acid (0.5mL), sodium triacetoxyborohydride (26.3g, 124.1mmol) and triethylamine (11.5mL, 82.7mmol). The reaction was stirred for 18 hours and the reaction mixture concentrated *in vacuo*. Aqueous sodium hydroxide was added and the aqueous phase extracted into dichloromethane (2x100mL). The combined organics were dried over magnesium sulphate and concentrated *in vacuo* to give methyl 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**6**) as a brown solid in quantitative yield.

MS ES^+: 260

^1H NMR (400 MHz, DMSO-d_6): δ 7.67 - 7.74 (m, 2H), 7.23 - 7.29 (m, 1H), 3.83 (s, 3H), 2.86 - 2.95 (m, 4H), 2.71 - 2.82 (m, 1H), 2.35 (br. s., 4H), 1.95 - 2.05 (m, 2H), 1.72 - 1.84 (m, 2H), 1.51 - 1.66 (m, 2H)

1.1.7 Synthesis of intermediate 7

To a solution of methyl 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**6**) (22.03g, 84.9mmol) in tetrahydrofuran (300mL) and water (100mL) was added lithium hydroxide (2.44g, 101.9mmol) and the reaction refluxed for 18hours. The reaction mixture was concentrated *in vacuo* and azeotroped with toluene (x3) to give the lithium salt of 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid (**7**) as a pale brown solid in quantitative yield.

MS ES^+: 246

^1H NMR (400 MHz, DMSO-d_6): δ 7.60 - 7.70 (m, 2H), 6.95 - 7.05 (m, 1H), 2.81 (br. s., 4H), 2.69 - 2.77 (m, 1H), 2.33 (br. s., 4H), 1.95 - 2.05 (m, 2H), 1.71 - 1.84 (m, 2H), 1.51 - 1.65 (m, 2H)

1.1.8 Synthesis of Compound 8 (Formula 1)/**Example 1**

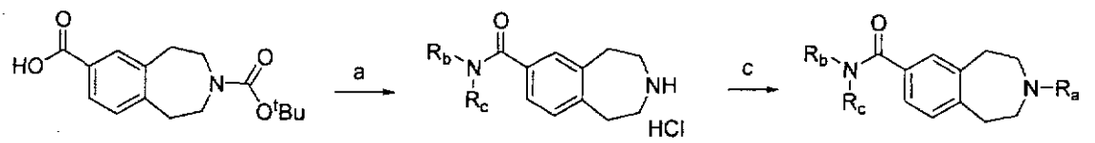
The lithium salt of 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid (**7**)(0.502g, 2mmol) was stirred in thionyl chloride (7.30mL, 100mmol) for 60 minutes and then concentrated *in vacuo* and azeotroped with toluene to give the acid chloride as a brown solid. This material was suspended in dichloromethane (10mL) and to this was added C-(2-methyl-2H-pyrazol-3-yl)-methylamine (0.22g, 2mmol)

and triethylamine (0.28mL, 8mmol) and the reaction stirred for 18 hours. The reaction mixture was concentrated *in vacuo* and loaded onto an SCX-2 cartridge (20g) eluting firstly with methanol (10mL x3) and then 2M ammonia/methanol. Fractions corresponding to the product were combined and concentrated *in vacuo* and then purified by silica chromatography using methanol/dichloromethane mixtures with added ammonia to give 3-cyclobutyl-N-((1-methyl-1H-pyrazol-5-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide (**8**) in 0.9mmol.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 - 8.91 (m, 1H), 7.57 - 7.66 (m, 2H), 7.26 - 7.33 (m, 1H), 7.16 - 7.23 (m, 1H), 6.11 - 6.18 (m, 1H), 4.45 - 4.53 (m, 2H), 3.81 (s, 3H), 2.81 - 2.94 (m, 4H), 2.69 - 2.80 (m, 1H), 2.34 (br. s., 4H), 1.95 - 2.06 (m, 2H), 1.71 - 1.84 (m, 2H), 1.49 - 1.65 (m, 2H)

Compounds of Formula 1 can also prepared as illustrated in scheme 2 using standard conditions well known in the art.

1.2 Scheme 2



4 **9** **8 (Formula 1)**

Reagents and conditions: a) R_bR_cNH,HATU, Et_3N, MeCN; b) 2 M HCl in dioxane;
c) R_aCO or R_aHCO, $NaB(OAc)_3H$, DCM

1.2.1 Synthesis of intermediate 9

To a solution of 3(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid (4.86g, 16.67mmol) (4) in acetonitrile (20mL) was added triethylamine(5.5mL, 40.01mmol), benzylamine (2mL, 18.34mmol) and 2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (7.61g, 20mmol) and the reaction stirred for 16 hours. The reaction mixture was concentrated *in vacuo*, washed with brine and extracted into ethyl acetate (3 x 50mL) and the combined organics dried over magnesium sulphate. The organics were concentrated *in vacuo* and the crude material purified by silica chromatography using methanol/dichloromethane mixtures with added ammonia to give *tert*-butyl 7-(benzylcarbamoyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate as a yellow solid in 15.7mmol.

MS ES$^+$: 381, 324

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 - 9.05 (m, 1H), 7.70 - 7.78 (m, 2H), 7.35 - 7.42 (m, 4H), 7.27 - 7.34 (m, 2H), 4.50 - 4.56 (m, 2H), 3.50 - 3.57 (m, 4H), 2.92 - 3.00 (m, 4H), 1.48 (s, 9H)

Tert-butyl 7-(benzylcarbamoyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (5.95g, 15.64mmol) was stirred in refluxing saturated methanolic HCl for 2 hours Reaction mixture was concentrated *in vacuo* to give N-benzyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide hydrochloride (**9**) as a pale yellow solid in quantitative yield.

MS ES$^+$: 281

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.27 (br. s., 1H), 8.93 - 9.06 (m, 1H), 7.69 - 7.78 (m, 2H), 7.17 - 7.39 (m, 6H), 4.43 - 4.50 (m, 2H), 3.61 - 3.88 (m, 8H)

1.2.2 Synthesis of Compound 8 (Formula 1)/**Example 115**

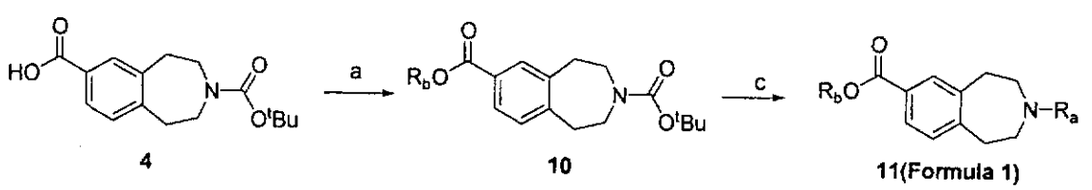
To a solution of N-benzyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide hydrochloride (**9**) (0.28g, 1mmol) in dichloromethane (5mL) was added 3-methylbutanal (0.18mL, 2mmol) and acetic acid (1drop). The reaction was stirred at room temperature for 15mins prior to the addition of sodium triacetoxyborohydride (0.42g, 2mmol). After 1 hour the crude material was loaded onto an SCX-2 cartridge eluting with methanol and then 2M ammonia/methanol. Fractions corresponding to the product were combined and concentrated *in vacuo* and then purified by preparative HPLC to give N-benzyl-3-isobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide (**8**) in 0.72mmol.

MS ES$^+$: 337

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 - 7.57 (m, 2H), 7.28 - 7.40 (m, 5H), 7.11 - 7.16 (m, 1H), 4.63 - 4.68 (m, 2H), 2.91 - 2.98 (m, 4H), 2.55 - 2.64 (m, 4H), 2.16 - 2.22 (m, 2H), 1.74 - 1.86 (m, 1H), 0.89 - 0.96 (m, 6H)

1.3 Scheme 3

Other examples of compounds of formula 1 can be synthesised as illustrated in **Scheme 3** using standard methods. This scheme, or **Scheme 4** (see below), is suitable for synthesising **example compounds 116-119**.



4 **10** **11(Formula 1)**

Reagents and conditions: a)R_bOH, EDC, DMAP, CH_2Cl_2; b) 2M HCl in Et_2O;
c) R_aCO or R_aHCO, AcOH, $Na(OAc)_3BH$, THF

1.3.1 Synthesis of intermediate 10

To a solution of (1-benzylpiperidin-4-yl)methanol (0.211g, 1mmol) in dichloromethane (15mL) was added 3(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid (**4**) (0.3g, 1mmol), N-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDC) (575mg, 3mmol), 4-dimethylaminopyridine (DMAP) (catalytic) and triethylamine (0.42mL, 3mmol) and the reaction stirred for 18 hours. Reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate and 5% aqueous citric acid/brine. The organics were washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulphate and concentrated *in vacuo*. Material was purified by silica chromatography using ethyl acetate/petrol mixtures to give 7-(1-benzylpiperidin-4-yl)methyl 3-tert-butyl 4,5-dihydro-1H-benzo[d]azepine-3,7(2H)-dicarboxylate (**10**) in 0.45mmol.

MS ES$^+$: 479

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 - 7.76 (m, 2H), 7.21 - 7.34 (m, 6H), 4.10 - 4.15 (m, 2H), 3.42 - 3.49 (m, 6H), 2.88 - 2.95 (m, 4H), 2.79 - 2.86 (m, 2H), 1.89 - 1.97 (m, 2H), 1.66 - 1.78 (m, 3H), 1.39 (s, 9H), 1.22 - 1.35 (m, 2H)

1.3.2 Synthesis of Compound 11 (Formula 1)/**Example 116**

To a solution of give 7-(1-benzylpiperidin-4-yl)methyl 3-tert-butyl 4,5-dihydro-1H-benzo[d]azepine-3,7(2H)-dicarboxylate (**10**) (0.214g, 0.45mmol) in diethyl ether (2mL) was added 2M HCl in diethyl ether (2mL) to give a white solid. Methanol was added to give a colourless solution that slowly precipitated over 1 hour. Reaction mixture was concentrated *in vacuo* to give (1-benzylpiperidin-4-yl)methyl 2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate hydrochloride in 0.39mmol. This was used without further purification in the next step.

MS ES$^+$: 379

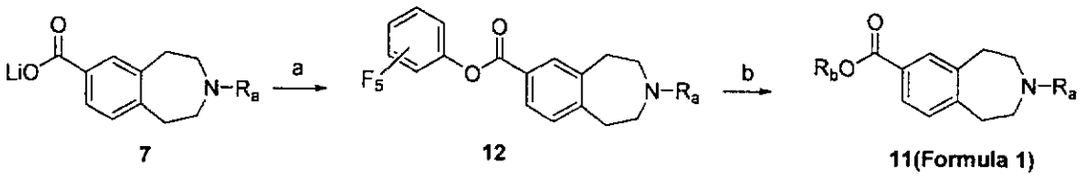
To a partial suspension of (1-benzylpiperidin-4-yl)methyl 2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate hydrochloride (0.162g, 0.39mmol) in tetrahydrofuran (8mL) was added acetaldehyde (0.12mL, 2.14mmol), acetic acid (0.05mL, 0.86mmol), 4Å molecular sieves and sodium triacetoxyborohydride (0.146g, 0.69mmol) and the reaction mixture stirred at room temperature for 1 hour. The reaction was filtered and concentrated *in vacuo* and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate and the organics washed with brine, dried over magnesium sulphate and reduced *in vacuo*. Purification by silica chromatography using methanol/dichloromethane mixtures afforded (1-benzylpiperidin-4-yl)methyl 3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**11**) in 0.32mmol.

MS ES$^+$: 407

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 - 7.67 (m, 2H), 7.13 - 7.29 (m, 6H), 4.01 - 4.08 (m, 2H), 3.38 (s, 2H), 2.81 - 2.89 (m, 4H), 2.72 - 2.79 (m, 2H), 2.36 - 2.50 (m, 6H), 1.81 - 1.91 (m, 2H), 1.59 - 1.70 (m, 3H), 1.15 - 1.29 (m, 2H), 0.90 - 0.97 (m, 3H)

1.4 Scheme 4

Compounds of the invention can also be synthesised using **Scheme 4** via a pentafluorophenoxy intermediate such as **12**. Intermediate **12** can be synthesised using methods similar to those outlined in the literature (J Med. Chem., 35, 15, 1992, 2843; J Org. Chem., 70, 2, 2005, 489).



7 12 11(Formula 1)

Reagents and conditions: a) C_6F_5OH, EDC, Et_3N, CH_2Cl_2; b)R_bOH, MeCN, reflux

1.4.1 Synthesis of intermediate 12

A suspension of the lithio-derivative of 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid (7) (1.08g, 4.40mmol) in dichloromethane (30mL) was treated with pentafluorophenol (0.81g, 4.4mmol), triethylamine (2.2mL, 15.4mmol) and N-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDC) (1.01g, 5.28mmol). The reaction was stirred for 18 hours at room temperature after which the reaction was concentrated *in vacuo*, washed with water and extracted into dichloromethane and dried over magnesium sulphate. The solvents were removed *in vacuo* and the residue was purified by silica chromatography using ethyl acetate/methanol mixtures to give perfluorophenyl 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**12**) in 1.94mmol.

^{1}H NMR (400 MHz, MeOD): δ 7.94 - 7.99 (m, 2H), 7.35 - 7.39 (m, 1H), 3.03 - 3.09 (m, 4H), 2.85 - 2.93 (m, 1H), 2.48 - 2.61 (m, 4H), 2.08 - 2.17 (m, 2H), 1.91 - 2.01 (m, 2H), 1.65 - 1.77 (m, 2H)

1.4.2 Synthesis of Compound 11 (Formula 1)/**Example 119**

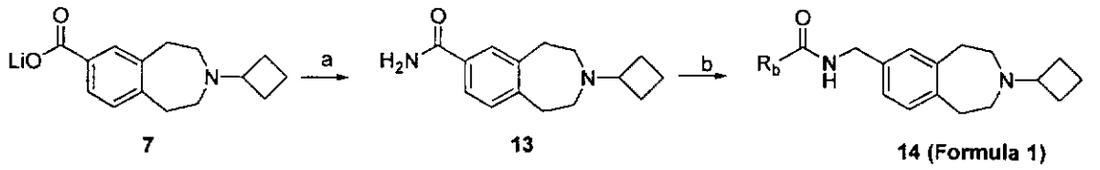
To an acetonitrile (10mL) solution of perfluorophenyl 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**12**) (0.087g, 0.20mmol) was added (4-methoxyphenyl)methanol (0.028g, 0.20mmol) and the reaction refluxed for 48 hours. The reaction mixture was concentrated *in vacuo* and purified by silica chromatography using ethyl acetate/methanol mixtures to afford 4-methoxybenzyl 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate (**11**) in 6.0mmol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.87 (m, 1H), 7.80 (s, 1H), 7.35 - 7.41 (m, 2H), 7.13 - 7.19 (m, 1H), 6.88 - 6.94 (m, 2H), 5.28 (s, 2H), 3.82 (s, 3H), 3.08 (br. s., 4H), 2.90 - 3.01 (m, 1H), 2.67 (br. s., 4H), 2.07 - 2.24 (m, 4H), 1.56 - 1.81 (m, 2H)

MS ES^+: 366

1.5 Scheme 5

Another example of compounds of Formula 1 can be synthesised as outlined in **Scheme 5** using standard conditions well known in the art.



7 13 14 (Formula 1)

Reagents and conditions: a)i.$SOCl_2$; ii. NH_4OH, THF; b)i.$LiAlH_4$, THF; ii. K_2CO_3, R_bCOCl, dioxane

1.5.1 Intermediate 13

A 100ml round-bottomed flask was charged with 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carbonyl chloride (2 g, 7.58 mmol) (prepared from intermediate 7) in THF, to give an orange suspension. Concentrated ammonium hydroxide was added and the reaction mixture was stirred for one hour. The reaction mixture was extracted with dichloromethane and dried and evaporated to yield 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide (6.14 mmol)

MS ES^+: 245

^1H NMR (400 MHz, MeOD): δ 7.61 (m, 2H), 7.15 - 7.21 (m, 1H), 2.96 (br. s., 4H), 2.77 - 2.86 (m, 1H), 2.47 (br. s., 4H), 2.03 - 2.14 (m, 2H), 1.86 - 1.98 (m, 2H), 1.60 - 1.76 (m, 2H).

1.5.2 Synthesis of Compound 14 (Formula 1)/**Example 120**

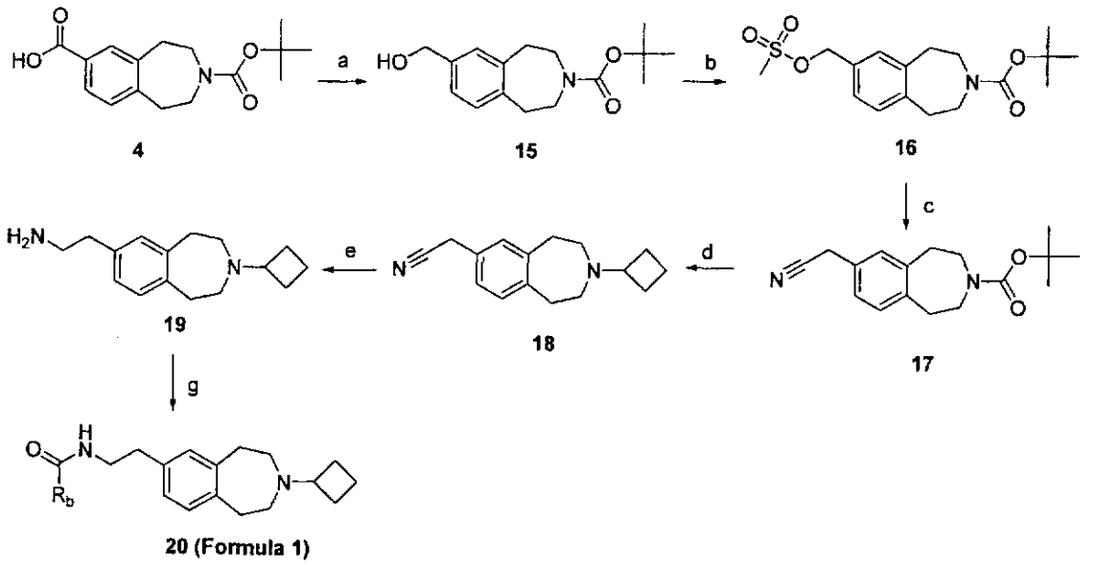
A 100ml round-bottomed flask was charged with 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide (2 g, 8.19 mmol) in tetrahydrofuran (20mL), to give a tan suspension. Lithium aluminium hydride (16.37 ml, 16.37 mmol) was added and the reaction was stirred at reflux for 2 hours. The reaction was cooled and carefully quenched with saturated sodium sulphate. The reaction was dried with magnesium sulphate, filtered through celite and evaporated. The residue was taken up into dioxane and saturated potassium carbonate was added followed by nicotinoyl chloride (1.159 g, 8.19 mmol). The reaction was stirred for 2 hours before extracting into dichloromethane (x3) and drying and evaporating. The residue was purified by Biotage SNAP 50g eluting with ammonia methanol dichloromethane to yield N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)nicotinamide (0.626 mmol,).

MS ES^+: 336

^1H NMR (400 MHz, MeOD): δ 8.96 - 9.02 (m, 1H), 8.65 - 8.71 (m, 1H), 8.21 - 8.30 (m, 1H), 7.50 - 7.58 (m, 1H), 7.02 - 7.14 (m, 3H), 4.53 (s, 2H), 2.87 - 2.96 (m, 4H), 2.76 - 2.86 (m, 1H), 2.36 - 2.53 (m, 4H), 2.05 - 2.14 (m, 2H), 1.86 - 1.99 (m, 2H), 1.61 - 1.78 (m, 2H)

1.6 Scheme 6

Another example of compounds of Formula 1 can be prepared as outlined in **Scheme 6** using standard conditions well known in the art.



Reagents and conditions: a) BH_3.THF, THF; b) $MeSO_2Cl$, TEA, EtOAc; c) NaCN, EtOH, H_2O;
d) i. 4M HCl, dioxan; ii. cyclobutanone, AcOH, $Na(OAc)_3BH$, DCM; e) $LiAlH_4$, THF; g) R_bCOCl, Pyridine

1.6.1 Intermediate 15

A 500ml round-bottomed flask was charged with 3-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid (5.83 g, 20 mmol) in tetrahydrofuran (100 ml), to give a colourless solution. Borane tetrahydrofuran complex (30.4 ml, 30.4 mmol) was added drop wise at 0° C. The solution was stirred at 0° C for one hour and then stirred at ambient temperature for 16 hours. The reaction was quenched by the addition of 100mL of saturated bicarbonate solution and the THF was removed by evaporation. The residue was taken up into ethyl acetate and washed with water (x2). The organic layer was evaporated and the residue was purified by Biotage SNAP 50g column using ethyl acetate petrol 1:1 to yield a colourless oil tert-butyl 7-(hydroxymethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (15.14 mmol).

ES^+ 278 (M+H)

^1H NMR (400 MHz, MeOD): δ 7.11 (s, 3H), 4.54 (s, 2H), 3.47 - 3.58 (m, 4H), 2.85 - 2.92 (m, 4H), 1.47 (s, 9H)

1.6.2 Intermediate 16

A 100ml round bottom flask was charged with tert-butyl 7-(hydroxymethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (4.2 g, 15.14 mmol) and triethylamine (2 ml, 15.14 mmol) in ethyl acetate (50 ml) to give a colourless solution. Methanesulfonyl chloride (1.3 ml, 16.7 mmol) was added and the reaction was stirred for 16 hours. The reaction mixture was diluted with ethyl acetate and washed with saturated bicarbonate, dried, filtered and evaporated. The residue was purified by Biotage SNAP 50g column ethyl acetate / petrol 1:1 to yield tert-butyl 7-((methylsulfonyloxy)methyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (11.25 mmol,).

MS ES^+: 378

1.6.3 Intermediate 17

A 100ml round-bottomed flask was charged with cyanosodium (0.551 g, 11.25 mmol) and tert-butyl 7-((methylsulfonyloxy)methyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (4 g, 11.25 mmol) in Water (2.500 ml) and Ethanol (10 ml) to give a colourless solution.The reaction was heated to reflux for 2 hours. After an aqueous workup and purification by Biotage (20% EtOAc/ Petrol) tert-butyl 7-(cyanomethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (2.79 mmol,) was obtained.

MS ES^+: 213

^1H NMR (400 MHz, MeOD): δ 7.06 - 7.16 (m, 3H), 3.78 (s, 2H), 3.50 (br. s., 4H), 2.79 - 2.93 (m, 4H), 1.45 (s, 9H)

1.6.4 Intermediate 18

tert-Butyl 7-(cyanomethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (**Intermediate 17**) (2.5 mmol) was stirred in 4M HCl in dioxane for 2 hours and then the solvent was removed by evaporation.

MS ES^+: 187

To this residue was added sodium triacetoxyborohydride (0.795 g, 3.75 mmol), acetic acid (0.215 ml, 3.75 mmol) and cyclobutanone (0.263 g, 3.75 mmol) in dichloromethane (10ml) to give a colourless solution. The reaction was stirred for 1 hour. The reaction mixture was diluted with 5% aqueous sodium hydroxide and extracted with dichloromethane (x3) dried and evaporated to yield an oil, triturated with ether to yield a white solid 2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)acetonitrile (2.351 mmol) which was used in the next step without further purification.

1.6.5 Intermediate 19

A 25ml round-bottomed flask was charged with lithium aluminium hydride (0.134 g, 3.53 mmol) in tetrahydrofuran (10 ml), to give a colourless solution. Lithium aluminium hydride (0.134 g, 3.53 mmol) in tetrahydrofuran (3.5mL) was added. The reaction was refluxed for 12 hours and then cooled and quenched with saturated sodium sulphate. The reaction mixture was dried, filtered and evaporated and used without further purification in the next step .2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethanamine (1.179 mmol).

1.6.6 Compound 20 (Formula 1)/**Example 121**

A 25ml round-bottomed flask was charged with 2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethanamine (0.288 g, 1.179 mmol) and nicotinoyl chloride (0.250 g, 1.769 mmol) in pyridine (10ml) to give a colourless solution. The reaction was stirred for one hour and then azeotroped with toluene. The residue was taken up into ethyl acetate and washed with 1M sodium hydroxide solution. The organic layer was dried and the residue was purified using 10% methanol in dichloromethane with 0.2% ammonium hydroxide to yield

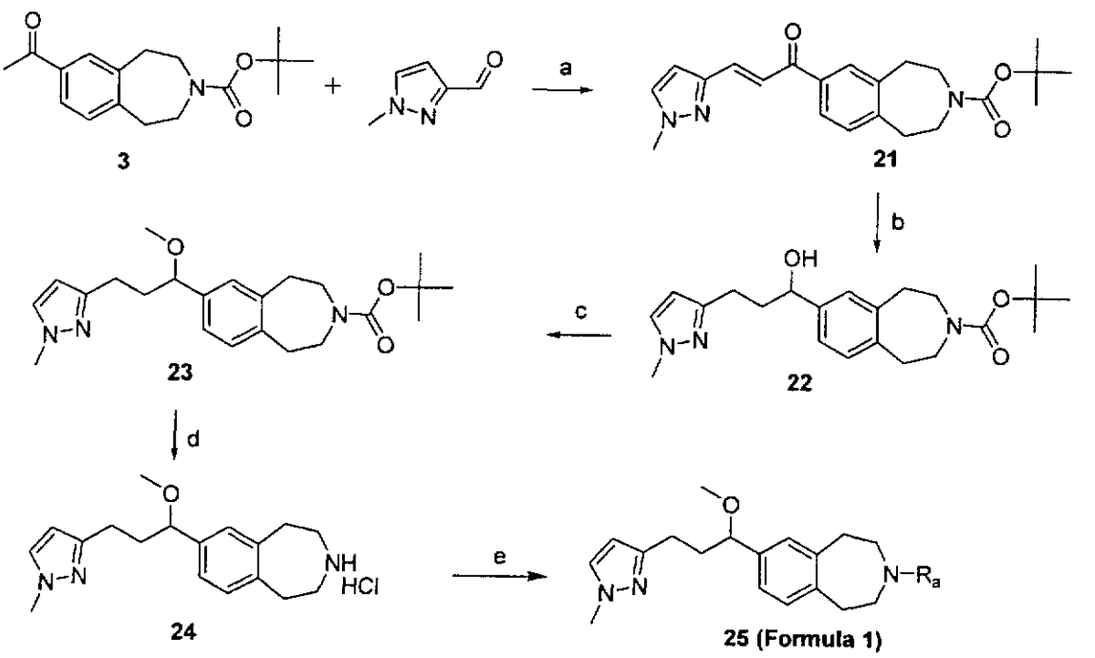
crude product which was purified using preparative HPLC to give N-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethyl)nicotinamide (0.086 mmol).

MS ES^+: 350

^1H NMR (400 MHz, MeOD): δ 8.87 - 8.91 (m, 1H), 8.64 - 8.69 (m, 1H), 8.15 - 8.20 (m, 1H), 7.50 - 7.56 (m, 1H), 6.97 - 7.05 (m, 3H), 3.55 - 3.62 (m, 2H), 2.77 - 2.96 (m, 7H), 2.44 (br. s., 4H), 2.05 - 2.14 (m, 2H), 1.86 - 1.99 (m, 2H), 1.61 - 1.77 (m, 2H)

1.7 Scheme 7

Other compounds of formula 1 can be synthesised as outlined in **Scheme 7** using standard conditions well known in the art. This scheme, as well as **Schemes 8 and 9** (see below), are suitable for preparing **example compounds 122-137.**



Reagents and conditions: a) DBU, MeCN; b) $Pt(IV)O_2$, H_2, EtOAc; c) NaH, MeI, NMP; d) 4M HCl; e) TEA, AcOH, $Na(OAc)_3BH$, DCM, R_aCO

1.7.1 Intermediate 21

A 25ml round-bottomed flask was charged with lithium chloride (0.366 g, 8.64 mmol), 1-methyl-1H-pyrazole-3-carbaldehyde (0.951 g, 8.64 mmol), and tert-butyl 7-acetyl-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (2.5 g, 8.64 mmol) in acetonitrile (10 ml) to give a colourless solution. DBU (1.302 ml, 8.64 mmol) was added and 4A molecular sieves. The reaction was stirred for one hour.The solvent was evaporated and the residue was taken up into ethyl acetate and washed with 5% citric acid (x2), saturated sodium bicarbonate, and dried and evaporated. The residue was purified by Biotage 50g SNAP column using 50%

EtOAc/ Petrol to yield pure (E)-tert-butyl 7-(3-(1-methyl-1H-pyrazol-3-yl)acryloyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (6.82 mmol)

MS ES^+: 326

^1H NMR (400 MHz, MeOD): δ 7.80 - 7.85 (m, 2H), 7.64 - 7.66 (m, 2H), 7.60 - 7.63 (m, 1H), 7.27 - 7.32 (m, 1H), 6.75 - 6.78 (m, 1H), 3.92 (s, 3H), 3.56 (br. s., 4H), 2.95 - 3.02 (m, 4H), 1.44 (s, 9H)

1.7.2 Intermediate 22

A 100ml round-bottomed flask was charged with (E)-tert-butyl 7-(3-(1-methyl-1H-pyrazol-3-yl)acryloyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (2.6 g, 6.82 mmol) and platinum (IV) oxide (0.077 g, 0.341 mmol) in ethyl acetate (50ml) to give a black suspension. The reaction was hydrogenated at atmospheric pressure monitoring by LCMS. The reaction was filtered through celite and evaporated to yield an oil, purified by Biotage 50g using ethyl acetate to elute product tert-butyl 7-(1-hydroxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (6.23 mmol).

MS ES^+: 408

^1H NMR (400 MHz, MeOD): δ 7.41 - 7.45 (m, 1H), 7.08 - 7.25 (m, 3H), 5.97 - 6.10 (m, 1H), 4.52 - 4.67 (m, 1H), 3.80 (s, 3H), 3.44 - 3.65 (m, 4H), 2.82 - 2.99 (m, 4H), 2.51 - 2.74 (m, 2H), 1.87 - 2.13 (m, 2H), 1.47 (s, 9H)

1.7.3 Intermediate 23

A 50ml round-bottomed flask was charged with tert-butyl 7-(1-hydroxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (1 g, 2.59 mmol) in N-methylpyrrolidone (NMP), to give a colourless solution. Sodium hydride (0.125 g, 3.11 mmol) was added and the reaction was stirred for one hour and then iodomethane was added to the mixture and the reaction was stirred for 16 hours. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was washed with water (x3) dried and evaporated. The residue was purified by Biotage SNAP 50g using ethyl acetate petrol (1:1) to yield tert-butyl 7-(1-methoxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (1.502 mmol).

MS ES^+: 422

^1H NMR (400 MHz, MeOD): δ 7.41 - 7.45 (m, 1H), 7.10 - 7.15 (m, 1H), 7.03 - 7.07 (m, 2H), 6.01 - 6.06 (m, 1H), 4.07 - 4.13 (m, 1H), 3.80 (s, 3H), 3.54 (br. s., 4H), 3.17 (s, 3H), 2.86 - 2.92 (m, 4H), 2.51 - 2.70 (m, 2H), 2.00 - 2.12 (m, 1H), 1.82 - 1.95 (m, 1H), 1.46 (s, 9H)

1.7.4 Intermediate 24

A 25ml round-bottomed flask was charged with tert-butyl 7-(1-methoxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (.65 g, 1.627 mmol) in 4M HCl, to give a colourless

solution. The reaction was stirred for two hours and then evaporated to yield 7-(1-methoxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepinium chloride (1.548 mmol). This material was used without further purification.

MS ES^+: 268

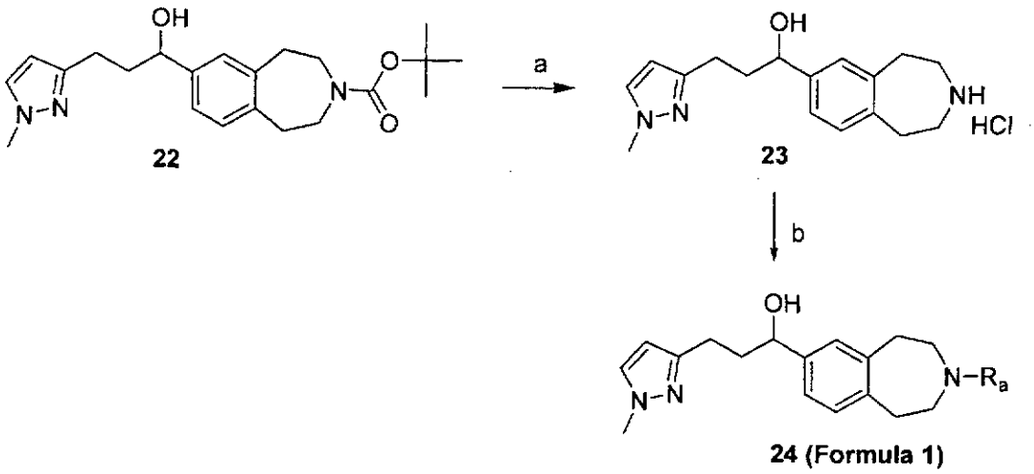
1.7.5 Synthesis of Compound 25 (Formula 1)/**Example 136**

A 50ml round-bottomed flask was charged with 7-(1-methoxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepinium chloride (0.520 g, 1.548 mmol), cyclobutanone (0.217 g, 3.10 mmol), and triethylamine (0.216 ml, 1.548 mmol) in dichloromethane (25mL) to give a colourless solution. Sodium triacetoxyborohydride (0.656 g, 3.10 mmol) and acetic acid (0.886 ml, 15.48 mmol) were added and the reaction was stirred for 16 hours before diluting with dichloromethane and washing with 5% sodium hydroxide solution. The organic phase was dried and evaporated and the residue was purified by Biotage SNAP 50g eluting with 2% ammonia methanol / dichloromethane (1-20%) to yield 3-cyclobutyl-7-(1-methoxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepinium chloride after treatment with ethereal HCl.

MS ES^+: 322

^{1}H NMR (400 MHz, MeOD): δ 7.85 - 7.90 (m, 1H), 7.09 - 7.20 (m, 3H), 6.35 - 6.41 (m, 1H), 4.09 - 4.15 (m, 1H), 3.96 (s, 3H), 3.56 - 3.70 (m, 4H), 3.27 - 3.39 (m, 2H), 3.12 (s, 3H), 2.97 - 3.08 (m, 2H), 2.67 - 2.84 (m, 4H), 2.26 - 2.45 (m, 4H), 1.67 - 2.10 (m, 3H)

1.8 Scheme 8



Reagents and conditions: a) 4M HCl, dioxan, b)R_aCHO, AcOH, $Na(OAc)_3BH$, DCM

1.8.1 Intermediate 23

A 25ml round-bottomed flask was charged with tert-butyl 7-(1-hydroxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (1.7 g, 4.41 mmol) in 4M HCl, to give a colourless solution. The reaction was stirred for two hours and then evaporated to yield 7-(1-hydroxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepinium chloride (4.35 mmol).

MS ES^+: 268 M-18

1.7.5 Synthesis of Compound 24 (Formula 1)/**Example 135**

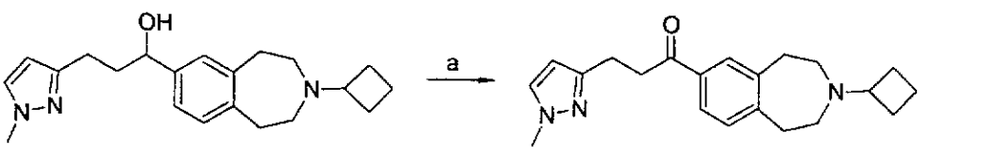
A 100ml round-bottomed flask was charged with acetic acid (2.490 ml, 43.5 mmol),sodium triacetoxyborohydride (1.844 g, 8.70 mmol), 7-(1-hydroxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepinium chloride (1.4 g, 4.35 mmol) and triethylamine (0.606 ml, 4.35 mmol) in DCM (50ml) to give a colourless solution. Cyclobutanone (0.610 g, 8.70 mmol) was added.The reaction was stirred for 16 hours and then the reaction mixture was washed with 5% NaOH solution and dried and evaporated. The residue was purified by Biotage SNAP 100g using 10% Methanol/ DCM with 2% ammonia to yield 1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(1-methyl-1H-pyrazol-3-yl)propan-1-ol (2.504 mmol)

MS ES^+: 323

^{1}H NMR (400 MHz, MeOD): δ 7.40 - 7.46 (m, 1H), 7.03 - 7.13 (m, 3H), 6.02 - 6.10 (m, 1H), 4.53 - 4.62 (m, 1H), 3.80 (s, 3H), 2.77 - 2.97 (m, 5H), 2.34 - 2.70 (m, 6H), 1.87 - 2.15 (m, 6H), 1.59 - 1.78 (m, 2H)

1.9 Scheme 9

Scheme 9



24 **25 (Formula 1)/Example Compound 134**

Reagents and conditions: a) MnO_2, THF

1.9.1 Synthesis of Compound 25 (Formula 1)/**Example 134**

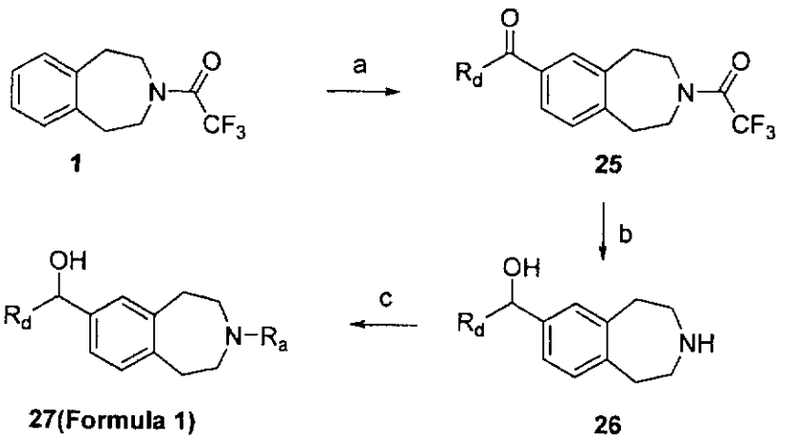
A 100ml round-bottomed flask was charged with 1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(1-methyl-1H-pyrazol-3-yl)propan-1-ol (0.5 g, 1.473 mmol) and manganese dioxide (1.280 g, 14.73 mmol) in tetrahydrofuran (50ml) to give a black suspension. The reaction was heated to reflux for 2 hours, and then filtered and evaporated and purified by biotage SNAP 100g eluting with 10% Methanol in dichloromethane with ammonia to yield 1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(1-methyl-1H-pyrazol-3-yl)propan-1-one (0.504 mmol).

MS ES^+: 338

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 - 7.78 (m, 2H), 7.23 - 7.26 (m, 1H), 7.15 - 7.20 (m, 1H), 6.05 - 6.11 (m, 1H), 3.88 (s, 3H), 3.30 - 3.39 (m, 2H), 3.03 - 3.12 (m, 2H), 2.97 (br. s., 4H), 2.72 - 2.85 (m, 1H), 2.45 (br. s., 4H), 2.03 - 2.15 (m, 2H), 1.84 - 1.99 (m, 2H), 1.55 - 1.79 (m, 2H).

1.10 Scheme 10

This scheme is suitable for preparing **example compounds 138-141**



a)i. RdCOOH, $SOCl_2$; ii. $AlCl_3$, CH_2Cl_2; b)$NaBH_4$, MeOH;
c) R_aCO or R_aHCO, $NaB(OAc)_3H$, DCM, AcOH

1.10.1 Intermediate 25

A round bottomed flask was charged with thionyl chloride (7.3 ml, 100 mmol) and 1-acetylpiperidine-4-carboxylic acid (1.7 g, 10.00 mmol) to give a colourless solution. After about 15 minutes crystals formed. The reaction was diluted with petrol and the reaction was filtered and washed with petrol.The crystals were dried and evaporated and 1-(4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (2.4 g, 10 mmol) was added and the mixture was dissolved in dichloromethane (20 mL). Aluminum trichloride (4 g, 30 mmol) was added cautiously, portion wise, and the mixture was stirred for two hours before pouring onto ice and extracting with ethyl acetate. The organic extract was washed with brine and dried and evaporated. The residue was purified by column chromatography on silica using 10% methanol in dichloromethane to yield 1-(7-(1-acetylpiperidine-4-carbonyl)-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (2.6 g, 6.6 mmol, 65.6 % yield) as an oil.

^{1}H NMR (400 MHz, MeOD-d4) δ 7.77 - 7.95 (m, 2H), 7.32 - 7.45 (m, 1H), 4.47 - 4.58 (m, 1H), 3.95 - 4.09 (m, 1H), 3.65 - 3.91 (m, 5H), 3.35-3.40 (m, 1H), 3.06 - 3.22 (m, 4H), 2.83 - 3.02 (m, 1H), 2.09 - 2.20 (m, 3H), 1.84 - 2.02 (m, 2H), 1.48 - 1.79 (m, 2H)

MS ES^+: 397

1.10.2 Intermediate 26

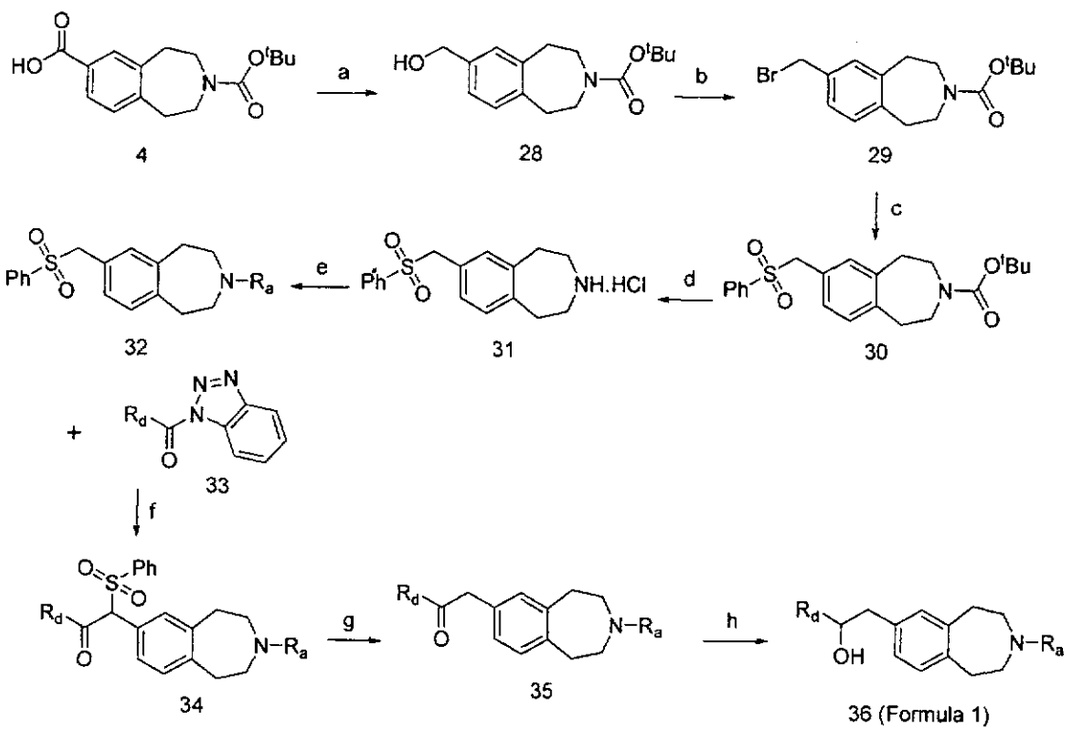
A flask was charged with 1-(7-(1-acetylpiperidine-4-carbonyl)-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (2.6 g, 6.6 mmol) and sodium borohydride (0.76 g, 20 mmol) in methanol (20 mL) to give a colourless solution. The reaction was stirred for 16h. The solvent was removed and the product was used crude in the next step

*1.10.3 Compound 27 (Formula 1)/ **Example 138***

A flask was charged with 1-(4-(hydroxy(2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)piperidin-1-yl)ethanone) (2.0g, 6.6mmol), cyclobutanone (0.25g, 13.2mmol) and triethylamine (0.69g, 6.6 mmol) in dichloromethane (20 mL) to give a colourless solution. Sodium triacetoxy borohydride (2.1 g, 9.9 mmol) was added and the reaction was stirred for two hours before diluting with 2M sodium hydroxide and extracting with dichloromethane. The organic layer was dried and evaporated and purified by silica chromatography, eluting with 10% methanol in dichloromethane to yield 1-(4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)(hydroxy)methyl)piperidin-1-yl)ethanone (0.9 g, 2.6 mmol, 40% yield) as a white solid after trituration with ether.

1.11 Scheme 11

This scheme is suitable for preparing **example compounds 142-157, 227-228, 240-241, 244, 305-307 and 325.**



a) BH_3.THF; b)CBr_4, PPh_3,CH_2Cl_2; c)PhSOONa,DMF;d)HCl, DCM/MeOH
e)$RaCO$ or $RaHCO$, $NaB(OAc)_3H$, DCM;f)n-BuLi, THF g)i.EtOH, sat NH_4Cl, AcOH, Zn;ii. 2M NaOH;
h) $NaBH_4$, MeOH

1.11.1 Intermediate 4

Made using a previous described method (see 1.1.4).

1.11.2 Intermediate 28

3-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-carboxylic acid (10 g, 34.32 mmol) was added portionwise to borane 1M in tetrahydrofuran (51.5 ml, 51.49 mmol) and resultant mixture stirred for 16 hr at room temperature under nitrogen. Sodium bicarbonate was added slowly until bubbling ceased. Reaction was then extracted with EtOAc and organic phase dried over magnesium sulphate, filtered and concentrated *in vacuo* to yield tert-butyl 7-(hydroxymethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate as a colourless oil (9.34 g, 33.67 mmol, 98 %).

^{1}H NMR (400 MHz, MeOD) δ ppm 1.49 (s, 9 H) 2.84 - 2.96 (m, 4 H) 3.48 - 3.62 (m, 4 H) 4.50 - 4.59 (m, 2 H) 7.12 (s, 3 H)

MS ES$^-$ 276

1.11.3 Intermediate 29

Tert-butyl 7-(hydroxymethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (19.85 g, 71.57 mmol) and triphenylphosphine (18.77 g, 71.57 mmol) in dichloromethane (60 mL) were cooled to 0 °C and a solution of carbon tetrabromide (23.73 g, 71.57 mmol) in dichloromethane (60 mL) was added via a dropping funnel over 1 h. Upon complete addition, the mixture was warmed to RT and stirred overnight (LCMS indicated mostly product after this time). The reaction mixture was poured into petrol (500 mL) and filtered through Celite. The residual solid remaining in the flask was triturated with petrol (3 x 200 mL) and filtered as before. The filtrate was concentrated and dichloromethane and silica gel were added. After concentration to dryness, the product was purified by dry flash chromatography on silica gel, eluting with 0 – 30% EtOAc / petrol step-gradient (product eluted at 10-20% EtOAc) to give 4 as an oil which crystallised to tert-butyl 7-(bromomethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate as a white solid upon scratching / seeding / standing (16.24 g, 47.73 mmol, 67%).

^{1}H NMR (400 MHz, MeOD) δ ppm 1.48 (s, 9 H) 2.85 - 2.98 (m, 4 H) 3.48 - 3.64 (m, 4 H) 4.48 - 4.59 (m, 2 H) 7.08 - 7.25 (m, 3 H)

MS ES$^+$ 340 342

1.11.4 Intermediate 30

Tert-butyl 7-(bromomethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (10.00 g, 29.4 mmol) was suspended in DMF (30 ml) and sodium benzenesulfinate (7.24 g, 44.1 mmol) was added. The reaction was stirred for 16 hr at room temperature.

The reaction mixture was diluted with EtOAc (50 mL) and washed with brine (5 x 50 mL). The organic phase was dried over magnesium sulphate, filtered and concentrated in vacuo to yield 12.097 g of white powder. This was washed with diethyl ether and filtered to yield tert-butyl 7-(phenylsulfonylmethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (8.75 g, 21.79 mmol, 74 %).

^{1}H NMR (400 MHz, MeOD) δ ppm 1.49 (s, 9 H) 2.72 - 2.84 (m, 2 H) 2.85 - 2.94 (m, 2 H) 3.41 - 3.61 (m, 4 H) 4.44 (s, 2 H) 6.75 - 7.00 (m, 2 H) 7.05 (s, 1 H) 7.56 (d, J=7.33 Hz, 2 H) 7.68 (d, J=7.58 Hz, 3 H)

MS ES$^+$ 402

1.11.5 Intermediate 31

Tert-butyl 7-(phenylsulfonylmethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (8.75 g, 21.79 mmol) was dissolved in 10 ml of DCM / MeOH (9:1) and 4M HCl in 1,4-Dioxane (25 ml, 25 mmol) was added and mixture stirred for 1 hour at room temperature. Mixture was concentrated *in vacuo* to dryness to yield 7-(phenylsulfonylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (6.781 g, 22.50 mmol, 100%) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ ppm 3.02 - 3.11 (m, 2 H) 3.12 - 3.19 (m, 2 H) 3.23 - 3.30 (m, 4 H) 4.49 (s, 2 H) 6.97 - 7.08 (m, 2 H) 7.13 - 7.20 (m, 1 H) 7.53 - 7.63 (m, 2 H) 7.66 - 7.78 (m, 3 H)

MS ES$^+$ 302

1.11.6 Intermediate 32

7-(phenylsulfonylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (6.78 g, 22.49 mmol) was suspended in CH_2Cl_2 (20 mL) and triethylamine (3.43 mL, 24.74 mmol) and cyclobutanone (2.52 mL, 33.70 mmol) were added. The mixture was stirred under nitrogen and sodium triacetoxyhydroborate (7.15 g, 33.70 mmol) and acetic acid (1.93 mL, 33.70 mmol) were added. The mixture was stirred at room temperature for 16 hrs. The mixture was quenched with NaOH (2M, aq, 50 mL) and the phases separated. The aqueous phase was extracted with DCM (3 x 10 mL) and the organic layers combined, dried over magnesium sulphate, filtered and concentrated in vacuo to yield a colourless oil. The oil was triturated with diethyl ether to yield 3-cyclobutyl-7-(phenylsulfonylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (5.361 g, 15.08 mmol, 67 %) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ ppm 1.59 - 1.83 (m, 2 H) 1.87 - 2.02 (m, 2 H) 2.05 - 2.19 (m, 2 H) 2.23 - 2.61 (m, 4 H) 2.74 - 2.97 (m, 5 H) 4.44 (s, 2 H) 6.78 - 6.85 (m, 1 H) 6.87 - 6.94 (m, 1 H) 6.98 - 7.07 (m, 1 H) 7.49 - 7.59 (m, 2 H) 7.66 (s, 3 H)

MS ES$^+$ 356

1.11.7 Intermediate 33

A 20mL microwave vial was charged with 1-(methylsulfonyl)-1H-benzo[d][1,2,3]triazole (0.986 g, 5.00 mmol) and 2-(1-propionylpiperidin-4-yl)acetic acid (0.996 g, 5 mmol) in THF (10 ml) to give a colourless solution. Triethylamine (0.976 mL, 7.00 mmol) was added and the reaction was microwaved at 130°C for 20 minutes. TLC 1:1 EtOAc / Petrol showed complete reaction. The solvent was evaporated and the residue was purified by silica chromatography using ethyl acetate / petrol 0-100% to yield 1-(4-(2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)piperidin-1-yl)propan-1-one (1.1 g, 3.66 mmol, 73.2 % yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 - 8.35 (m, 1H), 8.12 - 8.19 (m, 1H), 7.66 - 7.73 (m, 1H), 7.50 - 7.58 (m, 1H), 3.55 - 5.00 (bm, 2H), 3.37 - 3.44 (m, 2H), 2.50 - 3.33 (bm, 2H), 2.32 - 2.44 (m, 3H), 1.89 - 2.00 (m, 2H), 1.31 - 1.45 (m, 2H), 1.13 - 1.22 (m, 3H)

1.11.8 Intermediate 34

3-Cyclobutyl-7-(phenylsulfonylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (1.422 g, 4 mmol) was dissolved in THF (30mL) at 0°C and n-butyllithium (5.00 mL of 1.6M, 8.00 mmol) was added dropwise. The reaction was warmed to room temperature for one hour and then cooled to -78°C. 1-(4-(2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)piperidin-1-yl)propan-1-one (1.201 g, 4.00 mmol) in THF (5mL) was added dropwise. The reaction was allowed to warm to room temperature over 16 hours. The reaction was quenched with saturated ammonium chloride, diluted with DCM and basified with sodium carbonate solution. The aqueous layer was extracted (x3) with dichloromethane, dried and evaporated. The residue was purified by KPNH silica cartridge to yield1-(4-(3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-oxo-3-(phenylsulfonyl)propyl)piperidin-1-yl)propan-1-one (1.6 g, 2.98 mmol, 74.5 % yield)

^{1}H NMR (400 MHz, MeOD) δ 7.59 - 7.72 (m, 3H), 7.47 - 7.55 (m, 2H), 6.96 - 7.13 (m, 3H), 4.41 (br. s., 1H), 3.86 (br. s., 1H), 2.98 - 3.11 (m, 1H), 2.76 - 2.98 (m, 5H), 2.32 - 2.70 (m, 8H), 1.84 - 2.18 (m, 5H), 1.51 - 1.81 (m, 4H), 0.82 - 1.44 (m, 7H)

1.11.9 Intermediate 35

1-(4-(3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-oxo-3-(phenylsulfonyl)propyl)piperidin-1-yl)propan-1-one (1.6 g, 2.98 mmol) was dissolved in ethanol (50mL) and sat. ammonium chloride and acetic acid (3.41 mL, 59.6 mmol) were added followed by zinc (1.950 g, 29.8 mmol) and the reaction was refluxed for 1.5h. LCMS showed completion of reaction, and the reaction mixture was cooled, basified with 2M NaOH and extracted with dichloromethane (x3), dried and evaporated. The residue was purified by KPNH cartridge (55g) eluting with ethyl acetate petrol 0-100% to yield 1-(4-(3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-oxopropyl)piperidin-1-yl)propan-1-one (1.1 g, 2.77 mmol, 93 % yield)

^{1}H NMR (400 MHz, MeOD) δ 7.02 - 7.12 (m, 1H), 6.97 (br. s., 2H), 4.39 - 4.52 (m, 1H), 3.82 - 3.94 (m, 1H), 3.67 (s, 2H), 3.00 - 3.13 (m, 1H), 2.77 - 3.00 (m, 5H), 2.31 - 2.69 (m, 9H), 1.87 - 2.19 (m, 5H), 1.59 - 1.81 (m, 4H), 0.90 - 1.15 (m, 5H)

MS ES$^+$ 397

*1.11.10 Compound 36 (Formula 1) / **Example 147***

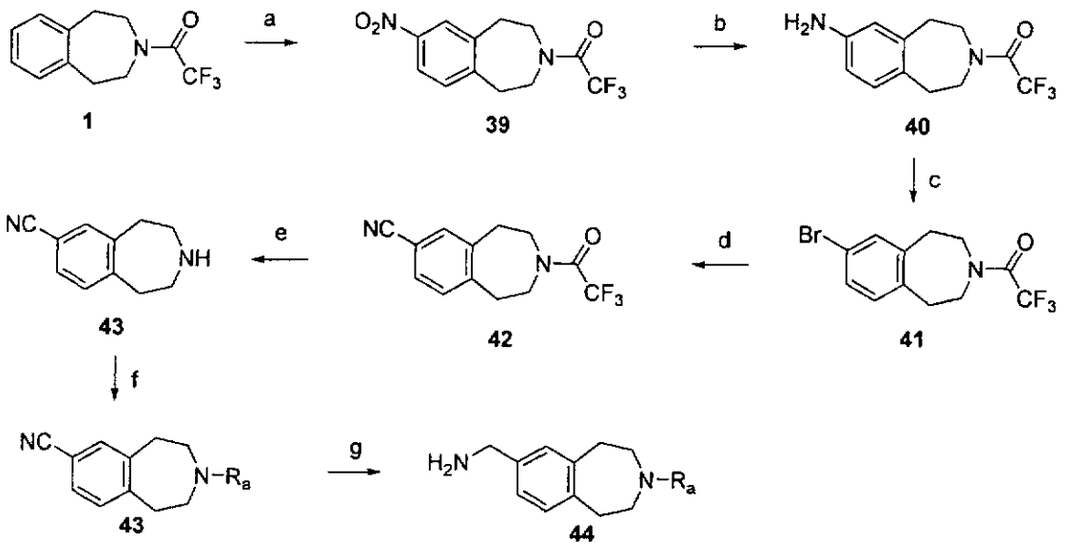
1-(4-(3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-oxopropyl)piperidin-1-yl)propan-1-one (1.1 g, 2.77 mmol) was dissolved in methanol (30mL) and sodium borohydride (0.315 g, 8.32 mmol) was added to the stirred solution. The reaction was stirred for an hour before quenching with 2M HCl (10mL) and evaporating. The residue was taken up into dichloromethane and basified with 2M NaOH and extracted with more dichloromethane. The extract was evaporated and the residue was purified by KPNH silica using ethyl acetate/ petrol to yield a solid which was recrystallised from ethyl acetate heptane to yield 1-(4-(3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)propan-1-one (.739 g, 1.854 mmol, 66.8 % yield) as a first crop.

^{1}H NMR (400 MHz, MeOD) δ 6.90 - 7.07 (m, 3H), 4.42 - 4.56 (m, 1H), 3.82 - 3.98 (m, 2H), 2.98 - 3.12 (m, 1H), 2.79 - 2.98 (m, 5H), 2.31 - 2.77 (m, 9H), 2.05 - 2.19 (m, 2H), 1.89 - 2.05 (m, 2H), 1.58 - 1.89 (m, 5H), 1.27 - 1.49 (m, 2H), 0.86 - 1.23 (m, 5H)

MS ES$^+$ 399

1.12 Scheme 12

This scheme can be used for synthesising **example compounds 175- 220, 248, 230, 234, 236-239, 242-243, 245-247, 249, 252, 254-257, 259-264, 265-276, 279-282, 284-285, 287-293, 295-302, 309-324** and as an alternative method for synthesising *intermediate 13.*



a) H_2SO_4, KNO_3, 0°C; b) $NH_4(HCOO)_2$, $Pd(OH)_2$; c) HBr, $NaNO_2$; d) $Pd(Ph_3)_4$; $Zn(CN)_2$, H_2O, DMF
e) aq. NaOH, MeCN, EtOH; f) R_aCO or RaHCO, $NaB(OAc)_3H$, DCM; g) $LiAlH_4$, THF

1.12.1 *Intermediate 39*

1-(4,5-Dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (100g, 411 mmol) was dissolved in sulfuric acid (400 ml) and the solution was cooled in an ice-bath. Potassium nitrate (45.7 g, 452 mmol) was added portion-wise over 20 minutes (no exotherm observed, solution turned pale yellow). The solution was stirred for a further 10 minutes after which time the reaction was complete by TLC (30% ethyl acetate in petrol, Potassium permanganate staining). The reaction mixture was slowly poured into 2 x 2 litre beakers full of ice with stirring. A thick white ppt. formed, and once about half of the product solution had been added, about 400 ml of DCM was added to the beakers to dissolve this. A further 200ml of DCM was added to the beakers and the ice-cold layers were separated and the aqueous layer was extracted with DCM (1 x 200 ml). The combined organic layers were washed with brine (500 ml) and dried (MgSO4) and the solvent was removed under reduced pressure. Ethyl acetate (200 ml) was added to the resulting oil, and the product was left to crystallise overnight and then filtered to give 2,2,2-trifluoro-1-(7-nitro-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)ethanone as a white solid, 50g, 42%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 - 8.16 (m, 2H), 7.24 - 7.47 (m, 1H), 3.62 - 4.01 (m, 4H), 2.95 - 3.32 (m, 4H)

1.12.2 Intermediate 40

2,2,2-Trifluoro-1-(7-nitro-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)ethanone (50g, 174 mmol) was dissolved in ethanol (1 litre) and ammonium formate (110g, 10 eq.) was added, followed by $Pd(OH)_2$ (20% on carbon, wet, 2 g). The mixture was stirred vigorously under nitrogen and the reaction was initiated by warming in a hot water bath for 5 minutes. The reaction mixture began to effervesce quite vigorously. After 30 minutes the

reaction was complete by tlc (30% EtOAc, petrol) and the mixture was filtered through celite with ethanol washing. The ethanol was then removed under reduced pressure and a water/ethyl acetate work-up was carried out and the combined organic layers were dried ($MgSO_4$) and the solvent removed to give an off-white solid which was triturated with ether to give 1-(7-Amino-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone as a white solid, 40g, 89%.

1H NMR (400 MHz, $CDCl_3$) δ 6.82 - 7.09 (m, 1H), 6.44 - 6.61 (m, 2H), 3.59 - 3.84 (m, 4H), 2.66 - 2.99 (m, 4H).

1.12.3 Intermediate 41

1-(7-Amino-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (70.3 g, 272 mmol) was suspended in hydrobromic acid (210 ml), and the mixture was cooled in a brine ice-bath and a solution of sodium nitrite in water (20 ml) was added drop-wise over 20 minutes to give a bright yellow thick suspension. Meanwhile 1-(7-amino-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (70.3 g, 272 mmol) was dissolved in hydrobromic acid (210 ml) and the solution was heated to 85 °C in a 2 litre 2 neck flask with condenser. The suspension of diazonium salt was then added by pouring portion-wise over 20 minutes through a funnel - effervescence was observed on each addition. The residual diazonium salt was washed out with about 20 ml of hydrobromic acid and the solution was stirred for a further 1 hour at 85 °C. After this time the TLC (30% ethyl acetate/petrol, Potassium permanganate staining, no uv) of an aliquot quenched in water and extracted with DCM showed complete conversion of the starting material to the desired product (top spot, and some of the phenol which shows up brightly with Potassium permanganate staining, The 1H NMR spectrum showed about 70% product + one other impurity, probably the phenol. The mixture was cooled to room temperature and diluted with water (about 600 ml) and the mixture was extracted with DCM (2 x 500 ml), and the combined organic layers washed with saturated $NaHCO_3$ (400 ml), dried (MgSO4) and the solvent was removed under reduced pressure to give a brown oil. This material was purified by dry flash column chromatography, eluting with 10-30% ethyl acetate in petrol to give 1-(7-Bromo-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone as a white crystalline solid, (40g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 - 7.07 (m, 1H), 6.40 - 6.61 (m, 2H), 3.62 - 3.87 (m, 4H), 2.69 - 3.05 (m, 4H).

1.12.4 Intermediate 42

1-(7-Bromo-4,5-dihydro-1H-benzo[d]azepin-3(2H)-yl)-2,2,2-trifluoroethanone (20 g, 62.1 mmol) was dissolved in DMF (150 ml) and water (0.50 ml) and tetrakis(triphenylphosphine) palladium (0) (0.789 g, 0.683 mmol) and dicyanozinc (5.04 g, 43.5 mmol) were added and the solution was heated under reflux under nitrogen for 3 hours. After this time there was still some starting material by tlc (30% EtOAc/petrol, Potassium permanganate staining, no uv) so another 500 mg of tetrakis(triphenylphosphine) palladium (0) was added and the solution was heated for a further hour after which time the reaction had gone to completion. Most of the

DMF was removed under reduced pressure and saturated brine and ethyl acetate were added and the layers were separated. The organic layer was washed with brine (3 x 100 ml), dried (MgSO4) and the solvent was removed to give a dark grey-brown oil. This crude product was purified by dry flash column chromatography, eluting with 30% ethyl acetate in petrol to give the product as a colourless oil which crystallised on standing to give 3-(2,2,2-Trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carbonitrile as a white solid, 12.8g, 77%

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 2H), 7.28 (s, 1H), 3.57 - 3.93 (m, 4H), 2.82 - 3.30 (m, 4H).

1.12.5 Intermediate 43

3-(2,2,2-Trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carbonitrile (2g, 7.46 mmol) was dissolved in ethanol (50 ml) and acetonitrile (10.0 ml) and 2 M aqueous sodium hydroxide (7.5 ml, 14.91 mmol) was added and the solution was stirred for 30 minutes, after which time the reaction had gone to completion by TLC (30% EtOAc/petrol). The solvent was removed under reduced pressure and water (50 ml) and DCM (100 ml) were added and the layers were separated and the organic layer was washed with brine (50 ml) and dried ($MgSO_4$) to give 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carbonitrile as a colourless oil, 1.1 g, 86%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.48 (m, 2H), 7.13 - 7.24 (m, 1H), 2.80 - 3.10 (m, 8H).

1.12.6 Intermediate 44

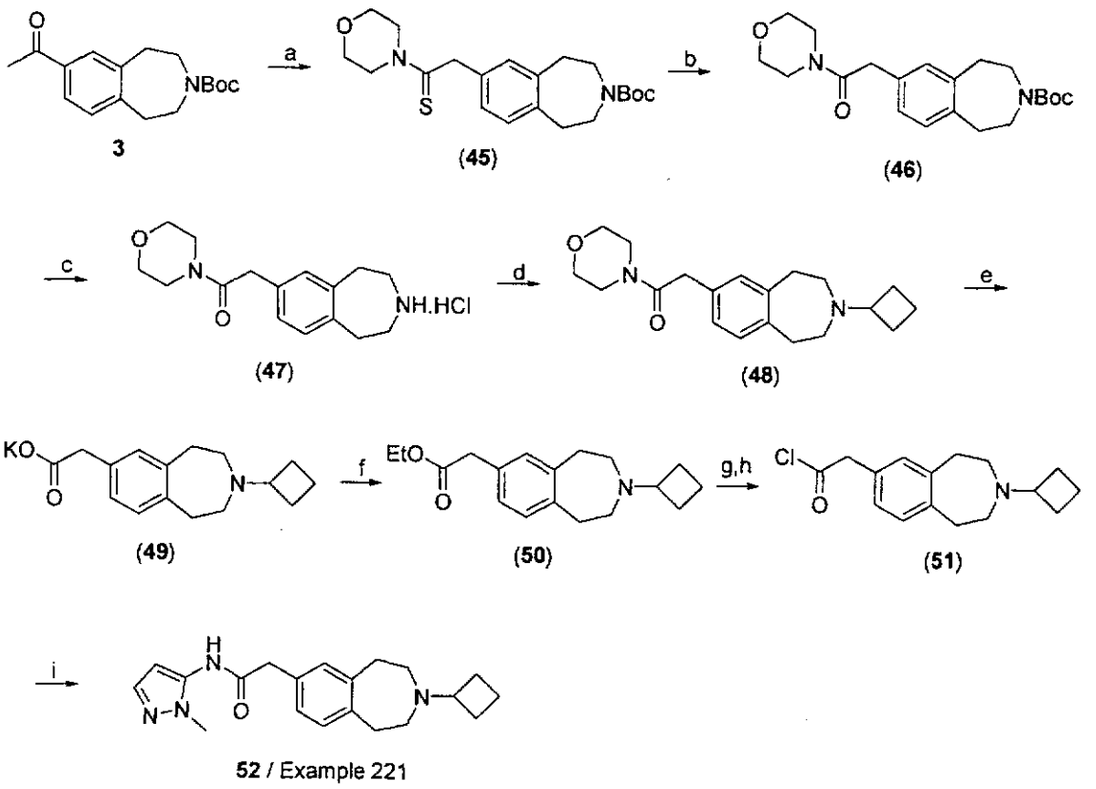
3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carbonitrile (8.1 g, 35.8 mmol) was dissolved in THF (50 ml) and the solution was added drop-wise over 20 minutes to a stirred solution of 1.0 M $LiAlH_4$ in THF (35.8 ml, 35.8 mmol) which was warmed to about 30 °C in a water bath. After 1 hour the reaction was complete by tlc of an aliquot quenched with water and diluted with ethyl acetate (10% MeOH/DCM + NH_3, ninhydrin). Hence the solution was cooled in an ice-bath and quenched by drop-wise addition of saturated Na_2SO_4 and then diluted with ethyl acetate (200 ml) and dried ($MgSO_4$) and the solution was filtered through celite and the solvent removed to give (3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methanamine as a waxy off-white solid, 6.96g, 84%.

MS ES+ 231

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 3H), 3.71 (s, 2H), 2.75 - 2.91 (m, 4H), 2.59 - 2.75 (m, 1H), 2.16 - 2.51 (m, 4H), 1.89 - 2.06 (m, 2H), 1.68 - 1.88 (m, 2H), 1.42 - 1.67 (m, 2H).

1.13 Scheme 13

This scheme is suitable for preparing example compounds 221-226, 274, 294.



a) S_8, Morpholine, $Ti(OEt)_4$, 60 °C, 45min, then 90 °C, 30 min; b) KOH, H_2O, Ethanol; c) 4M HCl in Dioxane; d) Cyclobutanone, $NaBH(OAc)_3$, Et_3N, AcOH, DCM; e) KOH, H_2O, Ethanol, reflux; f) H_2SO_4, Ethanol, reflux; g) LiOH, THF, H_2O; h) $SOCl_2$, reflux; i) Amine, Pyridine.

2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-N-(1-methyl-1H-pyrazol-5-yl)acetamide (**example 221**)

1.13.1 Intermediate 45

To a slurry of *tert*-butyl 7-acetyl-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (20.00 g, 69.12 mmol) in morpholine (9.1 mL, 9.03 g, 87.12 mmol) at RT was added sulphur powder (3.32 g, 103.67 mmol). The brown mixture was stirred for 5 min and then titanium(IV) ethoxide (29.0 mL, 31.53 g, 138.24 mmol) was added. The reaction was heated to 60 °C for 45 min and then to 90 °C for 30 min. LCMS indicated complete reaction, EtOAc (100 mL) and brine (50 mL) were added, the mixture was stirred at RT for 30 min and then filtered through celite and the solid washed with EtOAc. The filtrate was washed with brine (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated. Purified on Biotage silica gel column, eluting with 10 – 50% EtOAc / petrol gradient to afford *tert*-butyl 7-(2-morpholino-2-thioxoethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate as a brown gum (18.60 g, 47.63 mmol, 69%).

^{1}H NMR (400 MHz, MeOD) δ 7.05 - 7.21 (m, 3H), 4.26 - 4.38 (m, 4H), 3.64 - 3.81 (m, 4H), 3.45 - 3.64 (m, 4H), 3.38 - 3.46 (m, 2H), 2.78 - 3.01 (m, 4H), 1.40 - 1.58 (m, 9H)

MS ES^+ 391

1.13.2 Intermediate 46

To a solution of tert-butyl 7-(2-morpholino-2-thioxoethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (45) (18.60 g, 47.63 mmol) in ethanol (200 mL) was added KOH (1M, aq., 95.3 mL, 95.30 mmol). The mixture was stirred overnight at RT and then further KOH (1M, aq., 47.6 mL, 47.60 mmol) was added and the reaction stirred for a further 20 h at RT. The reaction was poured into water (50 mL) and DCM (150 mL) was added. The phases were separated and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic phases were washed with brine (2 x 100 mL), dried ($MgSO_4$), filtered and concentrated. Purified on silica gel, eluting with 20-40-60-80-100% EtOAc / petrol stepwise gradient.to yield tert-butyl 7-(2-morpholino-2-oxoethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate as a light yellow solid (13.04 g, 34.82 mmol, 73%).

^{1}H NMR (400 MHz, DMSO δ 7.03 - 7.12 (m, 1H), 6.92 - 7.03 (m, 2H), 3.64 (s, 2H), 3.38 - 3.57 (m, 12H), 2.81 (d, J = 3.54 Hz, 4H), 1.33 - 1.52 (m, 9H)

MS ES$^+$ 375

1.13.3 Intermediate 47

A solution of *tert*-butyl 7-(2-morpholino-2-oxoethyl)-4,5-dihydro-1H-benzo[d]azepine-3(2H)-carboxylate (13.00 g, 34.72 mmol) in dioxane (100 mL) was treated with HCl in dioxane (4M, 40 mL). The reaction was treated with further HCl in dioxane (4M, 25 mL) and allowed to stand over the weekend. Removal of the solvent under reduced pressure afforded the product as the HCl salt 1-morpholino-2-(2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethanone hydrochloride (47) in quantitative yield, which was used immediately in the next reaction.

^{1}H NMR (400 MHz, DMSO-d_6)δ 9.03 - 9.25 (m, 2 H), 7.09 - 7.17 (m, 1 H), 6.98 - 7.09 (m, 2 H), 3.63 - 3.69 (m, 2 H), 3.38 - 3.55 (m, 8 H), 2.98 - 3.22 (m, 8 H)

MS ES$^+$ 275

1.13.4 Intermediate 48

To a solution of 1-morpholino-2-(2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethanone hydrochloride (assume 34.72 mmol) in DCM (100 mL) was added triethylamine (5.32 mL, 3.86 g, 38.19 mmol) and cyclobutanone (3.9 mL, 3.65 g, 52.08 mmol). The mixture was stirred for 5 min and then sodium triacetoxyborohydride (11.04 g, 52.08 mmol) was added, followed by AcOH (1 mL). The mixture was stirred at RT for 3 h, LCMS indicated complete and the reaction mixture was poured into NaOH (2M, aq., 100 mL). The phases were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic phases washed with brine (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated. Purified by Biotage silica gel column, eluting with 1 – 10% of 2% NH_3 / methanol in DCM. Pure fractions concentrated and product crystallised by

addition of ether to yield 2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-morpholinoethanone (9.21 g, 28.04 mmol, 81%).

^{1}H NMR (400 MHz, DMSO) δ 6.99 - 7.07 (m, 1H), 6.90 - 6.99 (m, 2H), 3.63 (s, 2H), 3.41 - 3.56 (m, 8H), 2.65 - 2.85 (m, 5H), 2.32 (br. s., 4H), 1.92 - 2.08 (m, 2H), 1.69 - 1.85 (m, 2H), 1.49 - 1.67 (m, 2H)

MS ES$^+$ 329.

1.13.5 Intermediate 49

A mixture of 2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-morpholinoethanone (5.16 g, 15.72 mmol) and KOH (4M, aq., 19.7 mL, 78.60 mmol) in ethanol (100 mL) was heated at reflux for 6 h, cooled to RT and allowed to stir over the weekend and then heated at reflux for a further 7 h. The reaction mixture was concentrated and used directly in the esterification reaction.

To a solution of potassium 2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)acetate (**49**) (assume 17.24 mmol) in ethanol (200 mL) was added H_2SO_4 (conc., 30 mL). The mixture was heated at reflux and ethanol / water distilled off. Further ethanol was added as necessary, as well as further H_2SO_4 (10 mL). When complete by LCMS, the reaction mixture was poured onto ice and DCM (100 mL) was added. Solid Na_2CO_3 was added to neutralise the acid and raise the pH to ~10. The solid was filtered off, washed with DCM (200 mL) and the filtrate phases were separated. The aqueous phase was extracted with DCM (3 x 100 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by Biotage silica gel column, eluting with 0 – 10% of 2% NH_3 / MeOH in DCM afforded the ethyl 2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)acetate as a yellow oil (4.28 g, 14.89 mmol, 86% (2 steps)).

^{1}H NMR (400 MHz, MeOD) δ 6.95 - 7.14 (m, 3H), 4.07 - 4.24 (m, 2H), 3.57 (s, 2H), 2.80 - 3.01 (m, 5H), 2.50 (br. s., 4H), 2.06 - 2.22 (m, 2H), 1.89 - 2.03 (m, 2H), 1.61 - 1.82 (m, 2H), 1.17 - 1.33 (m, 3H)

MS ES$^+$ 288.

1.13.6 Compound 52 / (Example 221)

Ethyl 2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)acetate (1.4 g, 4.87 mmol) was hydrolysed with lithium hydroxide (0.117 g, 4.87 mmol) in THF water 5:1 at reflux for 16 hours. The reaction mixture was evaporated and azeotroped with toluene (x3) to yield crude acid. This was then converted to the acid chloride by heating to reflux with excess thionyl chloride. The solvents were removed and the residue was azeotroped with toluene (x3) to yield 2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)acetyl chloride (**51**) which was used unpurified in the next step.

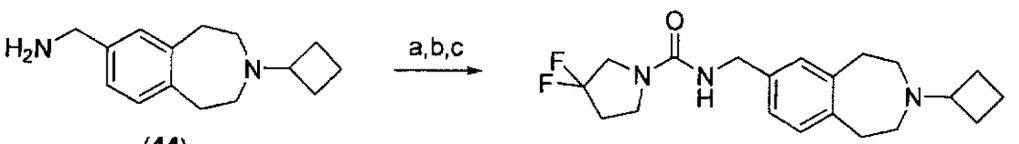
2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)acetyl chloride (**51**) (0.895g, 3.2mmol) was dissolved in pyridine (3 mL) and 1-methyl-1Hpyrazol-5-ylamine was added and stirred together for 65 hours. The solvent was removed by evaporation and the residue was partitioned between ethyl acetate and 2M NaOH. The organic extract was dried and evaporated and the residue was purified by silica chromatography using 0-10% Methanol DCM with ammonia to yield 2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-N-(1-methyl-1H-pyrazol-5-yl)acetamide (0.45g, 41%)

^{1}H NMR (400 MHz, MeOD) δ 7.33 - 7.44 (m, 1H), 7.07 - 7.19 (m, 3H), 6.18 - 6.26 (m, 1H), 3.60 - 3.74 (m, 5H), 2.82 - 3.01 (m, 5H), 2.52 (br. s., 4H), 2.07 - 2.21 (m, 2H), 1.87 - 2.04 (m, 2H), 1.59 - 1.83 (m, 2H)

MS ES$^+$ 339

1.14 Scheme 14

This scheme is suitable for preparing example compounds 255, 265, 277, 279, 283 and 286



(**44**) **56** / Example 286

a) DBU, DCM; b) Bis(trichloromethyl) carbonate ; c) difluoropyrrolidine hydrochloride

1.14.1 *Compound 56 / (Example 286)*

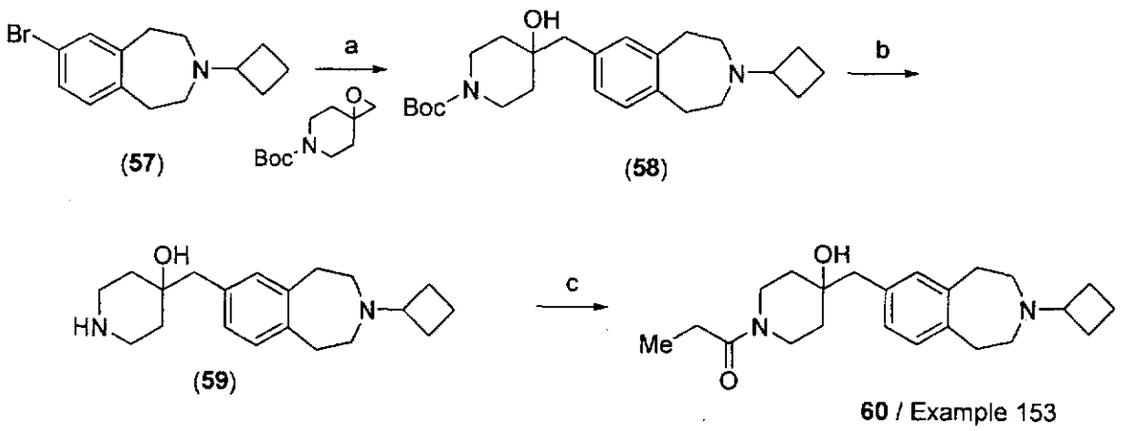
Bis(trichloromethyl) carbonate (587 mg, 1.978 mmol) was dissolved in 20 ml dichloromethane and the solution was cooled in an ice-bath. (3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methanamine dihydrochloride (500 mg, 1.649 mmol) was suspended in 20 ml DCM and DBU (1g, 6.6mmol) was added to give a colourless solution which was added drop-wise to the bis(trichloromethyl) carbonate solution . After 10 minutes 3,3-difluoropyrrolidine hydrochloride (473 mg, 3.30 mmol) was added and the solution was warmed to room temperature and stirred for one hour and then heated to reflux for 30 minutes. The reaction mixture was washed with saturated sodium carbonate solution and the organic extract was dried and evaporated. The residue was purified by silica chromatography eluting with 0-12% methanol / dichloromethane with ammonia to give a colourless oil which was converted into the hydrochloride salt by dissolving in ethanol and adding 2M hydrogen chloride in ether. The product was crystallised using *tert*-butylmethylether and ethanol to give N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3,3-difluoropyrrolidine-1-carboxamide Hydrochloride as a white solid white.

^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.07 (s, 3H), 4.21 (s, 2H), 3.42 - 3.67 (m, 7H), 3.06 - 3.17 (m, 2H), 2.90 - 3.04 (m, 2H), 2.61 - 2.76 (m, 2H), 2.12 - 2.39 (m, 6H), 1.60 - 1.91 (m, 2H)

ES+ 364

1.15 Scheme 15

This scheme is suitable for preparing example compounds 153, 155, 231 and 235



a) *n*-BuLi, THF, –78 °C, 1.5 h, 2. BF_3-OEt_2, –78 °C, 15 min, 3. epoxide, –78 °C to rt; b) TMSOTf, CH_2Cl_2, 0 °C, 1 h; c) EtCOCl, Et_3N, THF, 0 °C, 15 min.

1.15.1 Intermediate 57

Acetic acid (2 mL) was added to a solution of 7-bromo-2,3,4,5-tetrahydro-1H-benzo[d]azepine (3.73 g, 16.50 mmol) and cyclobutanone (6.16 mL, 82 mmol) in dichloromethane (38 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. Sodium triacetoxyborohydride (10.49 g, 49.5 mmol) was added at 0 °C and the reaction mixture was slowly allowed to warm to 20°C and stirred for 16 hours. To the reaction mixture was added 2N NaOH (aq.) (200 mL) and the mixture stirred for 20 minutes. The product was extracted with dichloromethane (3 x 150 mL), and the solvent removed under reduced pressure. The residue was purified by a strong cation exchange cartridge (50g), loading with dichloromethane, and washing with methanol and eluting with 2M ammonia in methanol. The eluted solvent was removed under reduced pressure to give 7-bromo-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (4.47 g, > 90%) as a white solid.

MS ES^+ 280, 282

^1H NMR (400 MHz, DMSO-d_6) δ 7.29 - 7.35 (m, 1H), 7.23 - 7.29 (m, 1H), 7.03 - 7.09 (m, 1H), 2.69 - 2.85 (m, 5H), 2.32 (br. s., 4H), 1.93 - 2.05 (m, 2H), 1.68 - 1.82 (m, 2H), 1.47 - 1.65 (m, 2H)

1.15.2 Intermediate 58

A solution of *n*-butyllithium in n-hexane (1.6 M, 3.35 mL) was added to a solution of 7-bromo-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (1.5g) in tetrahydrofuran (20 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1.5 hours. Boron trifluoride etherate (0.68 mL) was added at -78 °C. The resulting mixture was stirred at -78 °C for 15 minutes. A solution of *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (1.14 g) in tetrahydrofuran (10 mL) was added at -78 °C. The mixture was stirred at -78 °C for 2 hours and then warmed to room temperature for 16 hours. Saturated ammonium chloride aqueous solution (5.0 mL) was added at 0°C. The reaction mixture was partitioned between ethyl acetate and 2N NaOH (aq.). The organic

layer was washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified on basic silica eluting with 15-50% ethyl acetate in petrol) to give *tert*-butyl 4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-4-hydroxypiperidine-1-carboxylate (1.11 g, 50%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.39 - 1.49 (m, 13 H) 1.58 - 1.76 (m, 2 H) 1.81 - 1.94 (m, 2 H) 2.04 - 2.16 (m, 2 H) 2.34 - 2.52 (m, 4 H) 2.67 - 2.73 (m, 2 H) 2.75 - 2.95 (m, 5 H) 3.01 - 3.28 (m, 2 H) 3.65 - 3.82 (m, 2 H) 4.41 (s, 1 H) 6.96 - 7.13 (m, 3 H)

1.15.3 Intermediate 59

Trimethylsilyl trifluoromethane sulfonate (0.286 mL) was added to a solution of *tert*-butyl 4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-4-hydroxypiperidine-1-carboxylate (328 mg) in dichloromethane (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. The reaction mixture was partitioned between dichloromethane and 2N NaOH (aq.). The organic layer was washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)piperidin-4-ol (231 mg, 93%) as pale yellow foam.

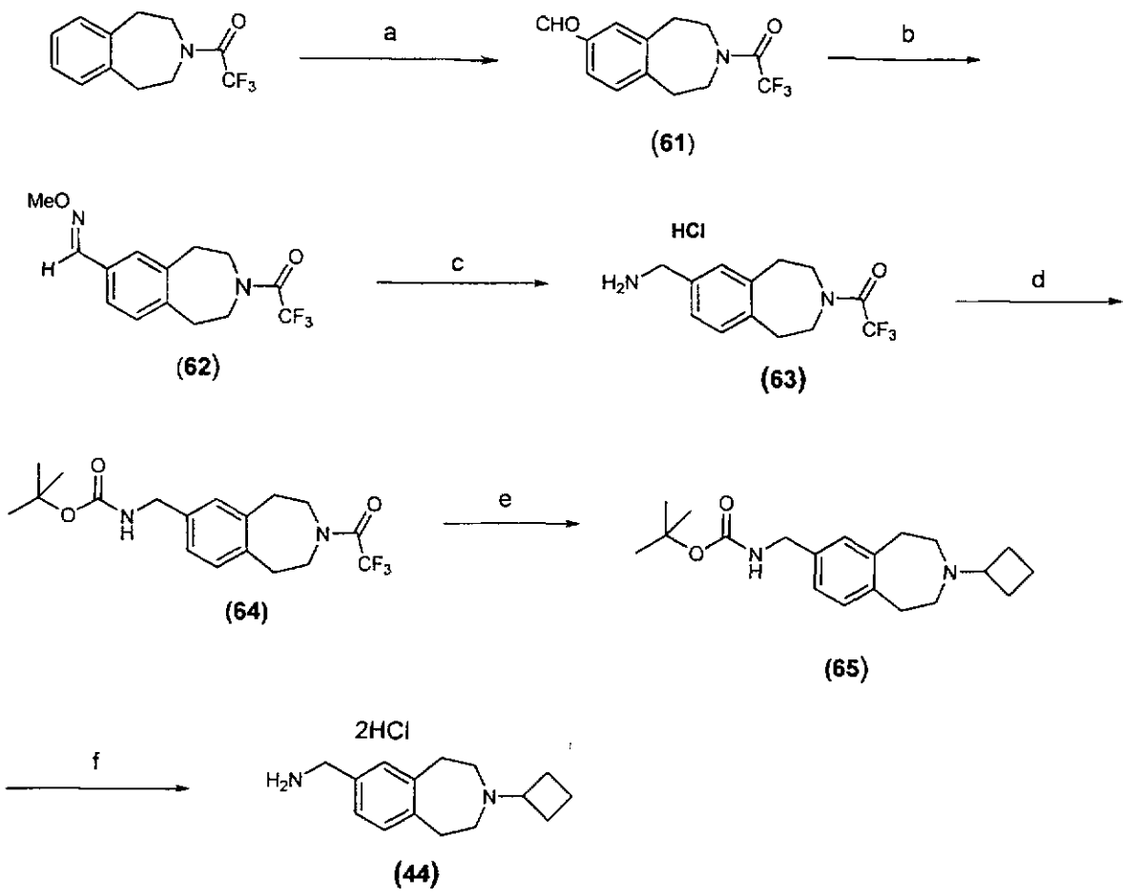
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.11 - 1.38 (m, 4 H) 1.41 - 1.61 (m, 2 H) 1.64 - 1.79 (m, 2 H) 1.88 - 2.00 (m, 2 H) 2.20 - 2.35 (m, 4 H) 2.47 - 2.78 (m, 12 H) 3.93 (s, 1 H) 6.79 - 6.96 (m, 3 H)

1.15.4 Compound 60 / Example 153

Propionyl chloride (70 μL) was added to a solution of 4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)piperidin-4-ol (230 mg) and triethylamine (150 μL) in THF (7.5 mL) at 0 °C. The mixture was stirred at 0 °C for 15 minutes. The reaction mixture was partitioned between ethyl acetate and 2N NaOH (aq.). The organic layer was washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified with basic silica, eluting with 25-100% ethyl acetate in petrol) and by recrystallisation from ethyl acetate to give 1-(4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-4-hydroxypiperidin-1-yl)propan-1-one (207 mg, 76%) as white crystals.

1.16 Scheme 16

This scheme is suitable for preparing intermediate 44.



a) Cl_2CHOMe, $AlCl_3$ / $PhNO_2$, b) $MeONH_2$ HCl, Na_2CO_3 c) H_2, Pd/C HCl d)$(Boc)_2O$,Et_3N

e) 1) NaOH 2) cyclobutanone, AcOH, $NaBH(OAc)_3$ f) 2M HCl in EtOH

1.16.1 Intermediate 61

To a mixture of compound 3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (24.3 g, 0.10 mol) and $PhNO_2$ (24 mL), was added $AlCl_3$ (26.7 g, 0.20 mol) at 5°C (internal temperature) in one portion and stirred for 15min. To the resulting mixture, was added a solution of Cl_2CHOCH_3 (34.5 g, 0.30 mol) in $PhNO_2$ (24 mL) dropwise at 5 °C over 50min and the mixture was stirred at r.t. for 8 hr. The reaction mixture was diluted with AcOEt (100 mL) and poured onto ice (150 g) carefully. The mixture was extracted with AcOEt (100 mL x 2) and was washed with water (50 mL x 2). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on SiO_2 (350 g) (AcOEt/hexane =1/20 to 3/7) to give crude solid (25.0 g). The obtained solid was dissolved in IPE (30 mL) and hexane (90 mL) was added dropwise to the solution with stirring at 50 °C. The mixture was cooled to r.t. and was stirred for 30 min. The deposited precipitate was filtered and was washed (AcOEt/hexane =1/5, 50 mL) to give 3-(Trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-carbaldehyde as pale yellow powder (20.3 g, 74.8%).

^{1}H-NMR (300MHz, $CDCl_3$) δ: 3.05–3.10 (4H, m), 3.72–3.82 (4H, m), 7.31–7.72 (2H, m), 9.981 (1H, s). MS (POS/ESI), m/z 272.00 $(M+1)^+$.

1.16.2 Intermediate 62

To a solution of Na_2CO_3 (6.36 g, 0.060 mol) in water (140 mL), was added $MeONH_2$ HCl (10.0 g, 0.120 mol) portionwise at 5 °C (internal temperature) and stirred for 30 min.To the mixture, was added a solution of 3-(Trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-carbaldehyde 1 (27.1 g, 0.100 mol) in THF (140 mL) dropwise at 5 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with AcOEt (280 mL) and undissolved material was filtered. The separated aqueous layer was extracted with AcOEt (140 mL) and organic layers were combined and washed with brine (140 mL), and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford yellow oil (31 g) which was dissolved in IPE (62 mL) and then hexane (124 m) was added dropwise with stirring. The precipitate appeared was collected by filtration and washed with IPE-hexane (1:2, 50 mL), and then was dried under reduced pressure to afford 3-(Trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-carbaldehyde O-methyloxime as pale yellow powder (23.0 g, 76.6%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.97–3.02 (4H, m), 3.68–3.71 (2H, m), 3.76–3.78 (2H, m), 3.97 (3H, s), 7.13–7.18 (1H, m), 7.33–7.36 (1H, m), 7.41–7.44 (1H, m), 8.03 (1H, s). MS (POS/ESI), m/z 300.98 M^+.

1.16.3 Intermediate 63

To a solution of 3-(Trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-carbaldehyde O-methyloxime 2 (21.0 g, 0.070 mol) in MeOH (420 mL) and aqueous 12 N HCl (5.3 mL, 175 mmol), was added 10% Pd/C (wet 50%, 2.1 g) and the mixture was hydrogenated under an atmospheric pressure at room temperature for 1 hr. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting solid was treated with IPE (200 mL) and was collected by filtration, and then was dried under reduced pressure to afford 1-[3-(Trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]methanamine hydrochloride (20.1 g, 92.8%) as white solid.

^{1}H-NMR (400MHz, DMSO-d_6) δ: 2.96–3.02 (4H, m), 3.66–3.71 (4H, m), 3.96 (2H, s), 7.21–7.30 (3H, m), 8.33 (3H, brs).

1.16.4 Intermediate 64

To a solution of 1-[3-(Trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]methanamine hydrochloride (18.5 g, 60 mmol) in THF (90 mL) and water (82 mL), was added (Boc)2O (13.1 g, 60 mmol) in one portion at 5°C (internal temperature), and then aqueous 8N NaOH (7.5 mL, 60 mL) solution dropwise at the same temperature. The mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with AcOEt (90 mL x 2) and combined organic layers were washed with brine (90 mL), and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give light brown syrup, which was treated with hexane (70 mL) to afford white precipitate. The obtained precipitate was collected by filtration and washed with hexane (20 mL), and then was dried under reduced pressure to give *tert*-Butyl {[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]methyl}carbamate (21.0 g, 94%) as white powder.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.46 (9H, s), 2.94–2.99 (4H, m), 3.67–3.69 (2H, m), 3.74

3.78 (2H, m), 4.27–4.29 (2H, m), 4.83 (1H, brs), 7.06–7.14 (3H, m).

1.16.5 Intermediate 65

To a solution of *tert*-Butyl {[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]methyl}carbamate (16.8 g, 45.0 mmol) in MeOH (170 mL), was added aqueous 8N NaOH solution (6.2 mL, 49.5 mmol) at 5°C (internal temperature) and the mixture was stirred at room temperature for 1 h. To the resulting mixture, were added AcOH (3.9 mL, 67.5 mmol), cyclobutanone (4.7 g, 67.5 mmol), and $NaBH(OAc)_3$ (14.3 g, 67.5 mmol) at 5°C and the mixture was stirred at room temperature for 3 h. To the mixture, were added cyclobutanone (4.7 g, 67.5 mmol) and $NaBH(OAc)_3$ (14.3 g, 67.5 mmol) again and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was treated with water (150 mL). The aqueous mixture was made basic (pH = 9) with aqueous NaOH solution under cooling and was extracted with AcOEt (150 mL x 2). The combined organic layers were washed with brine (150 mL) and dried over $MgSO_4$. The solution was subjected to short silica-gel pad (40 g) and the solvent was evaporated under reduced pressure. The obtained solid was treated with hexane-IPE (1:1, 100 mL) and was collected by filtration. The solid was washed with hexane (10 mL) and was dried under reduced pressure to afford *tert*-Butyl [(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]carbamate .(12.4 g, 83.3 %) as white solid.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.55–1.75 (2H, m), 1.85–1.97 (2H, m), 2.03–2.12 (2H, m), 2.35–2.50 (4H, m), 2.72–2.81 (1H, m), 2.87–2.94 (4H, m), 4.25–4.27 (2H, m), 4.78 (1H, brs), 7.01–7.07 (3H, m). MS (POS/ESI), m/z 331.22 $(M+1)^+$.

Deprotection of the benzazepine nitrogen of intermediate 64 (step (e)(1) of Scheme 17) leads to *tert*-butyl (2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methylcarbamate. ^{1}H-NMR (400MHz, CDCl3) δ 1.55–1.75 (2H, m), 1.85–1.97 (2H, m), 2.03–2.12 (2H, m), 2.35–2.50 (4H, m), 2.72–2.81 (1H, m), 2.87–2.94 (4H, m), 4.25–4.27 (2H, m), 4.78 (1H, brs), 7.01–7.07 (3H, m).

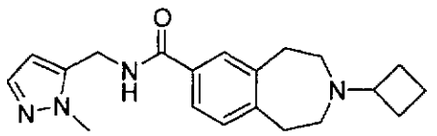
1.16.6 Intermediate 44

A mixture of *tert*-Butyl [(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]carbamate (11.6 g, 35.0 mmol) and 2M ethanolic HCl solution (87.5 mL, 175 mmol) was warmed at 50 °C for 30 min. The reaction mixture was cooled in an iced water bath and treated with IPE (100 mL). The deposited precipitate was collected by filtration and was washed with IPE (20 mL), and then was dried under reduced pressure to afford 1-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methanamine dihydrochloride (9.5 g, 90.0%) as white powder.

^{1}H-NMR (400MHz, DMSO-d_6) δ: 1.58–1.74 (2H, m), 2.15–2.17 (2H, m), 2.49–2.54 (2H, m), 2.68–2.71 (2H, m), 2.94–3.00 (2H, m), 3.50–3.52 (4H, m), 3.64–3.66 (1H, m), 7.23–7.26 (1H, m), 7.33–7.34 (2H, m), 8.56 (3H, brs), 11.94 (1H, brs). MS (POS/ESI), m/z 231.15 $(M+1)^+$.

2. Example Compounds

2.1 Example 1

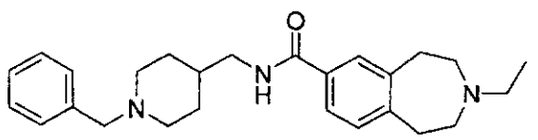


3-Cyclobutyl-N-((1-methyl-1H-pyrazol-5-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.79 - 8.96 (m, 1H), 7.56 - 7.68 (m, 2H), 7.27 - 7.34 (m, 1H), 7.15 - 7.25 (m, 1H), 6.11 - 6.20 (m, 1H), 4.43 - 4.55 (m, 2H), 3.35 (s, 3H), 2.81 - 2.96 (m, 4H), 2.69 - 2.80 (m, 1H), 2.34 (br. s., 4H), 1.91 - 2.08 (m, 2H), 1.70 - 1.85 (m, 2H), 1.47 - 1.67 (m, 2H)

Mass Spec: ES^+ 339

2.2 Example 2

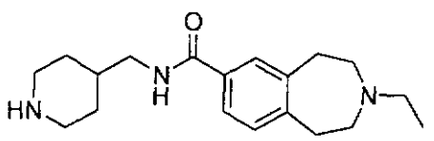


N-((1-Benzylpiperidin-4-yl)methyl)-3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.53 (m, 2H), 7.17 - 7.35 (m, 6H), 7.03 - 7.17 (m, 1H), 6.13 (t, J = 5.43 Hz, 1H), 3.46 (s, 2H), 3.31 (t, J = 6.32 Hz, 2H), 2.79 - 3.03 (m, 5H), 2.47 - 2.73 (m, 5H), 1.85 - 2.01 (m, 2H), 1.51 - 1.76 (m, 3H), 1.16 - 1.42 (m, 3H), 1.01 - 1.11 (m, 3H)

Mass Spec: ES^+ 406

2.3 Example 3

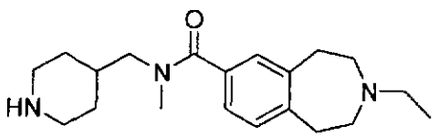


3-Ethyl-N-(piperidin-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide Hydrochloride

^{1}H NMR (400 MHz, MeOD) δ 7.69 - 7.78 (m, 2H), 7.33 - 7.41 (m, 1H), 3.76 - 3.86 (m, 2H), 3.27 - 3.49 (m, 9H), 3.14 - 3.26 (m, 2H), 2.94 - 3.13 (m, 4H), 1.93 - 2.09 (m, 3H), 1.38 - 1.59 (m, 5H)

Mass Spec: ES^+ 316

2.4 Example 4

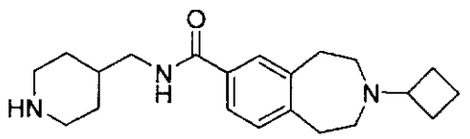


3-Ethyl-N-methyl-N-(piperidin-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.08 - 7.28 (m, 3H), 3.43 - 3.53 (m, 1H), 3.23 - 3.31 (m, 1H), 3.11 - 3.22 (m, 1H), 3.08 (br. s., 1H), 3.01 (br. s., 4H), 2.49 - 2.76 (m, 8H), 1.95 - 2.09 (m, 1H), 1.74 - 1.91 (m, 3H), 1.53 - 1.62 (m, 1H), 1.25 - 1.42 (m, 2H), 1.10 - 1.19 (m, 3H), 0.82 - 0.97 (m, 1H)

Mass Spec: ES$^+$ 330

2.5 Example 5

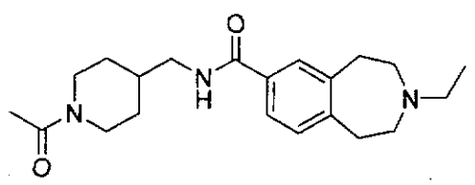


3-Cyclobutyl-N-(piperidin-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, D_2O) δ 7.43 - 7.60 (m, 2H), 7.19 - 7.34 (m, 1H), 3.37 - 3.46 (m, 1H), 3.24 - 3.37 (m, 4H), 3.06 - 3.21 (m, 1H), 2.88 - 3.06 (m, 7H), 2.73 (br. s., 4H), 2.08 - 2.22 (m, 1H), 1.87 - 2.07 (m, 5H), 1.56 - 1.80 (m, 2H), 1.35 - 1.53 (m, 2H)

Mass Spec: ES$^+$ 342

2.6 Example 6

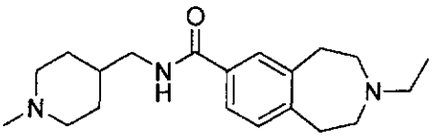


N-((1-Acetylpiperidin-4-yl)methyl)-3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.41 - 7.67 (m, 2H), 7.00 - 7.34 (m, 1H), 4.34 - 4.66 (m, 1H), 3.82 - 4.04 (m, 1H), 2.92 - 3.18 (m, 7H), 2.48 - 2.84 (m, 8H), 2.09 (s, 3H), 1.67 - 2.00 (m, 3H), 1.01 - 1.37 (m, 5H)

Mass Spec: ES$^+$ 358

2.7 Example 7

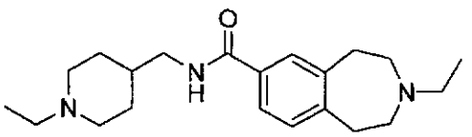


3-Ethyl-N-((1-methylpiperidin-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

1H NMR (400 MHz, MeOD) δ 7.52 - 7.62 (m, 2H), 7.14 - 7.28 (m, 1H), 3.24 - 3.28 (m, 1H), 2.94 - 3.10 (m, 4H), 2.79 - 2.94 (m, 2H), 2.46 - 2.79 (m, 6H), 2.17 - 2.37 (m, 3H), 1.92 - 2.14 (m, 2H), 1.51 - 1.89 (m, 4H), 1.23 - 1.44 (m, 2H), 1.01 - 1.22 (m, 3H)

Mass Spec: ES^+ 330

2.8 Example 8

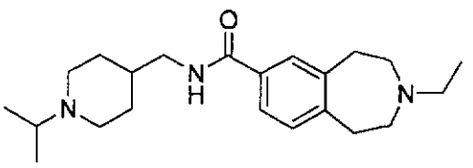


3-Ethyl-N-((1-ethylpiperidin-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ7.52 - 7.62 (m, 2H), 7.15 - 7.24 (m, 1H), 3.25 - 3.29 (m, 2H), 2.90 - 3.10 (m, 6H), 2.53 - 2.82 (m, 6H), 2.38-2.45, 2H), 1.87 - 2.08 (m, 2H), 1.59 - 1.85 (m, 3H), 1.23 - 1.45 (m, 2H), 0.99 - 1.23 (m, 6H)

Mass Spec: ES^+ 344

2.9 Example 9

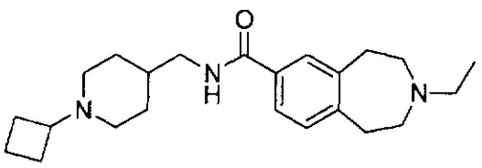


3-Ethyl-N-((1-isopropylpiperidin-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.51 - 7.63 (m, 2H), 7.16 - 7.25 (m, 1H), 3.26 (d, J = 6.57 Hz, 2H), 2.84 - 3.12 (m, 6H), 2.48 - 2.80 (m, 7H), 2.07 - 2.30 (m, 2H), 1.56 - 1.87 (m, 3H), 1.22 - 1.45 (m, 2H), 0.97 - 1.21 (m, 9H)

Mass Spec: ES^+ 358

2.10 Example 10

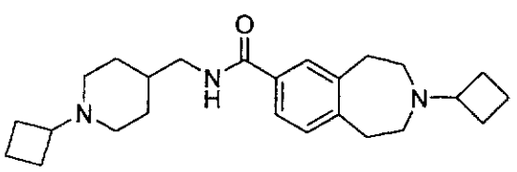


N-((1-Cyclobutylpiperidin-4-yl)methyl)-3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.51 - 7.63 (m, 2H), 7.16 - 7.24 (m, 1H), 3.24 - 3.29 (m, 2H), 2.88 - 3.10 (m, 6H), 2.51 - 2.88 (m, 7H), 1.99 - 2.16 (m, 2H), 1.59 - 2.00 (m, 9H), 1.22 - 1.45 (m, 2H), 1.05 - 1.21 (m, 3H)

Mass Spec: ES$^+$ 370

2.11 Example 11

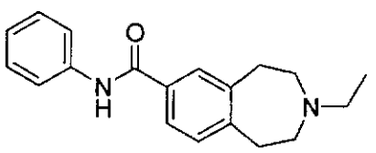


3-Cyclobutyl-N-((1-cyclobutylpiperidin-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.45 - 7.68 (m, 2H), 7.14 - 7.28 (m, 1H), 3.25 - 3.29 (m, 2H), 2.98 (br. s., 6H), 2.78 - 2.93 (m, 2H), 2.51 (br. s., 4H), 2.03 - 2.19 (m, 4H), 1.86 - 2.03 (m, 6H), 1.61 - 1.86 (m, 7H), 1.25 - 1.46 (m, 2H)

Mass Spec: ES$^+$ 396

2.12 Example 12

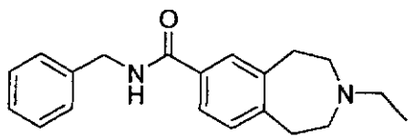


3-Ethyl-N-phenyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 7.76 (d, J = 7.83 Hz, 2H), 7.65 - 7.73 (m, 2H), 7.29 - 7.41 (m, 2H), 7.21 - 7.29 (m, 1H), 7.00 - 7.17 (m, 1H), 2.83 - 3.02 (m, 4H), 2.41 - 2.67 (m, 8H), 0.95 - 1.08 (m, 3H)

Mass Spec: ES$^+$ 295

2.13 Example 13

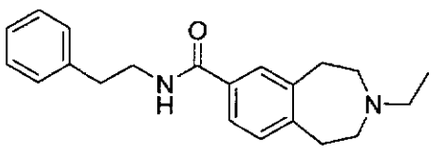


N-Benzyl-3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.53 - 7.69 (m, 2H), 7.15 - 7.44 (m, 6H), 4.49 - 4.65 (m, 2H), 2.90 - 3.08 (m, 4H), 2.47 - 2.79 (m, 6H), 1.04 - 1.20 (m, 3H)

Mass Spec: ES^+ 309

2.14 Example 14

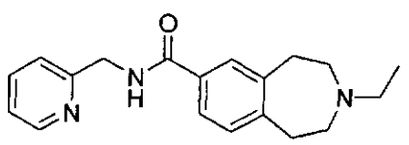


3-Ethyl-N-phenethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.45 - 7.64 (m, 2H), 7.03 - 7.36 (m, 6H), 3.48 - 3.65 (m, 2H), 2.83 - 3.07 (m, 6H), 2.45 - 2.75 (m, 6H), 0.98 - 1.29 (m, 3H)

Mass Spec: ES^+ 323

2.15 Example 15

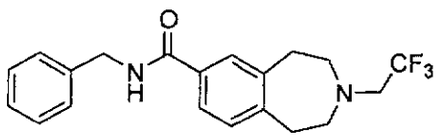


3-Ethyl-N-(pyridin-2-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 8.49 (d, 1H), 7.76 - 7.85 (m, 1H), 7.63 - 7.69 (m, 2H), 7.39-7.42, 1H), 7.27 - 7.35 (m, 1H), 7.19 - 7.27 (m, 1H), 4.68 (s, 2H), 2.92 - 3.13 (m, 4H), 2.45 - 2.81 (m, 6H), 1.05 - 1.22 (m, 3H)

Mass Spec: ES^+ 310

2.16 Example 16

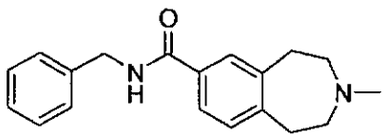


N-Benzyl-3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

1H NMR (400 MHz, $CDCl_3$) δ 7.49 - 7.65 (m, 2H), 7.24 - 7.46 (m, 5H), 7.10 - 7.20 (m, 1H), 6.48 (br. s., 1H), 4.35 - 4.92 (m, 2H), 3.11 - 3.27 (m, 2H), 2.82 - 3.03 (m, 8H)

Mass Spec: ES^+ 363

2.17 Example 17

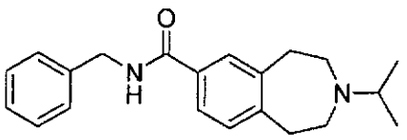


N-Benzyl-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^1H NMR (400 MHz, $CDCl_3$) δ7.49 - 7.66 (m, 2H), 7.24 - 7.45 (m, 5H), 7.01 - 7.21 (m, 1H), 6.51 (br. s., 1H), 4.64 (d, J = 5.56 Hz, 2H), 2.97 (br. s., 4H), 2.47 - 2.70 (m, 4H), 2.36 (s, 3H)

Mass Spec: ES^+ 295

2.18 Example 18

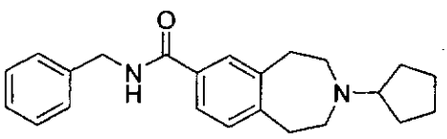


N-Benzyl-3-isopropyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^1H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.60 (m, 2H), 7.28 - 7.41 (m, 5H), 7.12 - 7.18 (m, 1H), 6.37 (br. s., 1H), 4.57 - 4.73 (m, 2H), 2.85 - 3.06 (m, 5H), 2.53 - 2.74 (m, 4H), 0.90 - 1.11 (m, 6H)

Mass Spec: ES^+ 323

2.19 Example 19

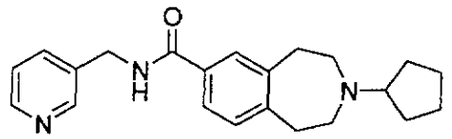


N-Benzyl-3-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 - 7.60 (m, 2H), 7.28 - 7.44 (m, 5H), 7.10 - 7.18 (m, 1H), 6.33 (br. s., 1H), 4.49 - 4.80 (m, 2H), 2.91 - 3.04 (m, 4H), 2.79 - 2.91 (m, 1H), 2.62 - 2.77 (m, 4H), 1.80 - 1.93 (m, 2H), 1.61 - 1.76 (m, 2H), 1.39 - 1.62 (m, 4H)

Mass Spec: ES^+ 349

2.20 Example 20

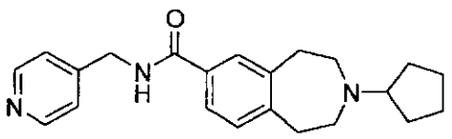


3-Cyclopentyl-N-(pyridin-3-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 8.52 - 8.58 (m, 1H), 8.41 - 8.49 (m, 1H), 7.82 - 7.89 (m, 1H), 7.67 - 7.76 (m, 2H), 7.38 - 7.46 (m, 1H), 7.29 - 7.36 (m, 1H), 4.60 (s, 2H), 3.57 (br. s., 1H), 3.15 - 3.27 (m, 8H), 2.08 - 2.22 (m, 2H), 1.61 - 1.90 (m, 6H)

Mass Spec: ES^+ 350

2.21 Example 21

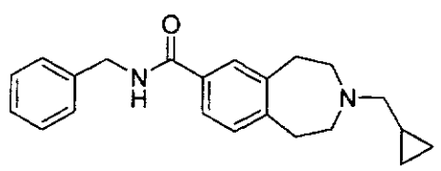


3-Cyclopentyl-N-(pyridin-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 - 8.96 (m, 1H), 8.44 - 8.56 (m, 2H), 7.57 - 7.70 (m, 2H), 7.24 - 7.35 (m, 2H), 7.15 - 7.24 (m, 1H), 4.39 - 4.55 (m, 2H), 2.90 (br. s., 4H), 2.64 (br. s., 4H), 1.69 - 1.88 (m, 2H), 1.28 - 1.69 (m, 6H)

Mass Spec: ES^+ 315

2.22 Example 22

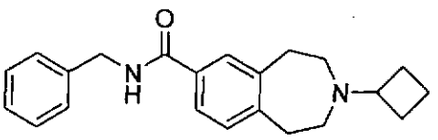


N-Benzyl-3-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.44 - 7.57 (m, 2H), 7.19 - 7.32 (m, 3H), 7.18 (s, 1H), 7.04 - 7.13 (m, 1H), 6.37 - 6.53 (m, 1H), 4.47 - 4.63 (m, 2H), 2.98 - 3.30 (m, 8H), 2.63 - 2.85 (m, 2H), 0.85 - 1.10 (m, 1H), 0.55 - 0.66 (m, 2H), 0.12 - 0.30 (m, 2H)

Mass Spec: ES^+ 335

2.23 Example 23

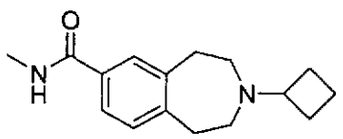


N-Benzyl-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.60 - 7.65 (m, 2H), 7.29 - 7.38 (m, 4H), 7.17 - 7.28 (m, 2H), 4.46 - 4.67 (m, 2H), 2.90 - 3.10 (m, 4H), 2.75 - 2.91 (m, 1H), 2.49 (br. s., 4H), 2.02 - 2.21 (m, 2H), 1.85 - 2.03 (m, 2H), 1.58 - 1.82 (m, 2H)

Mass Spec: ES^+ 335

2.24 Example 24

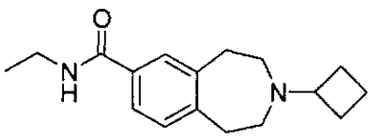


3-Cyclobutyl-N-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.54 - 7.59 (m, 2H), 7.17 - 7.22 (m, 1H), 2.94 - 3.04 (m, 4H), 2.91 (s, 3H), 2.80 - 2.88 (m, 1H), 2.49 (br. s., 4H), 2.06 - 2.16 (m, 2H), 1.88 - 2.01 (m, 2H), 1.62 - 1.79 (m, 2H)

Mass Spec: ES^+ 259

2.25 Example 25

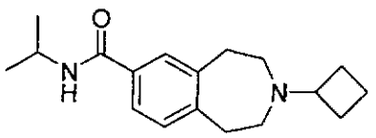


3-Cyclobutyl-N-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.58 (m, 2H), 7.09 - 7.27 (m, 1H), 3.36 - 3.49 (m, 2H), 2.93 - 3.08 (m, 4H), 2.74 - 2.92 (m, 1H), 2.50 (br. s., 4H), 2.02 - 2.22 (m, 2H), 1.83 - 2.05 (m, 2H), 1.60 - 1.82 (m, 2H), 1.12 - 1.36 (m, 3H)

Mass Spec: ES$^+$ 273

2.26 Example 26

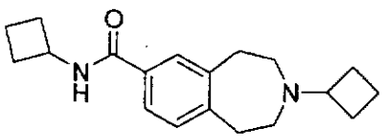


3-Cyclobutyl-N-isopropyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, 2H), 7.07 - 7.29 (m, 1H), 4.07 - 4.29 (m, 1H), 2.99 (br. s., 4H), 2.78 - 2.91 (m, 1H), 2.49 (br. s., 4H), 2.03 - 2.21 (m, 2H), 1.86 - 2.03 (m, 2H), 1.56 - 1.82 (m, 2H), 1.15 - 1.36 (m, 6H)

Mass Spec: ES$^+$ 287

2.27 Example 27

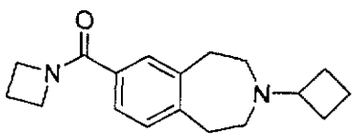


N,3-Dicyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.46 - 7.68 (m, 2H), 7.09 - 7.29 (m, 1H), 4.40 - 4.60 (m, 1H), 2.91 - 3.06 (m, 4H), 2.77 - 2.91 (m, 1H), 2.39 - 2.61 (m, 4H), 2.28 - 2.38 (m, 2H), 2.03 - 2.19 (m, 4H), 1.86 - 2.02 (m, 2H), 1.60 - 1.84 (m, 4H)

Mass Spec: ES$^+$ 299

2.28 Example 28

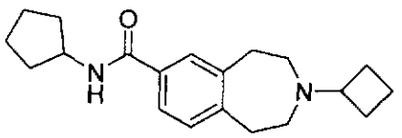


Azetidin-1-yl(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methanone

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 - 7.41 (m, 2H), 7.12 - 7.22 (m, 1H), 4.18 - 4.37 (m, 2H), 3.93 - 4.13 (m, 2H), 2.81 - 2.94 (m, 4H), 2.68 - 2.82 (m, 1H), 2.34 (br. s., 4H), 2.18 - 2.29 (m, 2H), 2.01 (q, J = 7.8 Hz, 2H), 1.70 - 1.86 (m, 2H), 1.49 - 1.67 (m, 2H)

Mass Spec: ES$^+$ 285

2.29 Example 29

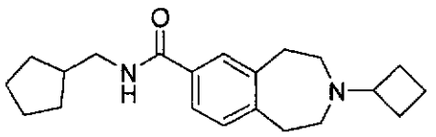


3-Cyclobutyl-N-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.44 - 7.65 (m, 2H), 7.11 - 7.26 (m, 1H), 4.20 - 4.41 (m, 1H), 2.90 - 3.05 (m, 4H), 2.76 - 2.91 (m, 1H), 2.35 - 2.61 (m, 4H), 1.48 - 2.20 (m, 14H)

Mass Spec: ES$^+$ 313

2.30 Example 30

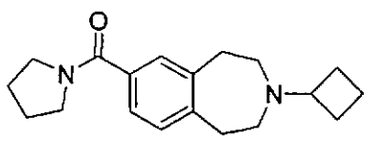


3-Cyclobutyl-N-(cyclopentylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 - 8.48 (m, 1H), 7.47 - 7.71 (m, 2H), 7.07 - 7.30 (m, 1H), 3.11 - 3.22 (m, 2H), 2.68 - 2.98 (m, 4H), 2.22 - 2.45 (m, 4H), 2.07 - 2.21 (m, 1H), 1.95 - 2.07 (m, 2H), 1.72 - 1.89 (m, 2H), 1.42 - 1.71 (m, 9H), 1.17 - 1.31 (m, 2H)

Mass Spec: ES$^+$ 327

2.31 Example 31

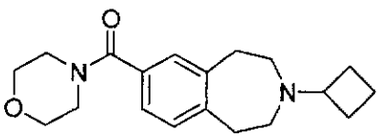


(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)(pyrrolidin-1-yl)methanone

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.04 - 7.42 (m, 3H), 3.39 (br. s., 4H), 2.81 - 3.13 (m, 4H), 2.47-2.52 (br. s.,4H), 2.10 (br. s., 2H), 1.75 - 1.96 (m, 6H), 1.53 - 1.74 (m, 2H)

Mass Spec: ES^+ 299

2.32 Example 32

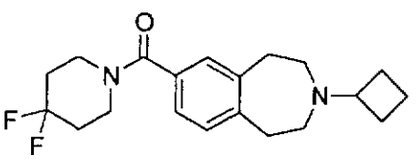


(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)(morpholino)methanone

^1H NMR (400 MHz, MeOD) δ 7.06 - 7.35 (m, 3H), 3.54 - 3.85 (m, 6H), 3.40 - 3.53 (m, 2H), 2.97 - 3.16 (m, 5H), 2.58 - 2.83 (m, 4H), 2.13 - 2.25 (m, 2H), 1.98 - 2.13 (m, 2H), 1.64 - 1.86 (m, 2H)

Mass Spec: ES^+ 315

2.33 Example 33

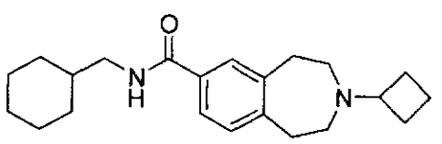


(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)(4,4-difluoropiperidin-1-yl)methanone

1H NMR (400 MHz, DMSO-d6) δ 7.04 - 7.29 (m, 3H), 3.57 (br. s., 4H), 2.88 (br. s., 6H), 2.40 (br. s., 3H), 2.02 (br. s., 6H), 1.71 - 1.92 (m, 2H), 1.50 - 1.68 (m, 2H)

Mass Spec: ES^+ 349

2.34 Example 34

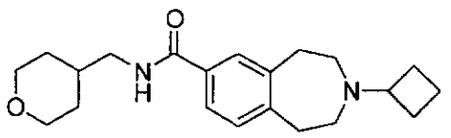


3-Cyclobutyl-N-(cyclohexylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

1H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.62 (m, 3H), 7.17 - 7.23 (m, 1H), 6.24 - 6.35 (m, 1H), 3.72 - 3.84 (m, 2H), 3.53 - 3.65 (m, 2H), 3.27 - 3.41 (m, 3H), 2.92 - 3.06 (m, 2H), 2.58 - 2.73 (m, 2H), 2.42 - 2.57 (m, 2H), 2.22 - 2.35 (m, 2H), 1.88 - 2.00 (m, 1H), 1.65 - 1.84 (m, 6H), 1.54 - 1.65 (m, 1H), 1.12 - 1.33 (m, 2H), 0.94 - 1.08 (m, 2H)

Mass Spec: ES^+ 341

2.35 Example 35

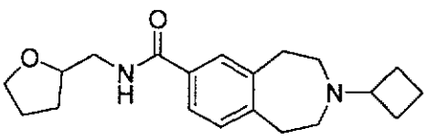


3-Cyclobutyl-N-((tetrahydro-2H-pyran-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.18 - 8.27 (m, 1H), 7.53 - 7.63 (m, 2H), 7.12 - 7.21 (m, 1H), 3.78 - 3.89 (m, 2H), 3.22 - 3.31 (m, 2H), 3.11 - 3.17 (m, 2H), 2.75 - 2.92 (m, 5H), 2.37 (br. s., 4H), 1.95 - 2.06 (m, 2H), 1.72 - 1.86 (m, 3H), 1.51 - 1.68 (m, 4H), 1.10 - 1.28 (m, 2H)

Mass Spec: ES$^+$ 350

2.36 Example 36

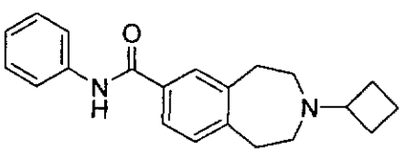


3-cyclobutyl-N-((tetrahydrofuran-2-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.49 - 7.77 (m, 2H), 7.13 - 7.39 (m, 1H), 4.00 - 4.18 (m, 1H), 3.84 - 3.95 (m, 1H), 3.71 - 3.82 (m, 1H), 3.36 - 3.53 (m, 2H), 2.93 - 3.13 (m, 5H), 2.66 (br. s., 4H), 2.11 - 2.26 (m, 2H), 1.84 - 2.11 (m, 5H), 1.59 - 1.84 (m, 3H)

Mass Spec: ES$^+$ 329

2.37 Example 37

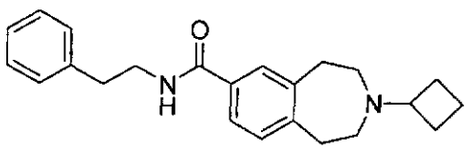


3-Cyclobutyl-N-phenyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 10.13 (s, 1H), 7.74 - 7.81 (m, 2H), 7.68 - 7.73 (m, 2H), 7.31 - 7.38 (m, 2H), 7.23 - 7.29 (m, 1H), 7.06 - 7.13 (m, 1H), 2.86 - 2.98 (m, 4H), 2.72 - 2.83 (m, 1H), 2.38 (br. s., 4H), 1.96 - 2.07 (m, 2H), 1.73 - 1.87 (m, 2H), 1.51 - 1.68 (m, 2H)

Mass Spec: ES$^+$ 321

2.38 Example 38

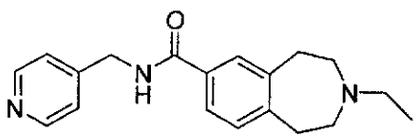


3-Cyclobutyl-N-phenethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.45 - 7.59 (m, 2H), 7.13 - 7.34 (m, 6H), 3.52 - 3.63 (m, 2H), 2.74 - 3.04 (m, 7H), 2.47 (br. s., 4H), 2.03 - 2.17 (m, 2H), 1.85 - 2.02 (m, 2H), 1.60 - 1.81 (m, 2H)

Mass Spec: ES$^+$ 349

2.39 Example 39

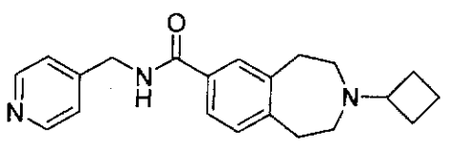


3-Ethyl-N-(pyridin-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 8.44 - 8.51 (m, 2H), 7.62 - 7.70 (m, 2H), 7.36 - 7.44 (m, 2H), 7.20 - 7.29 (m, 1H), 4.62 (s, 2H), 3.03 (br. s., 4H), 2.56 - 2.80 (m, 6H), 1.15 (m, 3H)

Mass Spec: ES$^+$ 310

2.40 Example 40

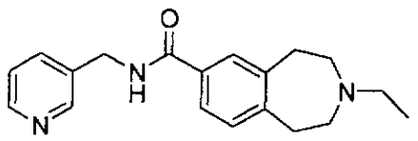


3-Cyclobutyl-N-(pyridin-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 8.40 - 8.50 (m, 2H), 7.58 - 7.69 (m, 2H), 7.34 - 7.45 (m, 2H), 7.17 - 7.30 (m, 1H), 4.61 (s, 2H), 2.99 (br. s., 4H), 2.77 - 2.90 (m, 1H), 2.48 (br. s., 4H), 2.05 - 2.17 (m, 2H), 1.85 - 2.02 (m, 2H), 1.60 - 1.81 (m, 2H)

Mass Spec: ES$^+$ 336

2.41 Example 41

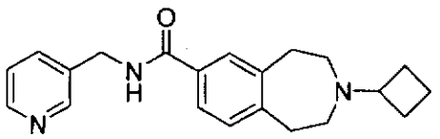


3-Ethyl-N-(pyridin-3-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 8.54 - 8.60 (m, 1H), 8.42 - 8.49 (m, 1H), 7.82 - 7.92 (m, 1H), 7.59 - 7.68 (m, 2H), 7.39 - 7.48 (m, 1H), 7.19 - 7.29 (m, 1H), 4.62 (s, 2H), 2.96 - 3.10 (m, 4H), 2.52 - 2.78 (m, 6H), 1.07 - 1.23 (m, 3H)

Mass Spec: ES^+ 310

2.42 Example 42

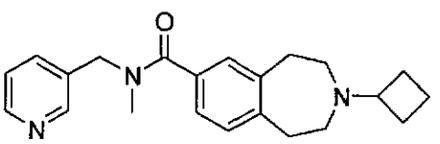


3-Cyclobutyl-N-(pyridin-3-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 8.55 (s, 1H), 8.37 - 8.50 (m, 1H), 7.78 - 7.94 (m, 1H), 7.56 - 7.67 (m, 2H), 7.35 - 7.50 (m, 1H), 7.13 - 7.31 (m, 1H), 4.59 (s, 2H), 2.99 (br. s., 4H), 2.77 - 2.91 (m, 1H), 2.50 (br. s., 4H), 2.05 - 2.18 (m, 2H), 1.85 - 2.03 (m, 2H), 1.60 - 1.81 (m, 2H)

Mass Spec: ES^+ 336

2.43 Example 43

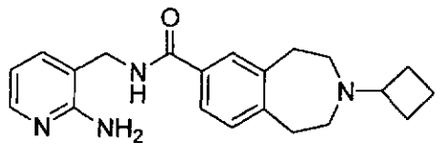


3-cyclobutyl-N-methyl-N-(pyridin-3-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 8.93 (br. s., 1H), 8.78 - 8.86 (m, 1H), 8.62 - 8.72 (m, 1H), 8.05 - 8.18 (m, 1H), 7.29 - 7.47 (m, 3H), 4.94 (br. s., 2H), 3.64 - 3.79 (m, 4H), 3.06 - 3.22 (m, 5H), 2.77 - 2.90 (m, 2H), 2.31 - 2.44 (m, 4H), 1.75 - 1.99 (m, 2H)

Mass Spec: ES^+ 350

2.44 Example 44

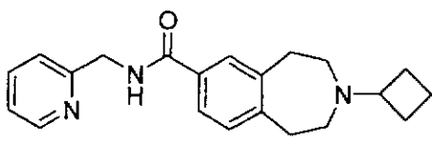


N-((2-Aminopyridin-3-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1H} NMR (400 MHz, MeOD) δ 7.77 - 7.91 (m, 1H), 7.53 - 7.65 (m, 2H), 7.40 - 7.52 (m, 1H), 7.15 - 7.29 (m, 1H), 6.53 - 6.72 (m, 1H), 4.44 (s, 2H), 2.98 (br. s., 4H), 2.77 - 2.92 (m, 1H), 2.50 (br. s., 4H), 2.04 - 2.20 (m, 2H), 1.84 - 2.03 (m, 2H), 1.57 - 1.82 (m, 2H)

Mass Spec: ES^+ 351

2.45 Example 45

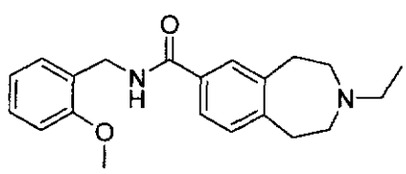


3-Cyclobutyl-N-(pyridin-2-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 8.36 - 8.55 (m, 1H), 7.73 - 7.87 (m, 1H), 7.55 - 7.72 (m, 2H), 7.36 - 7.51 (m, 1H), 7.26 - 7.36 (m, 1H), 7.16 - 7.26 (m, 1H), 4.68 (s, 2H), 2.99 (br. s., 4H), 2.76 - 2.90 (m, 1H), 2.49 (br. s., 4H), 2.05 - 2.18 (m, 2H), 1.86 - 2.00 (m, 2H), 1.59 - 1.82 (m, 2H)

Mass Spec: ES^+ 336

2.46 Example 46

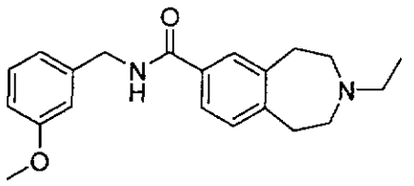


3-Ethyl-N-(2-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.56 - 7.64 (m, 2H), 7.16 - 7.27 (m, 3H), 6.93 - 6.99 (m, 1H), 6.86 - 6.93 (m, 1H), 4.56 (s, 2H), 3.86 (s, 3H), 2.93 - 3.06 (m, 4H), 2.52 - 2.75 (m, 6H), 1.07 - 1.19 (m, 3H)

Mass Spec: ES^+ 339

2.47 Example 47

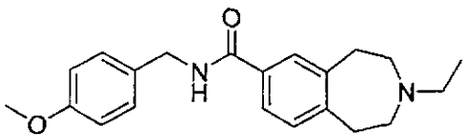


3-Ethyl-N-(3-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.56 - 7.65 (m, 2H), 7.18 - 7.26 (m, 2H), 6.88 - 6.95 (m, 2H), 6.77 - 6.85 (m, 1H), 4.55 (s, 2H), 3.79 (s, 3H), 2.89 - 3.12 (m, 4H), 2.49 - 2.79 (m, 6H), 1.03 - 1.27 (m, 3H)

Mass Spec: ES$^+$ 339

2.48 Example 48

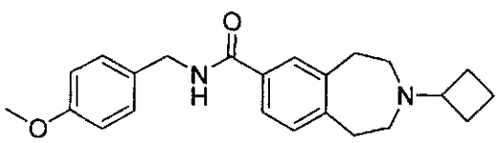


3-Ethyl-N-(4-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.54 - 7.64 (m, 2H), 7.58 (none, 2H), 7.21 - 7.31 (m, 2H), 7.13 - 7.20 (m, 1H), 6.81 - 6.92 (m, 2H), 4.48 (s, 2H), 3.75 (s, 3H), 2.89 - 3.05 (m, 4H), 2.48 - 2.73 (m, 6H), 1.03 - 1.19 (m, 3H)

Mass Spec: ES$^+$ 336

2.49 Example 49

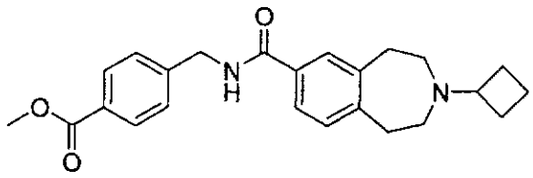


3-Cyclobutyl-N-(4-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 - 7.56 (m, 2H), 7.24 - 7.32 (m, 2H), 7.09 - 7.18 (m, 1H), 6.85 - 6.93 (m, 2H), 6.29 (br. s., 1H), 4.53 - 4.63 (m, 2H), 3.81 (s, 3H), 2.95 (br. s., 4H), 2.78 (t, J = 7.71 Hz, 1H), 2.44 (br. s., 4H), 2.02 - 2.15 (m, 2H), 1.83 - 1.98 (m, 2H), 1.57 - 1.77 (m, 2H)

Mass Spec: ES$^+$ 356

2.50 Example 50

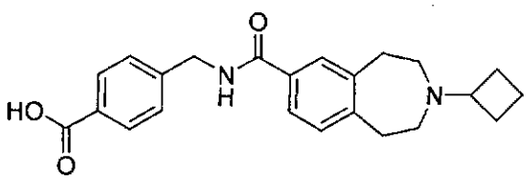


Methyl 4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamido)methyl)benzoate

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 - 8.08 (m, 2H), 7.49 - 7.62 (m, 2H), 7.38 - 7.47 (m, 2H), 7.11 - 7.21 (m, 1H), 6.25 - 6.59 (m, 1H), 4.63 - 4.79 (m, 2H), 3.92 (s, 3H), 2.97 (br. s., 4H), 2.72 - 2.85 (m, 1H), 2.45 (br. s., 4H), 2.01 - 2.16 (m, 2H), 1.82 - 1.97 (m, 2H), 1.55 - 1.78 (m, 2H)

Mass Spec: ES+ 393

2.51 Example 51

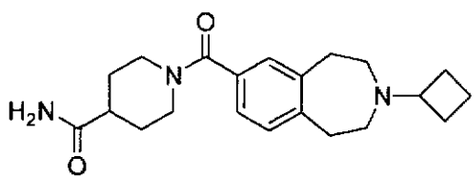


4-((3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamido)methyl)benzoic acid

^{1}H NMR (400 MHz, MeOD) δ 7.89 - 7.96 (m, 2H), 7.65 - 7.71 (m, 2H), 7.32 - 7.39 (m, 2H), 7.23 - 7.31 (m, 1H), 4.60 (s, 2H), 3.11 (br. s., 4H), 2.91 (br. s., 4H), 2.09 - 2.32 (m, 4H), 1.67 - 1.88 (m, 2H)

Mass Spec: ES^+ 379

2.52 Example 52

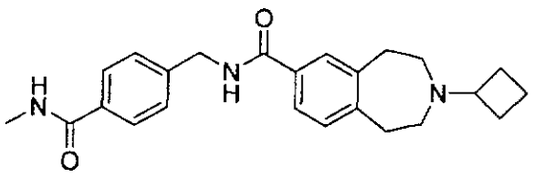


1-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carbonyl)piperidine-4-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.03 - 7.31 (m, 7H), 4.49 - 4.75 (m, 2H), 3.78 (br. s., 2H), 2.77 - 3.03 (m, 5H), 2.34 - 2.62 (m, 4H), 2.04 - 2.19 (m, 2H), 1.84 - 2.02 (m, 2H), 1.57 - 1.82 (m, 2H)

Mass Spec: ES^+ 356

2.53 Example 53

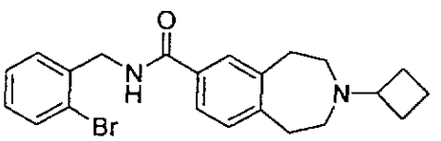


3-Cyclobutyl-N-(4-(methylcarbamoyl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.85 - 9.13 (m, 1H), 8.28 - 8.53 (m, 1H), 7.68 - 7.89 (m, 2H), 7.54 - 7.71 (m, 2H), 7.29 - 7.47 (m, 2H), 7.08 - 7.28 (m, 1H), 4.42 - 4.59 (m, 2H), 2.88 (br. s., 4H), 2.71 - 2.83 (m, 4H), 2.36 (br. s., 4H), 1.94 - 2.06 (m, 2H), 1.72 - 1.87 (m, 2H), 1.50 - 1.68 (m, 2H)

Mass Spec: ES$^+$ 392

2.54 Example 54

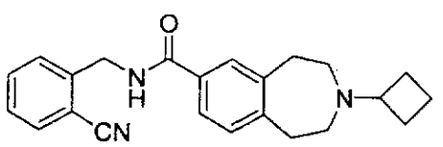


N-(2-Bromobenzyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.62 (m, 4H), 7.28 - 7.34 (m, 1H), 7.12 - 7.21 (m, 2H), 6.57 (br. s., 1H), 4.65 - 4.79 (m, 2H), 2.90 - 3.07 (m, 4H), 2.74 - 2.86 (m, 1H), 2.47 (br. s., 4H), 2.03 - 2.15 (m, 2H), 1.87 - 2.00 (m, 2H), 1.55 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 413, 415

2.55 Example 55

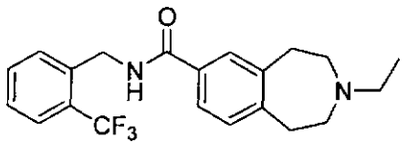


N-(2-Cyanobenzyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 - 7.74 (m, 5H), 7.33 - 7.43 (m, 1H), 7.11 - 7.19 (m, 1H), 6.72 - 6.90 (m, 1H), 4.73 - 4.89 (m, 2H), 2.96 (br. s., 4H), 2.70 - 2.84 (m, 1H), 2.44 (br. s., 4H), 2.01 - 2.14 (m, 2H), 1.82 - 1.99 (m, 2H), 1.56 - 1.79 (m, 2H)

Mass Spec: ES$^+$ 360

2.56 Example 56

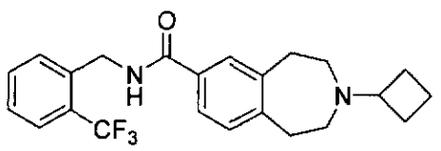


3-Ethyl-N-(2-(trifluoromethyl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.68 - 7.74 (m, 1H), 7.62 - 7.68 (m, 2H), 7.50 - 7.62 (m, 2H), 7.39 - 7.48 (m, 1H), 7.19 - 7.27 (m, 1H), 4.75 - 4.81 (m, 2H), 3.01 (br. s., 4H), 2.54 - 2.75 (m, 6H), 1.09 - 1.17 (m, 3H)

Mass Spec: ES$^+$ 377

2.57 Example 57

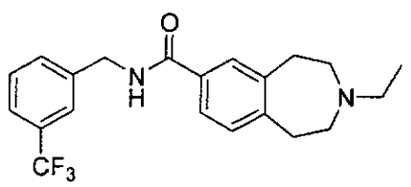


3-Cyclobutyl-N-(2-(trifluoromethyl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.67 - 7.73 (m, 1H), 7.62 - 7.67 (m, 2H), 7.50 - 7.61 (m, 2H), 7.38 - 7.47 (m, 1H), 7.18 - 7.25 (m, 1H), 4.74 - 4.81 (m, 2H), 2.98 (d, J = 4.04 Hz, 4H), 2.76 - 2.90 (m, 1H), 2.48 (br. s., 4H), 2.05 - 2.16 (m, 2H), 1.86 - 2.00 (m, 2H), 1.59 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 403

2.58 Example 58

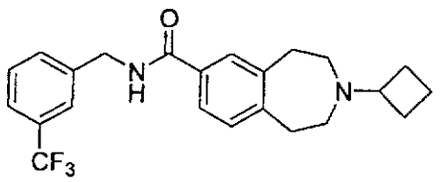


3-Ethyl-N-(3-(trifluoromethyl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.58 - 7.68 (m, 4H), 7.49 - 7.58 (m, 2H), 7.18 - 7.26 (m, 1H), 4.63 (s, 2H), 3.00 (br. s., 4H), 2.54 - 2.75 (m, 6H), 1.06 - 1.19 (m, 3H)

Mass Spec: ES$^+$ 377

2.59 Example 59

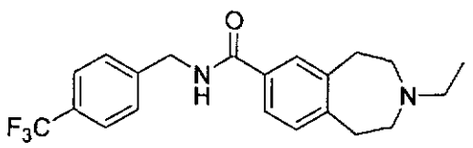


3-Cyclobutyl-N-(3-(trifluoromethyl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.58 - 7.68 (m, 4H), 7.49 - 7.58 (m, 2H), 7.17 - 7.25 (m, 1H), 4.62 (s, 2H), 2.98 (br. s., 4H), 2.77 - 2.91 (m, 1H), 2.49 (br. s., 4H), 2.03 - 2.18 (m, 2H), 1.85 - 2.01 (m, 2H), 1.60 - 1.80 (m, 2H)

Mass Spec: ES$^+$ 403

2.60 Example 60

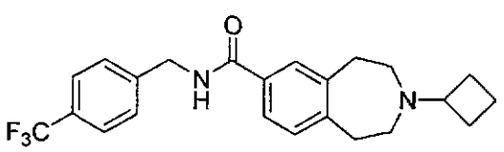


3-Ethyl-N-(4-(trifluoromethyl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 10.13 (s, 1H), 7.74 - 7.81 (m, 2H), 7.68 - 7.73 (m, 2H), 7.31 - 7.38 (m, 2H), 7.23 - 7.29 (m, 1H), 7.06 - 7.13 (m, 1H), 2.86 - 2.98 (m, 4H), 2.72 - 2.83 (m, 1H), 2.38 (br. s., 4H), 1.96 - 2.07 (m, 2H), 1.73 - 1.87 (m, 2H), 1.51 - 1.68 (m, 2H)

Mass Spec: ES$^+$ 377

2.61 Example 61

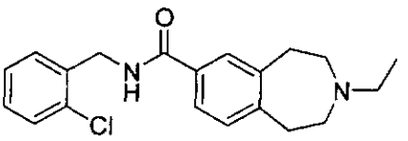


3-Cyclobutyl-N-(4-(trifluoromethyl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.58 - 7.66 (m, 4H), 7.48 - 7.57 (m, 2H), 7.17 - 7.25 (m, 2H), 4.63 (s, 2H), 2.98 (br. s., 4H), 2.76 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.04 - 2.17 (m, 2H), 1.86 - 2.01 (m, 2H), 1.60 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 403

2.62 Example 62

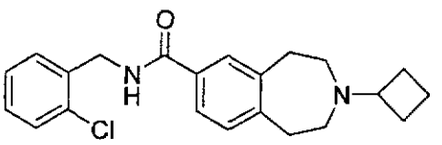


N-(2-Chlorobenzyl)-3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.58 - 7.69 (m, 2H), 7.34 - 7.44 (m, 2H), 7.19 - 7.32 (m, 3H), 4.65 (s, 2H), 3.01 (br. s., 4H), 2.54 - 2.77 (m, 6H), 1.08 - 1.19 (m, 3H)

Mass Spec: ES^+ 343

2.63 Example 63

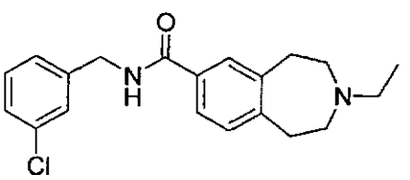


N-(2-Chlorobenzyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.59 - 7.67 (m, 2H), 7.34 - 7.43 (m, 2H), 7.17 - 7.31 (m, 3H), 4.65 (s, 2H), 2.90 - 3.05 (m, 4H), 2.76 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.04 - 2.16 (m, 2H), 1.86 - 2.00 (m, 2H), 1.61 - 1.78 (m, 2H)

Mass Spec: ES^+ 369

2.64 Example 64

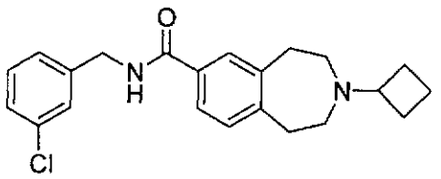


N-(3-Chlorobenzyl)-3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.58 - 7.66 (m, 2H), 7.18 - 7.40 (m, 5H), 4.54 (s, 2H), 3.01 (br. s., 4H), 2.54 - 2.75 (m, 6H), 1.09 - 1.18 (m, 3H)

Mass Spec: ES^+ 343

2.65 Example 65

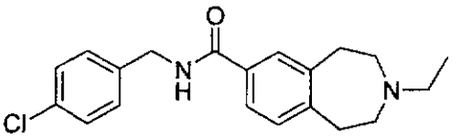


N-(3-Chlorobenzyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.57 - 7.65 (m, 2H), 7.15 - 7.37 (m, 5H), 4.56 (s, 2H), 2.89 - 3.04 (m, 4H), 2.75 - 2.87 (m, 1H), 2.46 (br. s., 4H), 2.02 - 2.15 (m, 2H), 1.84 - 2.00 (m, 2H), 1.58 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 369

2.66 Example 66

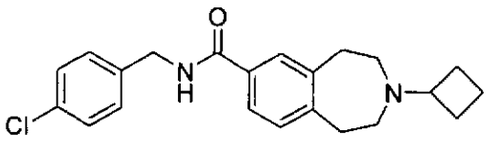


N-(4-Chlorobenzyl)-3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.57 - 7.64 (m, 2H), 7.27 - 7.36 (m, 4H), 7.16 - 7.23 (m, 1H), 4.52 (s, 2H), 2.90 - 3.04 (m, 4H), 2.53 - 2.72 (m, 6H), 1.06 - 1.16 (m, 3H)

Mass Spec: ES$^+$ 343

2.67 Example 67

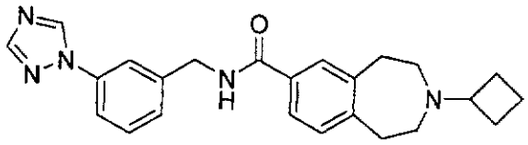


N-(4-Chlorobenzyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.55 - 7.64 (m, 2H), 7.27 - 7.37 (m, 4H), 7.17 - 7.24 (m, 1H), 4.53 (s, 2H), 2.98 (br. s., 4H), 2.76 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.02 - 2.17 (m, 2H), 1.86 - 2.00 (m, 2H), 1.58 - 1.80 (m, 2H)

Mass Spec: ES$^+$ 369

2.68 Example 68

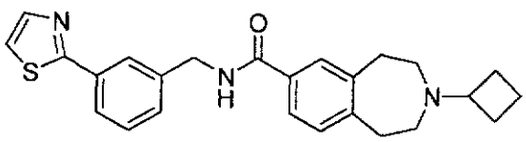


N-(3-(1H-1,2,4-Triazol-1-yl)benzyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 9.28 (s, 1H), 8.95 - 9.07 (m, 1H), 8.17 - 8.28 (m, 1H), 7.82 (s, 1H), 7.70 - 7.78 (m, 1H), 7.62 - 7.70 (m, 2H), 7.47 - 7.56 (m, 1H), 7.32 - 7.42 (m, 1H), 7.16 - 7.26 (m, 1H), 4.50 - 4.60 (m, 2H), 2.89 (br. s., 4H), 2.71 - 2.82 (m, 1H), 2.36 (br. s., 4H), 2.01 (d, J = 6.57 Hz, 2H), 1.71 - 1.89 (m, 2H), 1.50 - 1.69 (m, 2H)

Mass Spec: ES$^+$ 402

2.69 Example 69

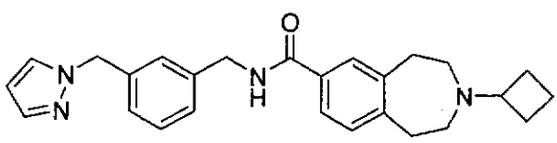


3-Cyclobutyl-N-(3-(thiazol-2-yl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.95 (s, 1H), 7.81 - 7.88 (m, 2H), 7.61 - 7.66 (m, 2H), 7.58 - 7.61 (m, 1H), 7.43 - 7.50 (m, 2H), 7.18 - 7.25 (m, 1H), 4.64 (s, 2H), 2.98 (br. s., 4H), 2.77 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.05 - 2.16 (m, 2H), 1.87 - 2.00 (m, 2H), 1.62 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 418

2.70 Example 70

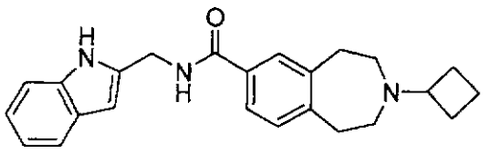


N-(3-((1H-Pyrazol-1-yl)methyl)benzyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.85 - 8.97 (m, 1H), 7.76 - 7.85 (m, 1H), 7.58 - 7.68 (m, 2H), 7.39 - 7.49 (m, 1H), 7.13 - 7.32 (m, 4H), 7.03 - 7.10 (m, 1H), 6.21 - 6.34 (m, 1H), 5.31 (s, 2H), 4.35 - 4.51 (m, 2H), 2.68 - 3.04 (m, 5H), 2.37 (br. s., 4H), 1.94 - 2.10 (m, 2H), 1.71 - 1.89 (m, 2H), 1.49 - 1.69 (m, 2H)

Mass Spec: ES$^+$ 415

2.71 Example 71

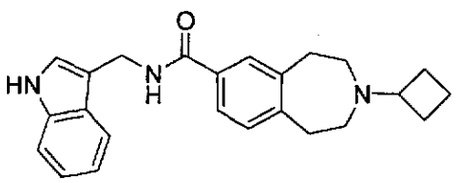


N-((1H-Indol-2-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.63 (br. s., 3H), 7.41 - 7.48 (m, 1H), 7.28 - 7.34 (m, 1H), 7.16 - 7.24 (m, 1H), 7.01 - 7.08 (m, 1H), 6.92 - 6.99 (m, 1H), 6.34 (s, 1H), 4.70 (s, 2H), 2.98 (br. s., 4H), 2.80 - 2.92 (m, 1H), 2.51 (br. s., 4H), 2.05 - 2.17 (m, 2H), 1.88 - 2.01 (m, 2H), 1.60 - 1.79 (m, 2H)

Mass Spec: ES$^+$ 374

2.72 Example 72

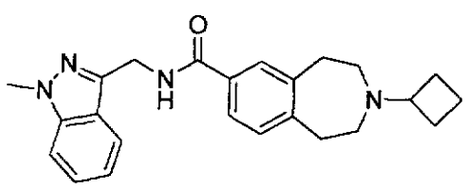


N-((1H-Indol-3-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.61 - 7.67 (m, 1H), 7.53 - 7.58 (m, 2H), 7.32 - 7.36 (m, 1H), 7.24 (s, 1H), 7.13 - 7.17 (m, 1H), 7.07 - 7.12 (m, 1H), 6.97 - 7.04 (m, 1H), 4.73 (s, 2H), 2.93 (br. s., 4H), 2.75 - 2.85 (m, 1H), 2.44 (br. s., 4H), 2.02 - 2.13 (m, 2H), 1.85 - 1.98 (m, 2H), 1.60 - 1.76 (m, 2H)

Mass Spec: ES$^+$ 374

2.73 Example 73

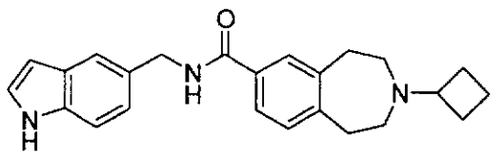


3-Cyclobutyl-N-((1-methyl-1H-indazol-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.79 - 7.85 (m, 1H), 7.57 - 7.62 (m, 2H), 7.45 - 7.51 (m, 1H), 7.36 - 7.44 (m, 1H), 7.15 - 7.21 (m, 1H), 7.08 - 7.15 (m, 1H), 4.02 (s, 3H), 2.89 - 3.01 (m, 4H), 2.76 - 2.87 (m, 1H), 2.46 (br. s., 4H), 2.03 - 2.15 (m, 2H), 1.84 - 2.01 (m, 2H), 1.61 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 389

2.74 Example 74

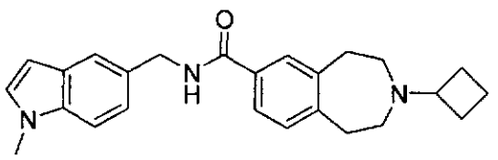


N-((1H-Indol-5-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.58 - 7.64 (m, 2H), 7.53 (s, 1H), 7.31 - 7.37 (m, 1H), 7.17 - 7.24 (m, 2H), 7.09 - 7.15 (m, 1H), 6.38 - 6.43 (m, 1H), 4.63 (s, 3H), 2.97 (br. s., 4H), 2.78 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.05 - 2.15 (m, 2H), 1.86 - 2.00 (m, 2H), 1.62 - 1.77 (m, 2H)

Mass Spec: ES$^+$ 374

2.75 Example 75

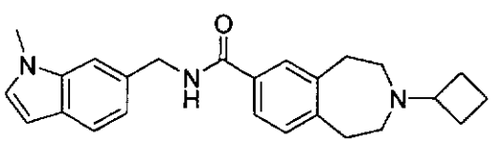


3-Cyclobutyl-N-((1-methyl-1H-indol-5-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.56 - 7.64 (m, 2H), 7.52 (br. s., 1H), 7.29 - 7.36 (m, 1H), 7.19 (m, 2H), 7.09 - 7.14 (m, 1H), 6.34 - 6.41 (m, 1H), 4.64 (s, 2H), 3.79 (s, 3H), 2.91 - 3.03 (m, 4H), 2.76 - 2.89 (m, 1H), 2.47 (br. s., 4H), 2.04 - 2.15 (m, 2H), 1.86 - 1.99 (m, 2H), 1.60 - 1.77 (m, 2H)

Mass Spec: ES$^+$ 388

2.76 Example 76

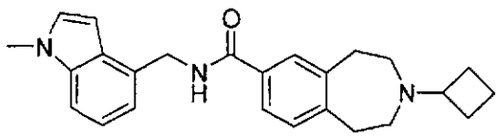


3-Cyclobutyl-N-((1-methyl-1H-indol-6-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.85 - 8.98 (m, 1H), 7.60 - 7.70 (m, 2H), 7.44 - 7.53 (m, 1H), 7.36 (s, 1H), 7.25 - 7.31 (m, 1H), 7.15 - 7.23 (m, 1H), 6.98 - 7.08 (m, 1H), 6.34 - 6.42 (m, 1H), 4.52 - 4.64 (m, 2H), 3.78 (s, 3H), 2.87 (br. s., 4H), 2.67 - 2.80 (m, 1H), 2.34 (br. s., 4H), 1.96-2.10 (m, 2H), 1.69 - 1.86 (m, 2H), 1.48 - 1.69 (m, 2H)

Mass Spec: ES$^+$ 388

2.77 Example 77

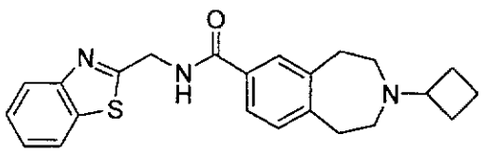


3-Cyclobutyl-N-((1-methyl-1H-indol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

1H NMR (400 MHz, DMSO-d6) δ 8.80 - 8.94 (m, 1H), 7.58 - 7.74 (m, 2H), 7.27 - 7.37 (m, 2H), 7.15 - 7.23 (m, 1H), 7.06 - 7.14 (m, 1H), 6.91 - 6.99 (m, 1H), 6.52 - 6.60 (m, 1H), 4.66 - 4.77 (m, 2H), 3.35 (s, 3H), 2.87 (br. s., 4H), 2.75 (br. s., 1H), 2.26 - 2.42 (m, 4H), 1.94 - 2.07 (m, 2H), 1.71 - 1.86 (m, 2H), 1.50 - 1.66 (m, 2H)

Mass Spec: ES^+ 388

2.78 Example 78

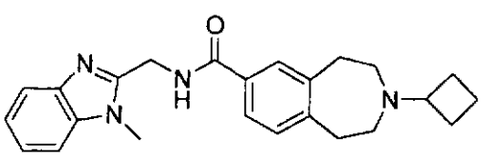


N-(Benzo[d]thiazol-2-ylmethyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.92 - 7.98 (m, 2H), 7.65 - 7.70 (m, 2H), 7.47 - 7.54 (m, 1H), 7.38 - 7.45 (m, 1H), 7.22 - 7.28 (m, 1H), 4.96 (s, 2H), 2.96 - 3.06 (m, 4H), 2.81 - 2.91 (m, 1H), 2.51 (br. s., 4H), 2.07 - 2.17 (m, 2H), 1.88 - 2.02 (m, 2H), 1.62 - 1.79 (m, 2H)

Mass Spec: ES^+ 392

2.79 Example 79

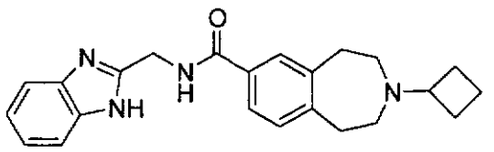


3-Cyclobutyl-N-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.93 - 9.05 (m, 1H), 7.62 - 7.71 (m, 2H), 7.55 - 7.61 (m, 1H), 7.49 - 7.55 (m, 1H), 7.13 - 7.29 (m, 3H), 4.69 - 4.82 (m, 2H), 3.32 (s, 3H), 2.88 (br. s., 4H), 2.70 - 2.82 (m, 1H), 2.35 (br. s., 4H), 1.93 - 2.07 (m, 2H), 1.70 - 1.86 (m, 2H), 1.48 - 1.68 (m, 2H)

Mass Spec: ES^+ 389

2.80 Example 80

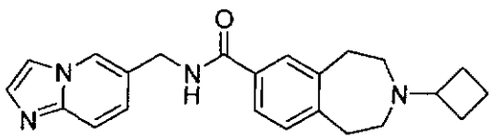


N-((1H-Benzo[d]imidazol-2-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.63 - 7.78 (m, 2H), 7.52 (br. s., 2H), 7.13 - 7.31 (m, 4H), 4.81 (s, 2H), 2.99 (br. s., 4H), 2.77 - 2.91 (m, 1H), 2.50 (br. s., 4H), 2.05 - 2.19 (m, 2H), 1.84 - 2.03 (m, 2H), 1.58 - 1.81 (m, 2H)

Mass Spec: ES$^+$ 375

2.81 Example 81

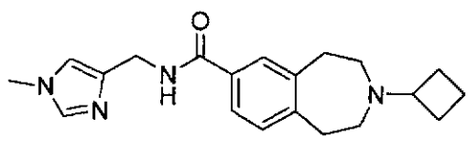


3-Cyclobutyl-N-(imidazo[1,2-a]pyridin-6-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.89 - 9.00 (m, 1H), 8.46 (s, 1H), 7.95 (s, 1H), 7.59 - 7.70 (m, 2H), 7.49 - 7.57 (m, 2H), 7.16 - 7.26 (m, 2H), 4.38 - 4.52 (m, 2H), 2.88 (br. s., 4H), 2.70 - 2.81 (m, 1H), 2.35 (br. s., 4H), 1.93 - 2.07 (m, 2H), 1.70 - 1.86 (m, 2H), 1.47 - 1.68 (m, 2H)

Mass Spec: ES$^+$ 375

2.82 Example 82

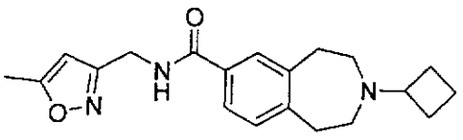


3-Cyclobutyl-N-((1-methyl-1H-imidazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.57 - 7.62 (m, 2H), 7.53 (s, 1H), 7.17 - 7.22 (m, 1H), 6.99 (s, 1H), 4.45 (s, 2H), 3.68 (s, 3H), 2.98 (br. s., 4H), 2.78 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.05 - 2.18 (m, 2H), 1.87 - 2.01 (m, 2H), 1.62 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 338

2.83 Example 83

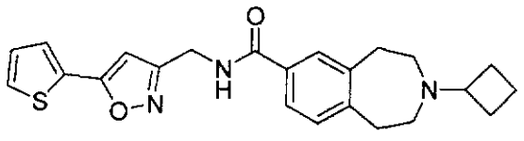


3-Cyclobutyl-N-((5-methylisoxazol-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.58 - 7.64 (m, 2H), 7.18 - 7.25 (m, 1H), 6.12 (s, 1H), 4.55 (s, 2H), 2.99 (br. s., 4H), 2.81 - 2.93 (m, 1H), 2.44 - 2.61 (m, 4H), 2.39 (s, 3H), 2.06 - 2.18 (m, 2H), 1.88 - 2.02 (m, 2H), 1.63 - 1.79 (m, 2H)

Mass Spec: ES$^+$ 340

2.84 Example 84

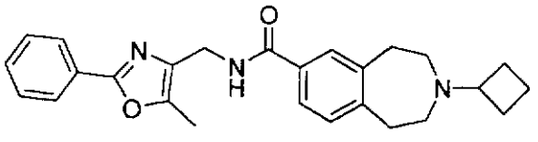


3-Cyclobutyl-N-((5-(thiophen-2-yl)isoxazol-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.60 - 7.66 (m, 3H), 7.56 - 7.59 (m, 1H), 7.20 - 7.25 (m, 1H), 7.14 - 7.19 (m, 1H), 6.60 (s, 1H), 4.63 (s, 2H), 2.99 (br. s., 4H), 2.81 - 2.92 (m, 1H), 2.51 (br. s., 4H), 2.07 - 2.17 (m, 2H), 1.88 - 2.01 (m, 2H), 1.60 - 1.79 (m, 2H)

Mass Spec: ES$^+$ 408

2.85 Example 85

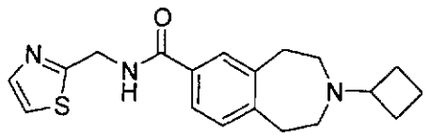


3-Cyclobutyl-N-((5-methyl-2-phenyloxazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.94 - 8.01 (m, 2H), 7.61 (br. s., 2H), 7.41 - 7.52 (m, 3H), 7.15 - 7.24 (m, 1H), 4.46 (s, 2H), 2.98 (br. s., 4H), 2.78 - 2.91 (m, 1H), 2.47 (s, 7H), 2.05 - 2.17 (m, 2H), 1.86 - 2.01 (m, 2H), 1.60 - 1.79 (m, 2H)

Mass Spec: ES$^+$ 416

2.86 Example 86

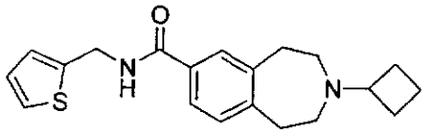


3-Cyclobutyl-N-(thiazol-2-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 9.21 - 9.33 (m, 1H), 7.69 - 7.78 (m, 1H), 7.58 - 7.70 (m, 3H), 7.18 - 7.28 (m, 1H), 4.67 - 4.79 (m, 2H), 2.89 (br. s., 4H), 2.78 (br. s., 1H), 2.37 (br. s., 4H), 1.94 - 2.08 (m, 2H), 1.70 - 1.87 (m, 2H), 1.46 - 1.69 (m, 2H)

Mass Spec: ES$^+$ 342

2.87 Example 87

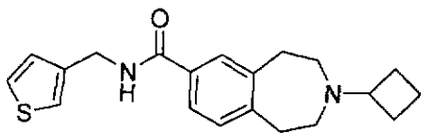


3-Cyclobutyl-N-(thiophen-2-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.55 - 7.62 (m, 2H), 7.25 - 7.29 (m, 1H), 7.16 - 7.22 (m, 1H), 7.01 - 7.04 (m, 1H), 6.91 - 6.96 (m, 1H), 4.71 (s, 2H), 2.92 - 3.02 (m, 4H), 2.77 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.05 - 2.15 (m, 2H), 1.86 - 2.00 (m, 2H), 1.61 - 1.77 (m, 2H)

Mass Spec: ES$^+$ 341

2.88 Example 88

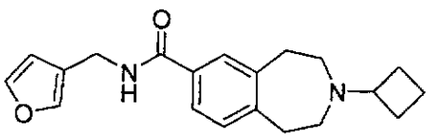


3-Cyclobutyl-N-(thiophen-3-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.55 - 7.63 (m, 2H), 7.33 - 7.37 (m, 1H), 7.22 - 7.27 (m, 1H), 7.17 - 7.22 (m, 1H), 7.06 - 7.11 (m, 1H), 4.55 (s, 2H), 2.97 (br. s., 4H), 2.77 - 2.87 (m, 1H), 2.38 - 2.58 (m, 4H), 2.02 - 2.16 (m, 2H), 1.86 - 2.00 (m, 2H), 1.59 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 341

2.89 Example 89

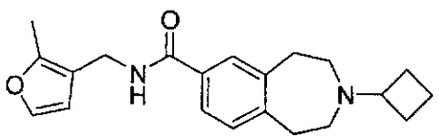


3-Cyclobutyl-N-(furan-3-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.54 - 7.61 (m, 2H), 7.47 (s, 1H), 7.43 (s, 1H), 7.15 - 7.24 (m, 1H), 6.45 (s, 1H), 4.39 (s, 2H), 2.97 (br. s., 4H), 2.77 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.04 - 2.15 (m, 2H), 1.87 - 2.00 (m, 2H), 1.61 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 325

2.90 Example 90

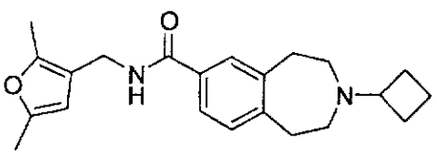


3-cyclobutyl-N-((2-methylfuran-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.60 - 8.73 (m, 1H), 7.55 - 7.64 (m, 2H), 7.37 - 7.44 (m, 1H), 7.15 - 7.23 (m, 1H), 6.31 - 6.38 (m, 1H), 4.15 - 4.25 (m, 2H), 2.87 (br. s., 5H), 2.22 - 2.45 (m, 7H), 1.94 - 2.07 (m, 2H), 1.72 - 1.87 (m, 2H), 1.48 - 1.67 (m, 2H)

Mass Spec: ES$^+$ 339

2.91 Example 91

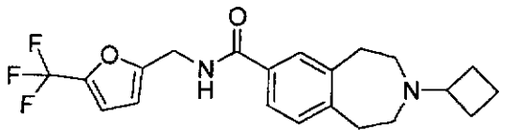


3-cyclobutyl-N-((2,5-dimethylfuran-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 - 8.65 (m, 1H), 7.54 - 7.62 (m, 2H), 7.15 - 7.20 (m, 1H), 5.93 (s, 1H), 4.10 - 4.15 (m, 2H), 2.82 - 2.90 (m, 4H), 2.72 - 2.79 (m, 1H), 2.34 (br. s., 4H), 2.21 (s, 3H), 2.16 (s, 3H), 1.96 - 2.05 (m, 2H), 1.72 - 1.84 (m, 2H), 1.51 - 1.66 (m, 2H)

Mass Spec: ES$^+$ 353

2.92 Example 92

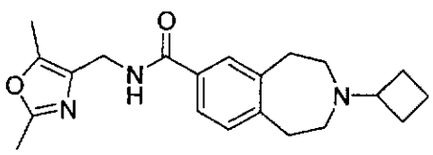


3-cyclobutyl-N-((5-(trifluoromethyl)furan-2-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 - 9.04 (m, 1H), 7.57 - 7.67 (m, 2H), 7.18 - 7.25 (m, 1H), 7.13 - 7.18 (m, 1H), 6.48 - 6.53 (m, 1H), 4.46 - 4.56 (m, 2H), 2.88 (br. s., 4H), 2.70 - 2.82 (m, 1H), 2.26 - 2.43 (m, 4H), 2.00 (br. s., 2H), 1.70 - 1.88 (m, 2H), 1.49 - 1.67 (m, 2H)

Mass Spec: ES$^+$ 393

2.93 Example 93

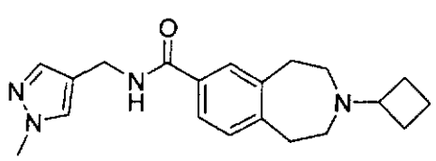


3-cyclobutyl-N-((2,5-dimethyloxazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 - 8.75 (m, 1H), 7.54 - 7.66 (m, 2H), 7.12 - 7.22 (m, 1H), 4.15 - 4.25 (m, 2H), 2.81 - 2.93 (m, 4H), 2.69 - 2.80 (m, 1H), 2.22 - 2.43 (m, 10H), 1.94 - 2.07 (m, 2H), 1.71 - 1.86 (m, 2H), 1.50 - 1.67 (m, 2H)

Mass Spec: ES$^+$ 354

2.94 Example 94

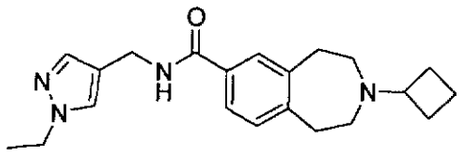


3-Cyclobutyl-N-((1-methyl-1H-pyrazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.54 - 7.59 (m, 3H), 7.45 (s, 1H), 7.16 - 7.22 (m, 1H), 4.39 (s, 2H), 3.84 (s, 3H), 2.97 (br. s., 4H), 2.77 - 2.89 (m, 1H), 2.47 (br. s., 4H), 2.05 - 2.15 (m, 2H), 1.87 - 2.00 (m, 2H), 1.62 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 339

2.95 Example 95

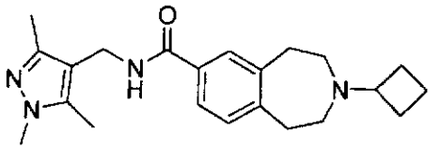


3-Cyclobutyl-N-((1-ethyl-1H-pyrazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.62 - 8.72 (m, 1H), 7.55 - 7.65 (m, 3H), 7.34 (s, 1H), 7.14 - 7.20 (m, 1H), 4.21 - 4.31 (m, 2H), 4.00 - 4.12 (m, 2H), 2.80 - 2.91 (m, 4H), 2.68 - 2.79 (m, 1H), 2.33 (br. s., 4H), 1.94 - 2.05 (m, 2H), 1.70 - 1.84 (m, 2H), 1.49 - 1.66 (m, 2H), 1.32 (t, 3H)

Mass Spec: ES$^+$ 353

2.96 Example 96

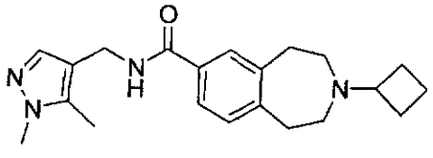


3-Cyclobutyl-N-((1,3,5-trimethyl-1H-pyrazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.39 - 8.50 (m, 1H), 7.53 - 7.63 (m, 2H), 7.12 - 7.21 (m, 1H), 4.12 - 4.22 (m, 2H), 3.35 (s, 3H), 2.80 - 2.92 (m, 4H), 2.67 - 2.79 (m, 1H), 2.33 (br. s., 4H), 2.20 (s, 3H), 2.10 (s, 3H), 1.94 - 2.05 (m, 2H), 1.70 - 1.84 (m, 2H), 1.47 - 1.67 (m, 2H)

Mass Spec: ES$^+$ 367

2.97 Example 97

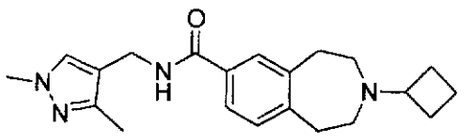


3-Cyclobutyl-N-((1,5-dimethyl-1H-pyrazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.54 - 8.65 (m, 1H), 7.52 - 7.65 (m, 2H), 7.25 (s, 1H), 7.12 - 7.21 (m, 1H), 4.16 - 4.26 (m, 2H), 3.34 (s, 3H), 2.86 (br. s., 4H), 2.68 - 2.79 (m, 1H), 2.39 (br. s., 4H), 2.19 - 2.25 (m, 3H), 1.94 - 2.07 (m, 2H), 1.69 - 1.85 (m, 2H), 1.50 - 1.67 (m, 2H)

Mass Spec: ES$^+$ 353

2.98 Example 98

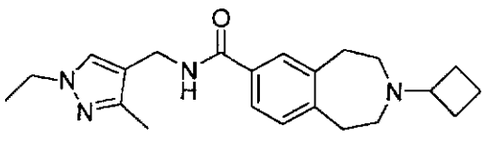


3-Cyclobutyl-N-((1,3-dimethyl-1H-pyrazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.54 - 8.63 (m, 1H), 7.54 - 7.66 (m, 2H), 7.46 (s, 1H), 7.13 - 7.20 (m, 1H), 4.16 - 4.26 (m, 2H), 3.69 (s, 3H), 2.81 - 2.95 (m, 4H), 2.68 - 2.80 (m, 1H), 2.24 - 2.43 (m, 4H), 2.09 (s, 3H), 1.94 - 2.06 (m, 2H), 1.71 - 1.85 (m, 2H), 1.49 - 1.67 (m, 2H)

Mass Spec: ES^+ 353

2.99 Example 99

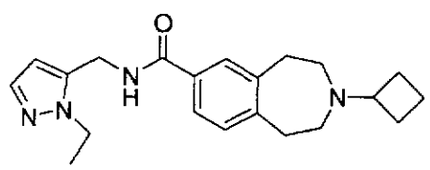


3-Cyclobutyl-N-((1-ethyl-3-methyl-1H-pyrazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 - 8.64 (m, 1H), 7.57 - 7.66 (m, 2H), 7.51 (s, 1H), 7.17 (d, J = 7.58 Hz, 1H), 4.18 - 4.26 (m, 2H), 3.92 - 4.03 (m, 2H), 2.87 (br. s., 4H), 2.70 - 2.81 (m, 1H), 2.27 - 2.43 (m, 4H), 2.13 (s, 3H), 1.95 - 2.07 (m, 2H), 1.78 (br. s., 2H), 1.49 - 1.68 (m, 2H), 1.26 - 1.34 (m, 3H)

Mass Spec: ES^+ 367

2.100 Example 100

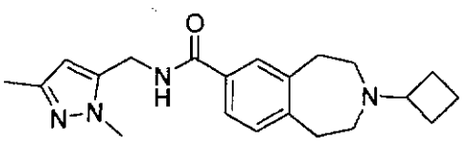


3-cyclobutyl-N-((1-ethyl-1H-pyrazol-5-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 - 8.93 (m, 1H), 7.55 - 7.70 (m, 2H), 7.29 - 7.38 (m, 1H), 7.15 - 7.23 (m, 1H), 6.09 - 6.18 (m, 1H), 4.46 - 4.55 (m, 2H), 4.09 - 4.19 (m, 2H), 2.81 - 2.95 (m, 4H), 2.68 - 2.80 (m, 1H), 2.34 (br. s., 4H), 1.93 - 2.10 (m, 2H), 1.70 - 1.85 (m, 2H), 1.49 - 1.67 (m, 2H), 1.24 - 1.34 (m, 3H)

Mass Spec: ES^+ 353

2.101 Example 101

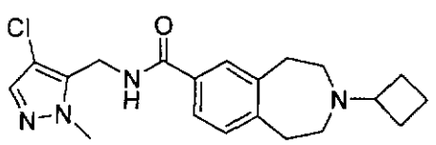


3-Cyclobutyl-N-((1,3-dimethyl-1H-pyrazol-5-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^1H NMR (400 MHz, DMSO-d6) δ 8.77 - 8.89 (m, 1H), 7.54 - 7.71 (m, 2H), 7.17 - 7.27 (m, 1H), 5.92 (s, 1H), 4.36 - 4.49 (m, 2H), 3.71 (s, 3H), 2.89 (br. s., 4H), 2.70 - 2.83 (m, 1H), 2.34 (br. s., 4H), 1.96 - 2.11 (m, 5H), 1.80 (br. s., 2H), 1.49 - 1.69 (m, 2H)

Mass Spec: ES^+ 353

2.102 Example 102

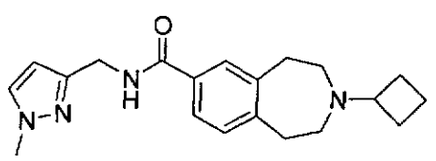


N-((4-chloro-1-methyl-1H-pyrazol-5-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^1H NMR (400 MHz, DMSO-d_6) δ 8.76 - 8.92 (m, 1H), 7.58 - 7.65 (m, 2H), 7.49 (s, 1H), 7.17 - 7.22 (m, 1H), 4.47 - 4.54 (m, 2H), 3.84 (s, 3H), 2.88 (br. s., 4H), 2.70 - 2.81 (m, 1H), 2.34 (br. s., 4H), 1.95 - 2.07 (m, 2H), 1.78 (br. s., 2H), 1.51 - 1.67 (m, 2H)

Mass Spec: ES^+ 373

2.103 Example 103

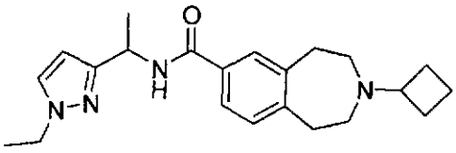


3-Cyclobutyl-N-((1-methyl-1H-pyrazol-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 - 8.82 (m, 1H), 7.50 - 7.70 (m, 3H), 7.12 - 7.24 (m, 1H), 6.07 - 6.14 (m, 1H), 4.32 - 4.44 (m, 2H), 3.78 (s, 3H), 2.66 - 2.98 (m, 5H), 2.24 - 2.44 (m, 4H), 2.01 (br. s., 2H), 1.79 (br. s., 2H), 1.48 - 1.69 (m, 2H)

Mass Spec: ES$^+$ 339

2.104 Example 104

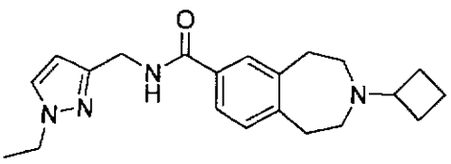


3-cyclobutyl-N-(1-(1-ethyl-1H-pyrazol-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 - 8.61 (m, 1H), 7.53 - 7.67 (m, 3H), 7.11 - 7.21 (m, 1H), 6.08 - 6.19 (m, 1H), 5.13 - 5.26 (m, 1H), 3.99 - 4.10 (m, 2H), 2.86 (br. s., 4H), 2.66 - 2.78 (m, 1H), 2.33 (br. s., 4H), 1.98 (d, *J* = 7.33 Hz, 2H), 1.70 - 1.84 (m, 2H), 1.48 - 1.66 (m, 2H), 1.39 - 1.47 (m, 3H), 1.33 (m, 3H)

Mass Spec: ES$^+$ 367

2.105 Example 105

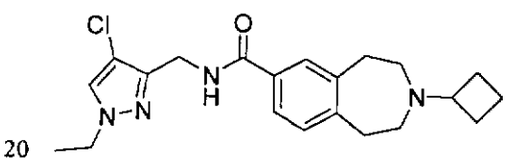


3-Cyclobutyl-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 - 8.84 (m, 1H), 7.55 - 7.70 (m, 3H), 7.13 - 7.23 (m, 1H), 6.06 - 6.16 (m, 1H), 4.33 - 4.46 (m, 2H), 4.02 - 4.11 (m, 2H), 2.87 (br. s., 4H), 2.69 - 2.82 (m, 1H), 2.35 (br. s., 4H), 1.93 - 2.09 (m, 2H), 1.70 - 1.87 (m, 2H), 1.48 - 1.68 (m, 2H), 1.28 - 1.39 (m, 3H)

Mass Spec: ES$^+$ 353

2.106 Example 106

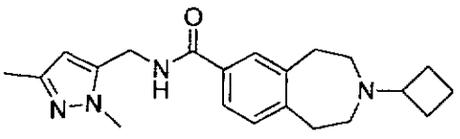


N-((4-chloro-1-ethyl-1H-pyrazol-3-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 - 8.75 (m, 1H), 7.95 (s, 1H), 7.58 - 7.69 (m, 2H), 7.14 - 7.22 (m, 1H), 4.37 - 4.48 (m, 2H), 3.99 - 4.12 (m, 2H), 2.87 (br. s., 5H), 2.36 (br. s., 4H), 1.95 - 2.07 (m, 2H), 1.79 (br. s., 2H), 1.48 - 1.68 (m, 2H), 1.28 - 1.39 (m, 3H)

Mass Spec: ES^+ 387

2.107 Example 107

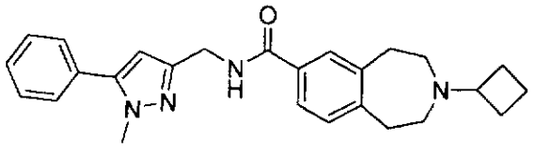


3-Cyclobutyl-N-((1,5-dimethyl-1H-pyrazol-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.67 - 8.80 (m, 1H), 7.55 - 7.68 (m, 2H), 7.13 - 7.25 (m, 1H), 5.90 (s, 1H), 4.24 - 4.36 (m, 2H), 3.63 (s, 3H), 2.70 - 2.81 (m, 1H), 2.88 (br. s., 4H), 2.34 (br. s., 4H), 2.19 (s, 3H), 2.02 (br. s., 2H), 1.79 (br. s., 2H), 1.60 (br. s., 2H)

Mass Spec: ES^+ 353

2.108 Example 108

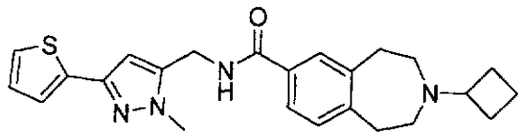


3-Cyclobutyl-N-((1-methyl-5-phenyl-1H-pyrazol-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.77 - 8.86 (m, 1H), 7.58 - 7.70 (m, 2H), 7.36 - 7.55 (m, 5H), 7.14 - 7.23 (m, 1H), 6.26 - 6.33 (m, 1H), 4.36 - 4.49 (m, 2H), 3.80 (s, 3H), 2.87 (br. s., 4H), 2.68 - 2.79 (m, 1H), 2.34 (br. s., 4H), 1.93 - 2.08 (m, 2H), 1.70 - 1.86 (m, 2H), 1.49 - 1.67 (m, 2H)

Mass Spec: ES^+ 415

2.109 Example 109

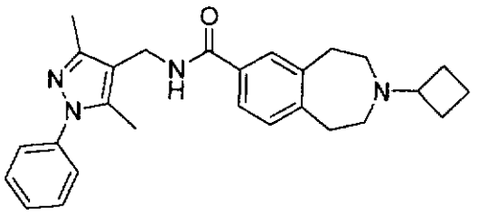


3-Cyclobutyl-N-((1-methyl-3-(thiophen-2-yl)-1H-pyrazol-5-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ 8.87 - 8.97 (m, 1H), 7.58 - 7.69 (m, 2H), 7.37 - 7.44 (m, 1H), 7.30 - 7.37 (m, 1H), 7.17 - 7.26 (m, 1H), 7.00 - 7.08 (m, 1H), 6.49 (s, 1H), 4.45 - 4.57 (m, 2H), 3.83 (s, 3H), 2.88 (br. s., 4H), 2.70 - 2.82 (m, 1H), 2.35 (br. s., 4H), 1.93 - 2.08 (m, 2H), 1.70 - 1.88 (m, 2H), 1.49 - 1.68 (m, 2H)

Mass Spec: ES$^+$ 421

2.110 Example 110

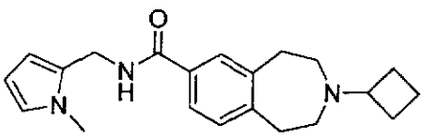


3-Cyclobutyl-N-((3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.55 - 7.60 (m, 2H), 7.47 - 7.55 (m, 2H), 7.37 - 7.47 (m, 3H), 7.16 - 7.22 (m, 1H), 4.43 (s, 2H), 2.91 - 3.03 (m, 4H), 2.77 - 2.88 (m, 1H), 2.38 - 2.56 (m, 4H), 2.27 - 2.35 (m, 6H), 2.05 - 2.16 (m, 2H), 1.86 - 1.99 (m, 2H), 1.60 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 429

2.111 Example 111

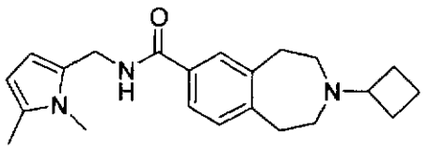


3-Cyclobutyl-N-((1-methyl-1H-pyrrol-2-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.51 - 7.60 (m, 2H), 7.11 - 7.25 (m, 1H), 6.56 - 6.66 (m, 1H), 6.02 - 6.09 (m, 1H), 5.91 - 5.99 (m, 1H), 4.53 (s, 2H), 3.61 (s, 3H), 2.89 - 3.04 (m, 4H), 2.76 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.04 - 2.16 (m, 2H), 1.84 - 2.00 (m, 2H), 1.59 - 1.78 (m, 2H)

Mass Spec: ES^+ 338

2.112 Example 112

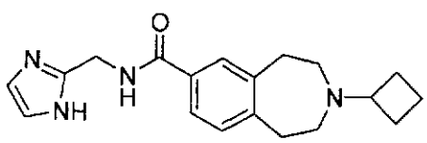


3-cyclobutyl-N-((1,5-dimethyl-1H-pyrrol-2-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^1H NMR (400 MHz, DMSO-d_6) δ 8.52 - 8.62 (m, 1H), 7.56 - 7.68 (m, 2H), 7.14 - 7.21 (m, 1H), 5.81 - 5.88 (m, 1H), 5.64 - 5.70 (m, 1H), 4.34 - 4.45 (m, 2H), 3.41 (s, 3H), 2.81 - 2.94 (m, 4H), 2.70 - 2.81 (m, 1H), 2.34 (br. s., 4H), 2.14 (s, 3H), 1.95 - 2.07 (m, 2H), 1.70 - 1.85 (m, 2H), 1.51 - 1.67 (m, 2H)

Mass Spec: ES^+ 352

2.113 Example 113

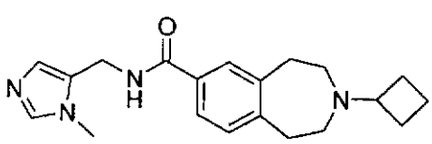


N-((1H-Imidazol-2-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^1H NMR (400 MHz, MeOD) δ 7.58 - 7.69 (m, 2H), 7.17 - 7.24 (m, 1H), 6.97 (s, 2H), 4.60 (s, 2H), 2.98 (br. s., 4H), 2.77 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.06 - 2.16 (m, 2H), 1.87 - 2.00 (m, 2H), 1.62 - 1.78 (m, 2H)

Mass Spec: ES^+ 325

2.114 Example 114

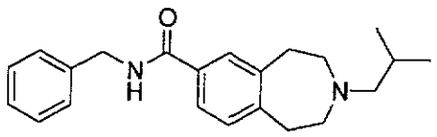


3-Cyclobutyl-N-((1-methyl-1H-imidazol-5-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^1H NMR (400 MHz, MeOD) δ 7.57 - 7.63 (m, 3H), 7.18 - 7.25 (m, 1H), 6.96 (s, 1H), 4.60 (s, 2H), 3.72 (s, 3H), 2.94 - 3.04 (m, 4H), 2.79 - 2.91 (m, 1H), 2.50 (br. s., 4H), 2.07 - 2.18 (m, 2H), 1.88 - 2.02 (m, 2H), 1.62 - 1.80 (m, 2H)

Mass Spec: ES^+ 338

2.115 Example 115

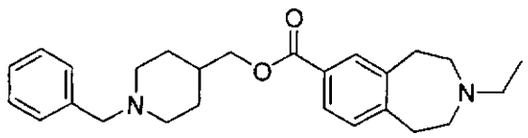


N-benzyl-3-isobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide.

MS ES^+ : 337 (M+H)

^1H NMR (400 MHz, $CDCl_3$): δ 7.49 - 7.57 (m, 2H), 7.28 - 7.40 (m, 5H), 7.11 - 7.16 (m, 1H), 4.63 - 4.68 (m, 2H), 2.91 - 2.98 (m, 4H), 2.55 - 2.64 (m, 4H), 2.16 - 2.22 (m, 2H), 1.74 - 1.86 (m, 1H), 0.89 - 0.96 (m, 6H)

2.116 Example 116

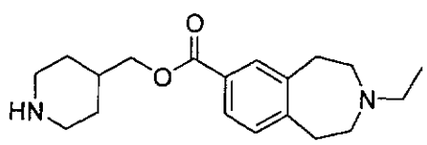


(1-Benzylpiperidin-4-yl)methyl 3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate

^1H NMR (400 MHz, DMSO-d6) δ 7.60 - 7.67 (m, 2H), 7.14 - 7.29 (m, 6H), 4.01 - 4.08 (m, 2H), 3.38 (s, 2H), 2.81 - 2.89 (m, 4H), 2.71 - 2.79 (m, 2H), 2.37 - 2.49 (m, 6H), 1.81 - 1.91 (m, 2H), 1.58 - 1.69 (m, 3H), 1.15 - 1.29 (m, 2H), 0.89 - 0.97 (m, 3H)

Mass Spec: ES^+ 407

2.117 Example 117

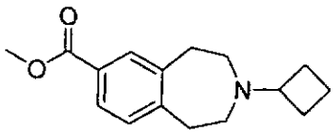


Piperidin-4-ylmethyl 3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate

^1H NMR (400 MHz, D_2O) δ 7.84 - 7.92 (m, 2H), 7.34 - 7.42 (m, 1H), 4.21 - 4.30 (m, 2H), 3.70 - 3.82 (m, 2H), 3.43 - 3.51 (m, 2H), 3.13 - 3.34 (m, 6H), 2.98 - 3.12 (m, 4H), 2.13 - 2.26 (m, 1H), 2.02 - 2.11 (m, 2H), 1.52 - 1.66 (m, 2H), 1.28 - 1.37 (m, 3H)

Mass Spec: ES^+ 316

2.118 Example 118

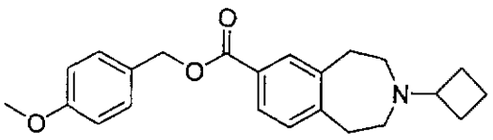


Methyl 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate

^{1}H NMR (400 MHz, MeOD) δ 7.71 - 7.81 (m, 2H), 7.17 - 7.25 (m, 1H), 3.88 (s, 3H), 2.98 (br. s., 4H), 2.78 - 2.89 (m, 1H), 2.39 - 2.59 (m, 4H), 2.05 - 2.16 (m, 2H), 1.87 - 2.00 (m, 2H), 1.60 - 1.78 (m, 2H)

Mass Spec: ES$^+$ 260

2.119 Example 119

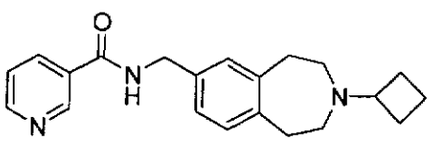


4-Methoxybenzyl 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylate

1H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.87 (m, 1H), 7.80 (s, 1H), 7.35 - 7.41 (m, 2H), 7.13 - 7.19 (m, 1H), 6.88 - 6.94 (m, 2H), 5.28 (s, 2H), 3.82 (s, 3H), 3.08 (br. s., 4H), 2.90 - 3.01 (m, 1H), 2.67 (br. s., 4H), 2.07 - 2.24 (m, 4H), 1.56 - 1.81 (m, 2H)

Mass Spec: ES$^+$ 366

2.120 Example 120

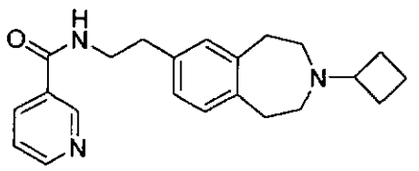


N-((3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)nicotinamide

MS ES$^+$: 336 (M+H)

^{1}H NMR (400 MHz, MeOD): δ 8.96 - 9.02 (m, 1H), 8.65 - 8.71 (m, 1H), 8.21 - 8.30 (m, 1H), 7.50 - 7.58 (m, 1H), 7.02 - 7.14 (m, 3H), 4.53 (s, 2H), 2.87 - 2.96 (m, 4H), 2.76 - 2.86 (m, 1H), 2.36 - 2.53 (m, 4H), 2.05 - 2.14 (m, 2H), 1.86 - 1.99 (m, 2H), 1.61 - 1.78 (m, 2H)

2.121 Example 121

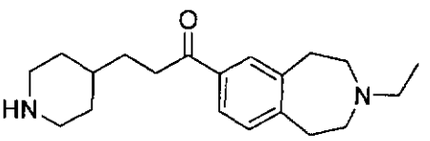


N-(2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethyl)nicotinamide

^{1}H NMR (400 MHz, MeOD) δ 8.78 - 8.98 (m, 1H), 8.58 - 8.71 (m, 1H), 8.08 - 8.27 (m, 1H), 7.39 - 7.64 (m, 1H), 6.92 - 7.14 (m, 3H), 3.49 - 3.72 (m, 2H), 2.71 - 3.01 (m, 7H), 2.44 (br. s., 4H), 2.01 - 2.19 (m, 2H), 1.82 - 2.01 (m, 2H), 1.54 - 1.82 (m, 2H)

Mass Spec: ES$^+$ 350

2.122 Example 122

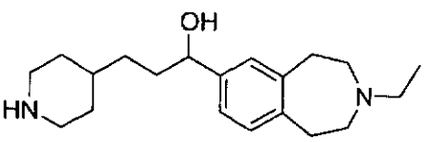


1-(3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(piperidin-4-yl)propan-1-one Hydrochloride

NMR: ^{1}H NMR (400 MHz, D_2O) δ 7.74 - 7.86 (m, 2H), 7.31 - 7.39 (m, 1H), 3.65 - 3.78 (m, 2H), 3.31 - 3.41 (m, 2H), 2.85 - 3.31 (m, 12H), 1.86 - 1.99 (m, 2H), 1.55 - 1.70 (m, 3H), 1.33 (none, 6H), 1.22 - 1.44 (m, 5H)

Mass Spec: ES$^+$ 315

2.123 Example 123

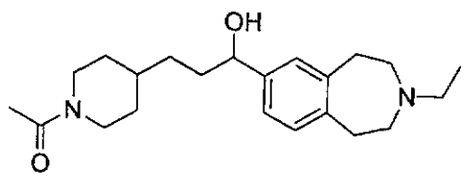


1-(3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(piperidin-4-yl)propan-1-ol Formate

NMR: ^{1}H NMR (400 MHz, MeOD) δ 8.47 (br. s., 2H), 7.11 - 7.29 (m, 3H), 4.50 - 4.65 (m, 1H), 3.43 - 3.55 (m, 2H), 3.06 - 3.41 (m, 10H), 2.89 - 2.99 (m, 2H), 1.83 - 2.01 (m, 2H), 1.63 - 1.83 (m, 2H), 1.51 - 1.66 (m, 1H), 1.12 - 1.50 (m, 9H)

Mass Spec: ES$^+$ 317

2.124 Example 124

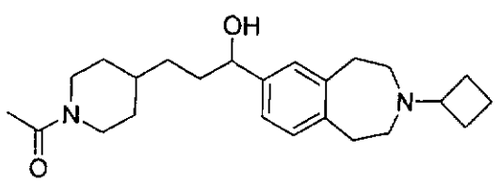


1-(4-(3-(3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-hydroxypropyl)piperidin-1-yl)ethanone

NMR: ^{1}H NMR (400 MHz, MeOD) δ 6.98 - 7.15 (m, 3H), 4.34 - 4.63 (m, 2H), 3.76 - 3.95 (m, 1H), 3.00 - 3.13 (m, 1H), 2.85 - 2.99 (m, 4H), 2.48 - 2.75 (m, 7H), 2.05 (s, 3H), 1.61 - 1.89 (m, 4H), 1.43 - 1.58 (m, 1H), 1.29 - 1.44 (m, 1H), 0.91 - 1.26 (m, 6H)

Mass Spec: ES$^+$ 359

2.125 Example 125

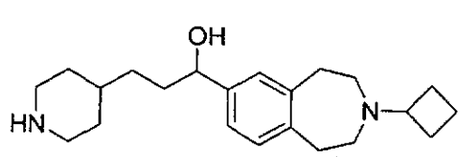


1-(4-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-hydroxypropyl)piperidin-1-yl)ethanone

NMR: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.95 - 7.08 (m, 3H), 4.99 - 5.10 (m, 1H), 4.22 - 4.47 (m, 2H), 3.64 - 3.82 (m, 1H), 2.85 - 3.02 (m, 1H), 2.65 - 2.86 (m, 5H), 2.21 - 2.47 (m, 5H), 1.88 - 2.06 (m, 5H), 1.69 - 1.86 (m, 2H), 1.47 - 1.68 (m, 6H), 1.35 - 1.45 (m, 1H), 1.20 - 1.34 (m, 1H), 1.05 - 1.19 (m, 1H), 0.90 - 1.04 (m, 1H), 0.74 - 0.90 (m, 1H)

Mass Spec: ES$^+$ 385

2.126 Example 126

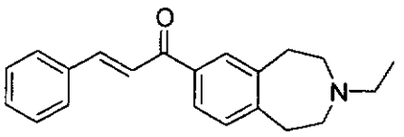


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(piperidin-4-yl)propan-1-ol

NMR: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.86 - 7.13 (m, 3H), 4.99 (br. s., 1H), 4.28 - 4.45 (m, 1H), 2.59 - 2.94 (m, 7H), 2.16 - 2.44 (m, 5H), 1.88 - 2.12 (m, 2H), 1.68 - 1.86 (m, 2H), 1.40 - 1.66 (m, 7H), 1.14 - 1.36 (m, 2H), 0.98 - 1.13 (m, 2H), 0.76 - 0.98 (m, 2H)

Mass Spec: ES$^+$ 343

2.127 Example 127

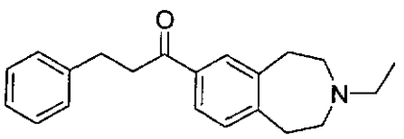


(E)-1-(3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-phenylprop-2-en-1-one

NMR: ^{1}H NMR (400 MHz, MeOD) δ 7.83 - 7.93 (m, 2H), 7.70 - 7.81 (m, 4H), 7.40 - 7.50 (m, 3H), 7.31 (d, *J* = 7.83 Hz, 1H), 2.99 - 3.16 (m, 4H), 2.53 - 2.86 (m, 6H), 1.07 - 1.22 (m, 3H)

Mass Spec: ES$^+$ 306

2.128 Example 128

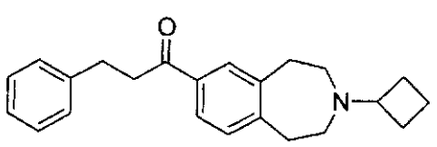


1-(3-ethyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-phenylpropan-1-one Hydrochloride

NMR: ^{1}H NMR (400 MHz, D_2O) δ 7.65 - 7.73 (m, 1H), 7.62 (s, 1H), 7.13 - 7.33 (m, 6H), 3.60 - 3.76 (m, 4H), 2.83 - 3.33 (m, 10H), 1.23 - 1.39 (m, 3H)

Mass Spec: ES$^+$ 308

2.129 Example 129

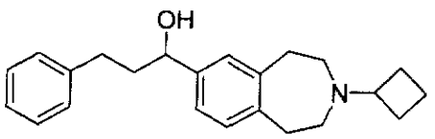


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-phenylpropan-1-one

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.55 - 1.79 (m, 2 H) 1.82 - 2.01 (m, 2 H) 2.01 - 2.15 (m, 2 H) 2.46 (br. s., 4 H) 2.72 - 2.86 (m, 1 H) 2.92 - 3.03 (m, 4 H) 3.01 - 3.14 (m, 2 H) 3.20 - 3.36 (m, 2 H) 7.09 - 7.42 (m, 6 H) 7.64 - 7.80 (m, 2 H)

Mass Spec: ES$^+$ 334

2.130 Example 130

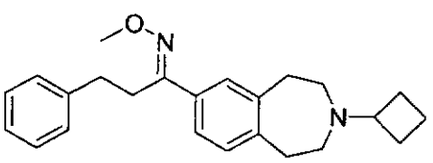


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-phenylpropan-1-ol Formate

NMR: ^{1}H NMR (400 MHz, MeOD) δ 8.52 (s, 1H), 6.98 - 7.42 (m, 8H), 4.49 - 4.67 (m, 1H), 3.51 - 3.69 (m, 1H), 2.92 - 3.26 (m, 8H), 2.51 - 2.80 (m, 2H), 2.19 - 2.42 (m, 4H), 1.66 - 2.13 (m, 4H)

Mass Spec: ES$^+$ 336

2.131 Example 131

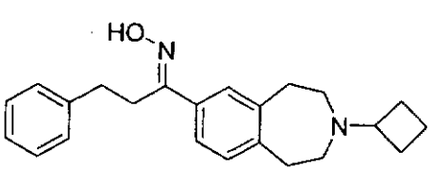


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-phenylpropan-1-one O-methyl oxime

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.54 - 1.81 (m, 4 H) 1.93 (br. s., 2 H) 2.01 - 2.18 (m, 2 H) 2.45 (br. s., 3 H) 2.73 - 3.06 (m, 6 H) 3.07 - 3.22 (m, 2 H) 3.61 (s, 3 H) 6.69 (s, 1 H) 6.76 - 6.90 (m, 1 H) 7.04 - 7.13 (m, 1 H) 7.13 - 7.21 (m, 3 H) 7.21 - 7.34 (m, 2 H)

Mass Spec: ES$^+$ 363

2.132 Example 132

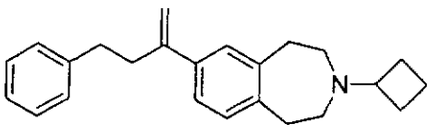


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-phenylpropan-1-one oxime

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 - 7.61 (m, 9H), 3.02 - 3.12 (m, 2H), 2.85 - 3.01 (m, 6H), 2.73 - 2.85 (m, 1H), 2.47 (br. s., 4H), 2.02 - 2.17 (m, 2H), 1.84 - 2.02 (m, 2H), 1.48 - 1.79 (m, 2H)

Mass Spec: ES$^+$ 349

2.133 Example 133

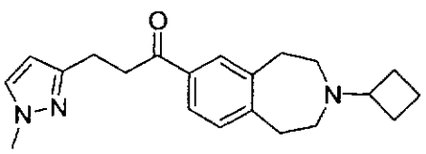


3-cyclobutyl-7-(4-phenylbut-1-en-2-yl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 - 7.40 (m, 7H), 7.02 - 7.13 (m, 1H), 5.22 - 5.38 (m, 1H), 5.04 (s, 1H), 2.93 (br. s., 4H), 2.68 - 2.86 (m, 5H), 2.47 (br. s., 4H), 1.99 - 2.17 (m, 2H), 1.82 - 2.00 (m, 2H), 1.51 - 1.79 (m, 2H)

Mass Spec: ES^+ 332

2.134 Example 134

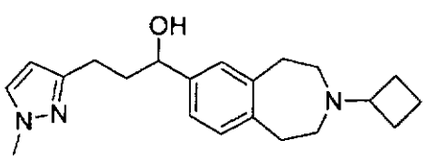


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(1-methyl-1H-pyrazol-3-yl)propan-1-one

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 - 7.82 (m, 2H), 7.22 - 7.31 (m, 1H), 7.12 - 7.22 (m, 1H), 6.04 - 6.14 (m, 1H), 3.85 (s, 3H), 3.29 - 3.41 (m, 2H), 3.07 (t, J = 7.58 Hz, 2H), 2.97 (br. s., 4H), 2.71 - 2.84 (m, 1H), 2.45 (br. s., 4H), 2.02 - 2.16 (m, 2H), 1.82 - 2.01 (m, 2H), 1.53 - 1.79 (m, 2H)

Mass Spec: ES^+ 338

2.135 Example 135

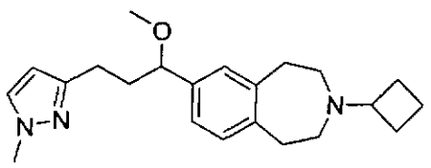


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(1-methyl-1H-pyrazol-3-yl)propan-1-ol

NMR: ^{1}H NMR (400 MHz, MeOD) δ 7.35 - 7.54 (m, 1H), 6.94 - 7.24 (m, 3H), 5.94 - 6.21 (m, 1H), 4.46 - 4.71 (m, 1H), 3.69 - 3.90 (m, 3H), 2.75 - 3.04 (m, 5H), 2.29 - 2.73 (m, 6H), 1.84 - 2.28 (m, 5H), 1.55 - 1.82 (m, 3H)

Mass Spec: ES^+ 323 (M-16)

2.136 Example 136



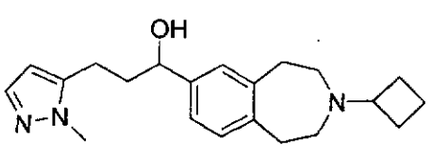
3-cyclobutyl-7-(1-methoxy-3-(1-methyl-1H-pyrazol-3-yl)propyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine Hydrochloride

NMR: ^{1}H NMR (400 MHz, MeOD) δ 7.74 - 8.08 (m, 1H), 6.98 - 7.38 (m, 3H), 6.31 - 6.53 (m, 1H), 4.10 - 4.26 (m, 1H), 3.93 - 4.09 (m, 3H), 3.60 - 3.85 (m, 4H), 3.33 - 3.50 (m, 2H), 2.98 - 3.24 (m, 4H), 2.65 - 2.96 (m, 4H), 2.26 - 2.62 (m, 4H), 1.68 - 2.22 (m, 4H)

Mass Spec: ES$^+$ 322 (M-32)

2.137 Example 137

1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(1-methyl-1H-pyrazol-5-yl)propan-1-ol

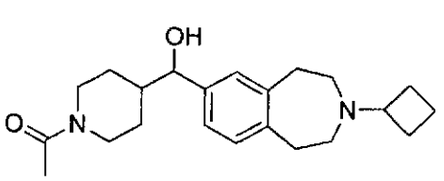


^{1}H NMR: (400 MHz, MeOD) δ 7.34 (s, 1H), 7.06 - 7.18 (m, 3H), 6.09 (s, 1H), 4.52 - 4.70 (m, 1H), 3.66 - 3.79 (m, 3H), 2.79 - 3.01 (m, 5H), 2.61 - 2.79 (m, 2H), 2.49 (br. s., 4H), 1.87 - 2.19 (m, 6H), 1.59 - 1.82 (m, 2H)

MS ES$^+$: 340

2.138 Example 138

1-(4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)(hydroxy)methyl)piperidin-1-yl)ethanone

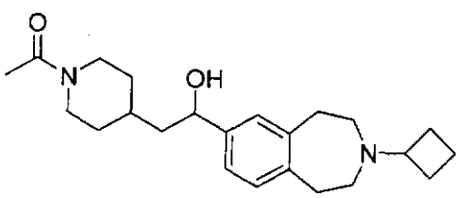


^{1}H NMR: (400 MHz, MeOD) δ 7.00 - 7.16 (m, 3H), 4.42 - 4.64 (m, 1H), 4.27 - 4.34 (m, 1H), 3.80 - 4.01 (m, 1H), 2.78 - 3.12 (m, 6H), 2.36 - 2.63 (m, 5H), 1.61 - 2.21 (m, 10H), 1.05 - 1.44 (m, 4H)

MS ES$^+$: 357

2.139 Example 139

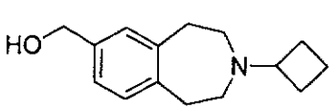
1-(4-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxyethyl)piperidin-1-yl)ethanone



^{1}H NMR: (400 MHz, MeOD) δ 7.00 - 7.18 (m, 3H), 4.66 - 4.74 (m, 1H), 4.42 - 4.55 (m, 1H), 3.84 - 3.96 (m, 1H), 3.01 - 3.16 (m, 1H), 2.86 - 3.01 (m, 5H), 2.46 - 2.69 (m, 5H), 2.05 - 2.20 (m, 5H), 1.91 - 2.05 (m, 2H), 1.62 - 1.91 (m, 6H), 1.48 - 1.62 (m, 1H), 1.03 - 1.31 (m, 2H)

MS ES$^+$: 371

2.140 Example 140

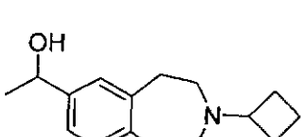


(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methanol

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) δ 7.01 - 7.15 (m, 3H), 4.55 (s, 2H), 2.72 - 3.03 (m, 5H), 2.30 - 2.61 (m, 4H), 2.05 - 2.19 (m, 2H), 1.86 - 2.04 (m, 2H), 1.59 - 1.81 (m, 2H)

MS ES$^+$: 232

2.141 Example 141

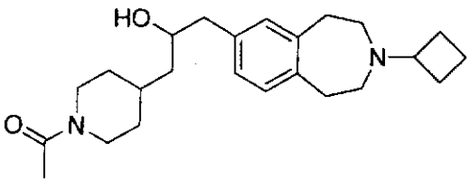


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethanol

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) δ7.04 - 7.16 (m, 3H), 4.75 - 4.81 (m, 1H), 2.81 - 2.98 (m, 5H), 2.41 - 2.59 (m, 4H), 2.07 - 2.17 (m, 2H), 1.89 - 2.03 (m, 2H), 1.63 - 1.79 (m, 2H), 1.39 - 1.46 (m, 3H)

MS ES$^+$: 246

2.142 Example 142 racemic

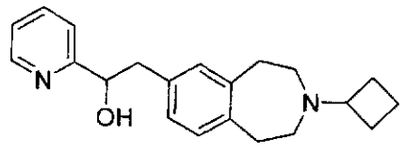


1-(4-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)ethanone

^{1}H NMR (400 MHz, MeOD) δ 6.92 - 7.09 (m, 3H), 4.38 - 4.54 (m, 1H), 3.81 - 3.96 (m, 2H), 3.01 - 3.17 (m, 1H), 2.81 - 2.98 (m, 5H), 2.38 - 2.76 (m, 7H), 2.05 - 2.18 (m, 5H), 1.90 - 2.04 (m, 2H), 1.61 - 1.89 (m, 5H), 1.28 - 1.48 (m, 2H), 0.83 - 1.27 (m, 2H)

MS ES+ :385

2.143 Example 143



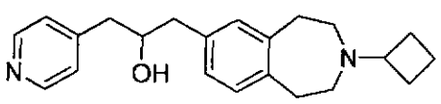
2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-(pyridin-2-yl)ethanol

^{1}H NMR (400 MHz, MeOD) δ 8.41 - 8.53 (m, 1H), 7.75 - 7.87 (m, 1H), 7.41 - 7.57 (m, 1H), 7.26 - 7.37 (m, 1H), 6.85 - 7.02 (m, 3H), 4.86 - 4.97 (m, 1H), 3.04 - 3.14 (m, 1H), 2.77 - 2.98 (m, 6H), 2.46 (br. s., 4H), 2.04 - 2.20 (m, 2H), 1.87 - 2.03 (m, 2H), 1.57 - 1.82 (m, 2H)

MS ES+ :323

2.144 Example 144 racemic

1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(pyridin-4-yl)propan-2-ol

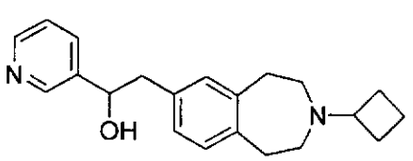


^{1}H NMR (400 MHz, MeOD) δ 8.29 - 8.36 (m, 2H), 7.19 - 7.28 (m, 2H), 6.88 - 7.02 (m, 3H), 3.94 - 4.03 (m, 1H), 2.75 - 2.91 (m, 6H), 2.59 - 2.73 (m, 3H), 2.43 (br. s., 4H), 1.99 - 2.12 (m, 2H), 1.82 - 1.98 (m, 2H), 1.55 - 1.75 (m, 2H)

MS ES+ :337

2.145 Example 145

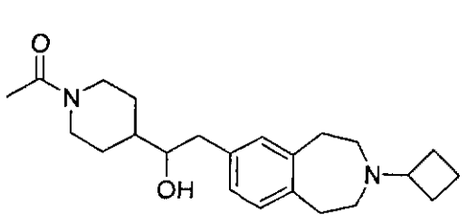
2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-(pyridin-3-yl)ethanol



^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.61 – 8.62 (m, 1H), 8.53 – 8.55 (m, 1H), 7.73 – 7.75 (m, 1H), 7.28 – 7.31 (m, 1H), 7.03 – 7.05 (m, 1H), 6.96 – 6.98 (m, 2H), 4.92 – 4.95 (m, 1H), 2.88 – 3.04 (m, 2H), 2.86 (s, 4H), 2.78 (s, 1H), 2.53 (s, 1H), 2.44 (s, 4H), 2.04 – 2.10 (m, 2H), 1.63 (s, 2H), 1.58 – 1.72 (m, 2H).

MS ES^+: 323

2.146 Example 146 racemic



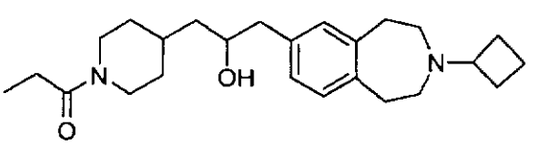
1-(4-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-hydroxyethyl)piperidin-1-yl)ethanone

^{1}H NMR (400 MHz, MeOD) δ 6.95 - 7.09 (m, 3H), 4.51 - 4.66 (m, 1H), 3.97 (br. s., 1H), 3.54 - 3.69 (m, 1H), 3.01 - 3.13 (m, 1H), 2.73 - 2.99 (m, 6H), 2.34 - 2.69 (m, 6H), 2.05 - 2.20 (m, 5H), 1.84 - 2.05 (m, 3H), 1.56 - 1.82 (m, 4H), 1.16 - 1.56 (m, 2H)

MS ES+ :371

2.147 Example 147

1-(4-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)propan-1-one - racemate

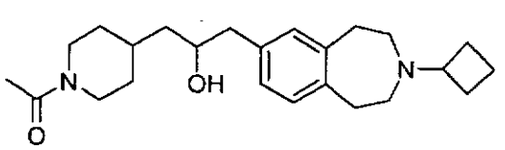


^{1}H NMR: (400 MHz, MeOD) δ 6.92 - 7.06 (m, 3 H), 4.42 - 4.53 (m, 1 H), 3.80 - 3.98 (m, 2 H), 2.98 - 3.17 (m, 1 H), 2.79 - 2.97 (m, 5 H), 2.34 - 2.76 (m, 9 H), 2.06 - 2.18 (m, 2 H), 1.89 - 2.04 (m, 2 H), 1.59 - 1.89 (m, 5 H), 1.26 - 1.48 (m, 2 H), 1.11 (m, 5 H)

MS ES$^+$: 399

2.148 Example 148

1-(4-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)ethanone – single enantiomer

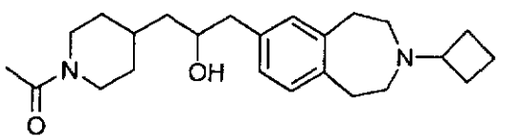


^{1}H NMR: (400 MHz, MeOD) δ

MS ES$^+$:

2.149 Example 149

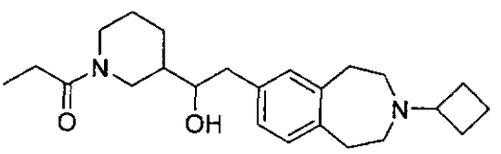
1-(4-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)ethanone – single enantiomer



^{1}H NMR: (400 MHz, MeOD) δ

MS ES$^+$:

2.150 Example 150 (racemic)

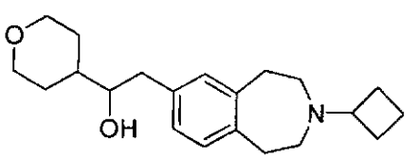


1-(4-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-hydroxyethyl)piperidin-1-yl)propan-1-one

^{1}H NMR (400 MHz, MeOD) δ 6.72 - 6.88 (m, 3H), 4.38 (br. s., 1H), 3.79 (br. s., 1H), 3.32 - 3.44 (m, 1H), 2.76 - 2.90 (m, 1H), 2.52 - 2.76 (m, 6H), 2.12 - 2.48 (m, 8H), 1.90 (br. s., 2H), 1.63 - 1.84 (m, 3H), 1.33 - 1.59 (m, 4H), 1.13 (br. s., 2H), 0.85 - 0.96 (m, 3H)

MS ES+ :385

2.151 Example 151 racemic

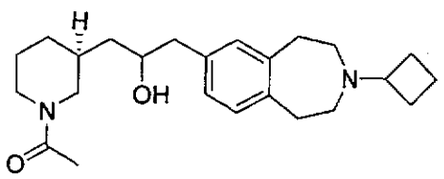


2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-(tetrahydro-2H-pyran-4-yl)ethanol

^{1}H NMR (400 MHz, MeOD) δ 6.92 - 7.08 (m, 3H), 3.90 - 4.06 (m, 2H), 3.49 - 3.62 (m, 1H), 3.37 - 3.45 (m, 1H), 2.75 - 2.99 (m, 7H), 2.32 - 2.66 (m, 5H), 2.05 - 2.19 (m, 2H), 1.87 - 2.04 (m, 2H), 1.38 - 1.85 (m, 7H)

MS ES+ : 330

2.152 Example 152

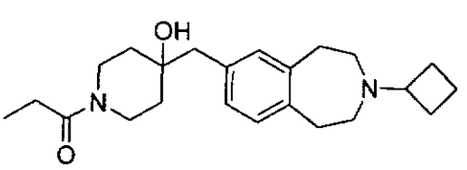


1-((3S)-3-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)ethanone

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.11 - 1.31 (m, 1 H) 1.58 (br. s., 13 H) 2.01 - 2.25 (m, 5 H) 2.77 (d, *J*=2.02 Hz, 11 H) 3.61 - 4.04 (m, 2 H) 4.25 - 4.49 (m, 1 H) 6.96 (br. s., 2 H) 7.05 (d, *J*=7.83 Hz, 1 H)

MS ES+ :385

2.153 Example 153

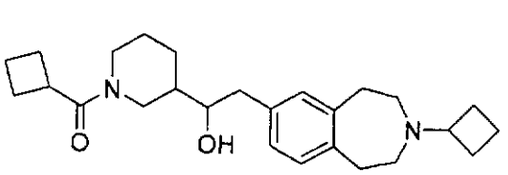


1-(4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-4-hydroxypiperidin-1-yl)propan-1-one

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 0.96 (m, 3 H) 1.15 - 1.40 (m, 4 H) 1.42 - 1.61 (m, 2 H) 1.62 - 1.80 (m, 2 H) 1.86 - 2.03 (m, 2 H) 2.11 - 2.35 (m, 6 H) 2.54 (s, 2 H) 2.60 - 2.87 (m, 6 H) 3.11 - 3.22 (m, 1 H) 3.44 - 3.57 (m, 1 H) 3.93 - 4.08 (m, 1 H) 4.29 (s, 1 H) 6.80 - 6.96 (m, 3 H)

MS ES+ :371

2.154 Example 154

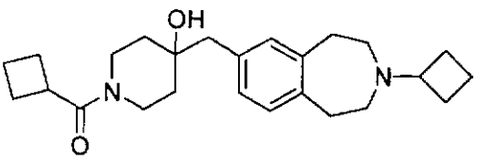


cyclobutyl(3-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-hydroxyethyl)piperidin-1-yl)methanone

^{1}H NMR (400 MHz, MeOD) δ 6.84 - 7.09 (m, 3 H) 4.43 - 4.66 (m, 1 H) 3.76 - 3.94 (m, 1 H) 3.52 - 3.66 (m, 1 H) 3.35 - 3.47 (m, 1 H) 2.93 - 3.02 (m, 1 H) 2.85 - 2.93 (m, 4 H) 2.76 - 2.83 (m, 1 H) 2.57 - 2.65 (m, 1 H) 2.52 - 2.59 (m, 1 H) 2.47 (s, 4 H) 2.06 - 2.35 (m, 6 H) 1.78 - 2.05 (m, 5 H) 1.52 - 1.78 (m, 4 H) 1.16 - 1.43 (m, 3 H).

MS ES$^+$ 411

2.155 Example 155

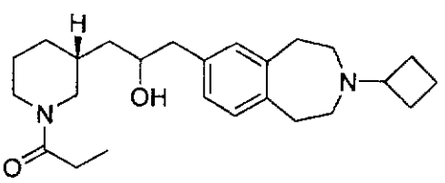


cyclobutyl(4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-4-hydroxypiperidin-1-yl)methanone

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 - 1.36 (m, 4 H) 1.42 - 1.85 (m, 6 H) 1.87 - 2.10 (m, 6 H) 2.15 - 2.39 (m, 4 H) 2.53 (s, 2 H) 2.59 - 2.89 (m, 6 H) 3.03 - 3.23 (m, 2 H) 3.28 - 3.39 (m, 1 H) 3.87 - 4.03 (m, 1 H) 4.27 (s, 1 H) 6.75 - 6.99 (m, 3 H)

MS ES+ :397

2.156 Example 156

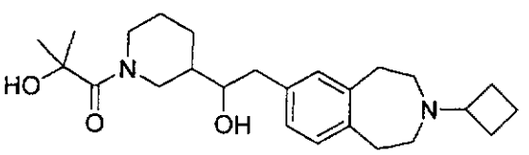


1-((3R)-3-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)ethanone

^{1}H NMR (400 MHz, MeOD) δ 6.85 - 7.11 (m, 3 H) 4.19 - 4.43 (m, 1 H) 3.68 - 3.98 (m, 2 H) 2.58 - 3.19 (m, 9 H) 2.28 - 2.57 (m, 5 H) 1.55 - 2.18 (m, 9 H) 1.01 - 1.55 (m, 8 H)

MS ES$^+$ 399

2.157 Example 157

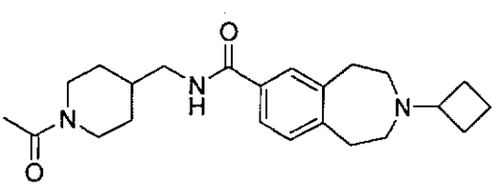


1-(4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-4-hydroxypiperidin-1-yl)-2-hydroxy-2-methylpropan-1-one

^{1}H NMR (400 MHz, DMSO-d_6) d ppm 1.28 (s, 6 H) 1.31 - 1.47 (m, 4 H) 1.49 - 1.68 (m, 2 H) 1.68 - 1.86 (m, 2 H) 1.91 - 2.07 (m, 2 H) 2.23 - 2.43 (m, 4 H) 2.60 (s, 2 H) 2.67 - 2.86 (m, 5 H) 4.33 (s, 1 H) 5.27 (s, 1 H) 6.84 - 7.06 (m, 3 H) 4H were not assigned.

MS ES+ :401

2.158 Example 158

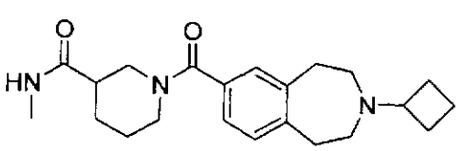


N-((1-acetylpiperidin-4-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.36 - 7.49 (m, 2H), 7.04 - 7.14 (m, 1H), 6.06 - 6.18 (m, 1H), 4.48 - 4.64 (m, 1H), 3.69 - 3.83 (m, 1H), 3.30 - 3.41 (m, 1H), 3.17 - 3.29 (m, 1H), 2.81 - 3.04 (m, 5H), 2.64 - 2.79 (m, 1H), 2.23 - 2.56 (m, 5H), 1.94 - 2.08 (m, 6H), 1.43 - 1.90 (m, 4H), 0.98 - 1.27 (m, 4H)

MS ES$^+$ 384

2.159 Example 159

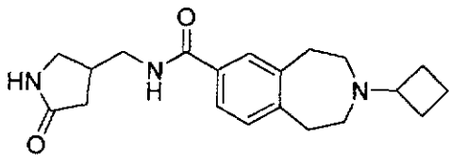


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carbonyl)-N-methylpiperidine-3-carboxamide

NMR: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.00 - 7.47 (m, 3H), 4.38 - 4.65 (m, 1H), 3.61 - 3.86 (m, 1H), 2.25 - 3.21 (m, 15H), 2.06 - 2.22 (m, 2H), 1.40 - 2.04 (m, 8H)

MS ES$^+$ 370

2.160 Example 160

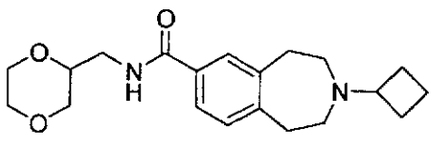


3-cyclobutyl-N-((5-oxopyrrolidin-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.52 - 7.68 (m, 2H), 7.17 - 7.29 (m, 1H), 3.39 - 3.59 (m, 3H), 3.18 - 3.28 (m, 1H), 2.93 - 3.08 (m, 4H), 2.76 - 2.92 (m, 2H), 2.36 - 2.63 (m, 5H), 2.06 - 2.26 (m, 3H), 1.87 - 2.04 (m, 2H), 1.61 - 1.82 (m, 2H)

MS ES$^+$ 342

2. 161 Example 161

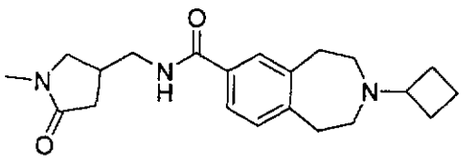


N-((1,4-dioxan-2-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.38 - 7.54 (m, 2H), 7.02 - 7.16 (m, 1H), 3.53 - 3.76 (m, 5H), 3.41 - 3.52 (m, 1H), 3.23 - 3.34 (m, 3H), 2.81 - 2.96 (m, 4H), 2.67 - 2.80 (m, 1H), 2.25 - 2.51 (m, 4H), 1.93 - 2.07 (m, 2H), 1.76 - 1.90 (m, 2H), 1.50 - 1.69 (m, 2H)

MS ES$^+$ 345

2.162 Example 162

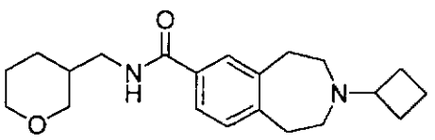


3-cyclobutyl-N-((1-methyl-5-oxopyrrolidin-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.43 - 7.57 (m, 2H), 7.12 - 7.21 (m, 1H), 6.24 - 6.39 (m, 1H), 3.40 - 3.65 (m, 3H), 3.19 - 3.28 (m, 1H), 2.90 - 3.03 (m, 4H), 2.67 - 2.89 (m, 5H), 2.35 - 2.64 (m, 5H), 2.15 - 2.28 (m, 1H), 2.03 - 2.15 (m, 2H), 1.85 - 1.99 (m, 2H), 1.58 - 1.77 (m, 2H)

MS ES$^+$ 356

2.163 Example 163

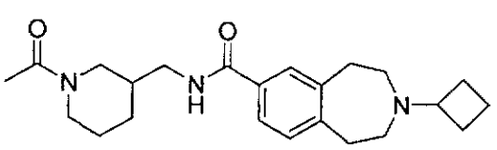


3-cyclobutyl-N-((tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.52 - 7.64 (m, 2H), 7.16 - 7.26 (m, 1H), 3.77 - 3.94 (m, 2H), 3.37 - 3.52 (m, 2H), 3.21 - 3.29 (m, 2H), 2.94 - 3.05 (m, 4H), 2.78 - 2.92 (m, 1H), 2.36 - 2.61 (m, 4H), 2.06 - 2.19 (m, 2H), 1.84 - 2.01 (m, 4H), 1.54 - 1.80 (m, 5H)

MS ES$^+$ 343

2.164 Example 164

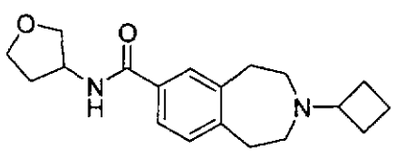


N-((1-acetylpiperidin-3-yl)methyl)-3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.53 - 7.69 (m, 2H), 7.16 - 7.28 (m, 1H), 4.23 - 4.41 (m, 1H), 3.74 - 3.92 (m, 1H), 3.13 - 3.27 (m, 2H), 2.74 - 3.09 (m, 6H), 2.39 - 2.73 (m, 4H), 2.05 - 2.18 (m, 5H), 1.64 - 2.05 (m, 7H), 1.28 - 1.61 (m, 2H), 0.83 - 0.95 (m, 1H)

MS ES$^+$ 384

2.165 Example 165

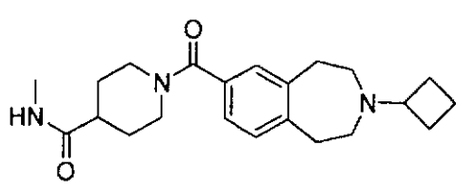


3-cyclobutyl-N-(tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.53 - 7.67 (m, 2H), 7.16 - 7.26 (m, 1H), 4.52 - 4.65 (m, 1H), 3.92 - 4.07 (m, 2H), 3.78 - 3.91 (m, 1H), 3.65 - 3.77 (m, 1H), 2.93 - 3.07 (m, 4H), 2.79 - 2.93 (m, 1H), 2.38 - 2.67 (m, 4H), 2.24 - 2.38 (m, 1H), 2.06 - 2.20 (m, 2H), 1.87 - 2.07 (m, 3H), 1.59 - 1.82 (m, 2H)

MS ES$^+$ 315

2.166 Example 166

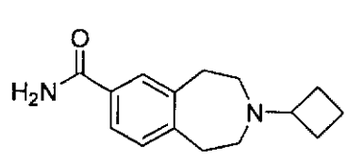


1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carbonyl)-N-methylpiperidine-4-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.14 - 7.25 (m, 3H), 4.53 - 4.76 (m, 1H), 3.74 - 3.91 (m, 1H), 2.79 - 3.21 (m, 7H), 2.67 - 2.78 (m, 4H), 2.36 - 2.63 (m, 4H), 2.06 - 2.21 (m, 2H), 1.83 - 2.03 (m, 3H), 1.55 - 1.82 (m, 5H)

MS ES$^+$ 370

2.167 Example 167

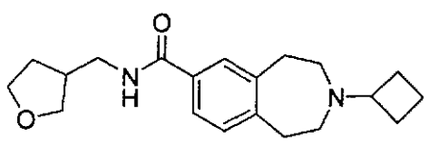


3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.64 (br. s., 2H), 7.22 (d, J = 7.83 Hz, 1H), 2.76 - 3.09 (m, 5H), 2.50 (br. s., 4H), 2.12 (br. s., 2H), 1.86 - 2.04 (m, 2H), 1.57 - 1.86 (m, 2H)

MS ES$^+$ 245

2.168 Example 168

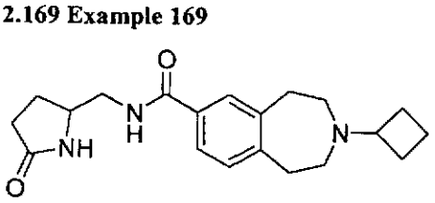


3-cyclobutyl-N-((tetrahydrofuran-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.48 - 7.67 (m, 2H), 7.12 - 7.29 (m, 1H), 3.66 - 3.96 (m, 3H), 3.53 - 3.66 (m, 1H), 3.35 - 3.45 (m, 2H), 2.91 - 3.06 (m, 4H), 2.74 - 2.92 (m, 1H), 2.28 - 2.68 (m, 5H), 1.84 - 2.19 (m, 5H), 1.57 - 1.81 (m, 3H)

MS ES$^+$ 329

2.169 Example 169

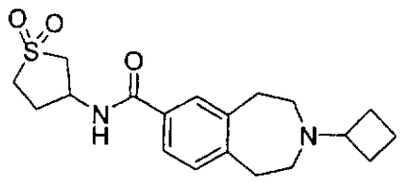


3-cyclobutyl-N-((5-oxopyrrolidin-2-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, MeOD) δ 7.42 - 7.54 (m, 2H), 7.02 - 7.16 (m, 1H), 3.74 - 3.86 (m, 1H), 3.26 - 3.43 (m, 2H), 2.81 - 2.93 (m, 4H), 2.64 - 2.80 (m, 1H), 2.28 - 2.51 (m, 4H), 2.10 - 2.29 (m, 3H), 1.92 - 2.05 (m, 2H), 1.74 - 1.90 (m, 3H), 1.50 - 1.68 (m, 2H)

MS ES$^+$ 342

2.170 Example 170

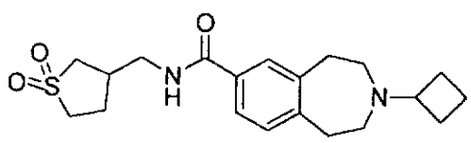


3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid (1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-amide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.58 (m, 2H), 7.09 - 7.22 (m, 1H), 6.64 - 6.80 (m, 1H), 4.95 - 5.09 (m, 1H), 3.39 - 3.53 (m, 1H), 3.05 - 3.36 (m, 3H), 2.87 - 3.03 (m, 4H), 2.72 - 2.87 (m, 1H), 2.56 - 2.69 (m, 1H), 2.31 - 2.54 (m, 4H), 2.02 - 2.15 (m, 2H), 1.81 - 1.99 (m, 2H), 1.65 - 1.78 (m, 2H)

MS ES$^+$ 363

2.171 Example 171

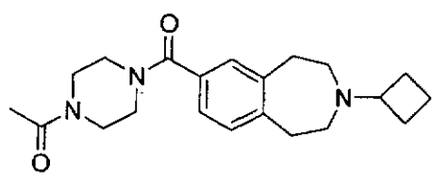


3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxylic acid (1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-ylmethyl)-amide

^{1}H NMR (400 MHz, MeOD) δ 7.55 - 7.66 (m, 2H), 7.19 - 7.26 (m, 1H), 3.45 - 3.60 (m, 2H), 3.18 - 3.29 (m, 2H), 3.05 - 3.17 (m, 1H), 2.95 - 3.05 (m, 4H), 2.74 - 2.95 (m, 3H), 2.31 - 2.62 (m, 5H), 2.06 - 2.19 (m, 2H), 1.88 - 2.04 (m, 3H), 1.62 - 1.80 (m, 2H)

MS ES$^+$ 377

2.172 Example 172

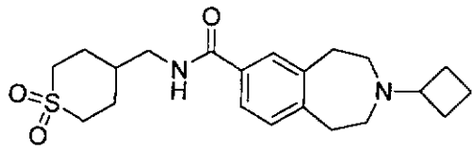


1-(4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carbonyl)piperazin-1-yl)ethanone

^{1}H NMR (400 MHz, MeOD) δ ppm 1.67 - 2.01 (m, 2 H) 2.07 - 2.28 (m, 3 H) 2.40 (br. s., 4 H) 2.70 - 2.95 (m, 2 H) 3.04 - 3.27 (m, 2 H) 3.41 - 4.00 (m, 13 H) 7.17 - 7.45 (m, 3 H)

MS ES+ 356

2.173 Example 173

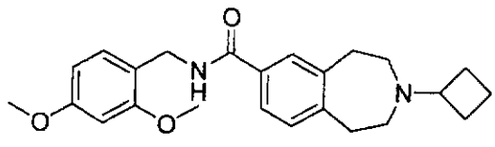


1,1-Dioxo-tetrahydro-1lambda*6*-thiopyran-4-carboxylic acid (3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ylmethyl)-amide

^{1}H NMR (400 MHz, MeOD) δ 7.00 - 7.11 (m, 3H), 4.27 - 4.35 (m, 2H), 3.06 - 3.23 (m, 5H), 2.86 - 3.00 (m, 5H), 2.42 - 2.62 (m, 4H), 2.08 - 2.36 (m, 6H), 1.90 - 2.06 (m, 2H), 1.63 - 1.81 (m, 2H)

MS ES$^+$ 391

2.174 Example 174



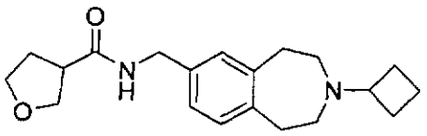
3-cyclobutyl-N-(2,4-dimethoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-carboxamide

^{1}H NMR (400 MHz, DMSO)δ 8.63 (t, 1H), 7.64 (d, 1H), 7.62 (d, 1H), 7.19 (d, 1H), 7.07 (d, 1H), 6.55 (d, 1H), 6.47 (dd, 1H), 4.35 (d, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 2.81-2.91 (m, 4H), 2.71-2.81 (m, 1H), 2.28-2.43 (bs, 4H), 1.96-2.05 (m, 2H), 1.71-1.84 (m, 2H), 1.51-1.66 (m, 2H)

MS ES$^+$ 395

2.175 Example 175

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)tetrahydrofuran-3-carboxamide

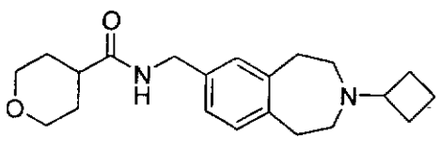


^{1}H NMR: (400 MHz, MeOD) δ 6.96 - 7.13 (m, 3H), 4.25 - 4.39 (m, 2H), 3.85 - 4.02 (m, 2H), 3.74 - 3.85 (m, 2H), 3.00 - 3.13 (m, 1H), 2.79 - 2.99 (m, 5H), 2.49 (br. s., 4H), 2.05 - 2.21 (m, 4H), 1.87 - 2.04 (m, 2H), 1.59 - 1.84 (m, 2H)

MS ES$^+$ 329

2.176 Exampel 176

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)tetrahydro-2H-pyran-4-carboxamide

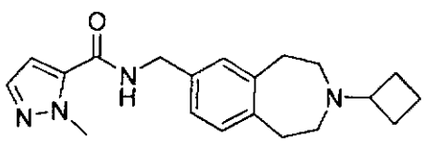


^{1}H NMR: (400 MHz, MeOD) δ 6.99 - 7.12 (m, 3H), 4.31 (s, 2H), 3.95 - 4.02 (m, 2H), 3.39 - 3.53 (m, 2H), 2.77 - 3.01 (m, 5H), 2.33 - 2.59 (m, 4H), 2.06 - 2.20 (m, 2H), 1.88 - 2.04 (m, 2H), 1.64 - 1.87 (m, 6H)

MS ES$^+$ 343

2.177 Example 177

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-1-methyl-1H-pyrazole-5-carboxamide

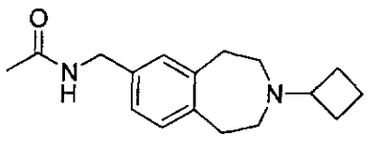


^{1}H NMR: (400 MHz, MeOD)δ 7.39 - 7.55 (m, 1H), 7.04 - 7.19 (m, 3H), 6.76 - 6.86 (m, 1H), 4.48 (s, 2H), 4.09 - 4.21 (m, 3H), 2.79 - 3.00 (m, 5H), 2.50 (br. s., 4H), 2.06 - 2.22 (m, 2H), 1.86 - 2.04 (m, 2H), 1.58 - 1.84 (m, 2H)

MS ES$^+$ 339

2.178 Example 178

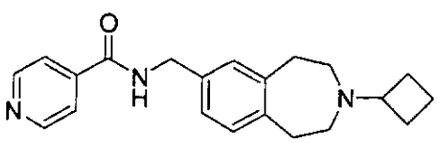
1-(4-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxyethyl)piperidin-1-yl)ethanone



^{1}H NMR: (400 MHz, MeOD) δ 6.93 - 7.24 (m, 3H), 4.30 (br. s., 2H), 2.77 - 3.03 (m, 5H), 2.48 (br. s., 4H), 2.06 - 2.21 (m, 2H), 1.88 - 2.05 (m, 5H), 1.61 - 1.82 (m, 2H)

MS ES$^+$ 273

2.179 Example 2.179

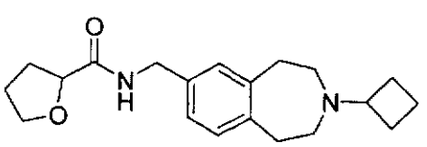


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)isonicotinamide

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) δ 8.55 - 8.80 (m, 2H), 7.74 - 7.90 (m, 2H), 7.01 - 7.22 (m, 3H), 4.40 - 4.65 (m, 2H), 2.71 - 3.03 (m, 5H), 2.25 - 2.68 (m, 4H), 2.03 - 2.18 (m, 2H), 1.85 - 2.02 (m, 2H), 1.59 - 1.80 (m, 2H)

MS ES$^+$ 336

2.180 Example 180

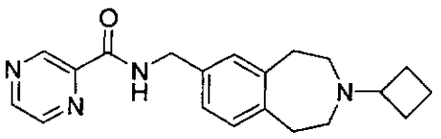


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)tetrahydrofuran-2-carboxamide

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) δ 6.93 - 7.12 (m, 3H), 4.24 - 4.41 (m, 3H), 3.93 - 4.07 (m, 1H), 3.78 - 3.93 (m, 1H), 2.70 - 3.00 (m, 5H), 2.19 - 2.59 (m, 5H), 2.03 - 2.18 (m, 2H), 1.79 - 2.04 (m, 5H), 1.58 - 1.80 (m, 2H)

MS ES$^+$ 329

2.181 Example 181

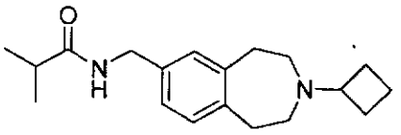


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)pyrazine-2-carboxamide

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) δ 9.20 - 9.34 (m, 1H), 8.76 - 8.87 (m, 1H), 8.61 - 8.74 (m, 1H), 7.12 - 7.27 (m, 3H), 4.50 - 4.69 (m, 2H), 3.22 - 3.61 (m, 5H), 3.02 - 3.18 (m, 4H), 2.09 - 2.43 (m, 4H), 1.71 - 1.96 (m, 2H)

MS ES$^+$ 337

2.182 Example 182

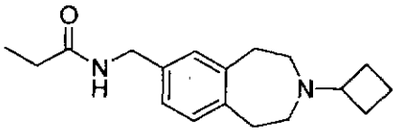


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)isobutyramide

^{1}H NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 - 6.99 (m, 3H), 5.43 - 5.62 (m, 1H), 4.21 - 4.34 (m, 2H), 2.73 - 2.88 (m, 4H), 2.60 - 2.73 (m, 1H), 2.19 - 2.45 (m, 4H), 1.89 - 2.02 (m, 2H), 1.73 - 1.88 (m, 2H), 1.44 - 1.65 (m, 3H), 1.01 - 1.12 (m, 6H)

MS ES$^+$ 301

2.183 Example 183

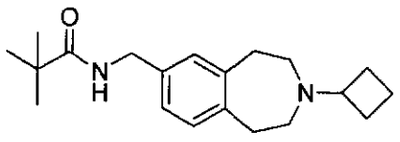


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)propionamide

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) δ6.98 - 7.11 (m, 3H), 4.28 - 4.36 (m, 2H), 2.77 - 2.98 (m, 5H), 2.37 - 2.57 (m, 4H), 2.21 - 2.30 (m, 2H), 2.05 - 2.18 (m, 2H), 1.87 - 2.02 (m, 2H), 1.63 - 1.80 (m, 2H), 1.10 - 1.21 (m, 3H)

MS ES$^+$ 287

2.184 Example 184

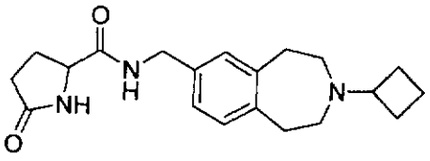


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)pivalamide

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) δ6.95 - 7.11 (m, 3H), 4.26 - 4.35 (m, 2H), 2.80 - 2.96 (m, 5H), 2.39 - 2.57 (m, 4H), 2.06 - 2.18 (m, 2H), 1.89 - 2.02 (m, 2H), 1.61 - 1.81 (m, 2H), 1.22 (s, 9H)

MS ES$^+$ 315

2.185 Example 185

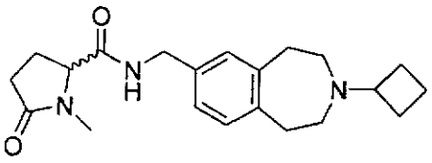


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-5-oxopyrrolidine-2-carboxamide

^{1}H NMR (400 MHz, MeOD) δ ppm 1.59 - 1.81 (m, 2 H) 1.85 - 2.03 (m, 2 H) 2.05 - 2.20 (m, 3 H) 2.24 - 2.62 (m, 7 H) 2.76 - 3.05 (m, 5 H) 4.21 (s, 1 H) 4.28 - 4.41 (m, 2 H) 7.07 (d, 3 H)

MS ES+ 342

2.186 Example 186

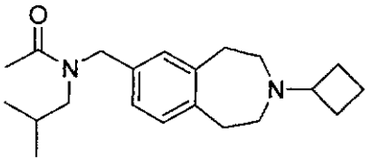


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yl)methyl)-1-methyl-5-oxopyrrolidine-2-carboxamide

^{1}H NMR (400 MHz, MeOD) δ ppm 1.50 - 1.85 (m, 2 H) 1.87 - 2.21 (m, 4 H) 2.49 (br. s., 6 H) 2.78 (s, 3 H) 2.93 (br. s., 5 H) 4.05 - 4.25 (m, 1 H) 4.37 (s, 2 H) 7.01 - 7.20 (m, 3 H)

MS ES$^+$ 326

2.187 Example 187

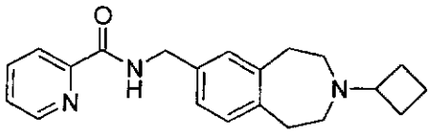


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-N-isobutylacetamide

^{1}H NMR (400 MHz, MeOD) δ 7.04 - 7.15 (m, 1H), 6.92 - 7.02 (m, 2H), 4.56 - 4.62 (m, 2H), 3.19 - 3.23 (m, 1H), 3.10 - 3.16 (m, 1H), 2.81 - 2.99 (m, 5H), 2.49 (br. s., 4H), 2.19 (s, 2H), 2.07 - 2.17 (m, 6H), 1.88 - 2.07 (m, 5H), 1.61 - 1.79 (m, 3H)

MS ES$^+$ 329

2.188 Example 188

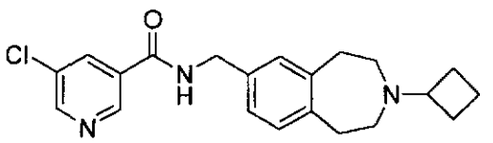


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)picolinamide

^{1}H NMR (400 MHz, DMSO) d ppm 1.41 - 1.83 (m, 2 H) 1.86 - 2.27 (m, 3 H) 2.53 - 2.76 (m, 4 H) 2.75 - 3.13 (m, 3 H) 4.33 - 4.56 (m, 2 H) 6.97 - 7.24 (m, 3 H) 7.51 - 7.69 (m, 1 H) 7.89 - 8.14 (m, 2 H) 8.56 - 8.72 (m, 1 H) 9.09 - 9.33 (m, 1 H)

MS ES+ 336

2.189 Example 189

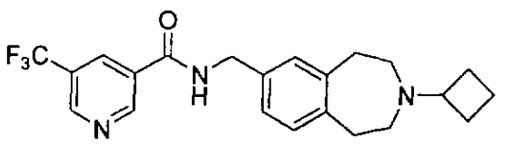


5-chloro-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)nicotinamide

^{1}H NMR (400 MHz, DMSO)δ ppm 1.44 - 1.68 (m, 2 H) 1.69 - 1.87 (m, 2 H) 1.93 - 2.08 (m, 2 H) 2.18 - 2.45 (m, 4 H) 2.82 (br. s., 5 H) 4.44 (d, 2 H) 6.98 - 7.17 (m, 3 H) 8.34 (t, 1 H) 8.79 (d, 1 H) 8.99 (d, 1 H) 9.17 - 9.30 (m, 1 H)

MS ES+ 370

2.190 Example 190

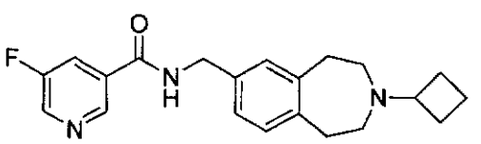


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-5-(trifluoromethyl)nicotinamide

^{1}H NMR (400 MHz, DMSOδ ppm 1.47 - 1.70 (m, 2 H) 1.70 - 1.93 (m, 2 H) 1.93 - 2.12 (m, 2 H) 2.18 - 2.46 (m, 4 H) 2.63 - 3.03 (m, 5 H) 4.39 - 4.54 (m, 2 H) 7.10 (br. s., 3 H) 8.61 (br. s., 1 H) 9.14 (s, 1 H) 9.32 (s, 2 H)

MS ES+ 404

2.191 Example 191

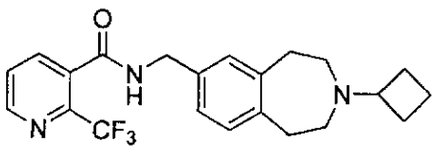


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-5-fluoronicotinamide

^{1}H NMR (400 MHz, DMSO) δ ppm 1.56 (m, 2 H) 1.69 - 1.87 (m, 2 H) 1.92 - 2.08 (m, 2 H) 2.17 - 2.43 (m, 4 H) 2.82 (br. s., 5 H) 4.41 (s, 2 H) 7.00 - 7.16 (m, 3 H) 7.42 - 7.51 (m, 1 H) 8.12 - 8.26 (m, 1 H) 8.29 - 8.42 (m, 1 H) 8.95 - 9.11 (m, 1 H)

MS ES$^+$ 354

2.192 Example 192

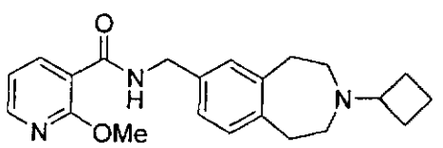


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-(trifluoromethyl)nicotinamide

^{1}H NMR (400 MHz, DMSO) δppm 1.44 - 1.68 (m, 2 H) 1.69 - 1.87 (m, 2 H) 1.92 - 2.07 (m, 2 H) 2.22 - 2.43 (m, 4 H) 2.66 - 2.90 (m, 5 H) 4.32 - 4.46 (m, 2 H) 6.99 - 7.15 (m, 3 H) 7.72 - 7.86 (m, 1 H) 7.98 - 8.12 (m, 1 H) 8.75 - 8.85 (m, 1 H) 9.06 - 9.19 (m, 1 H)

MS ES$^+$ 404

2.193 Example 193

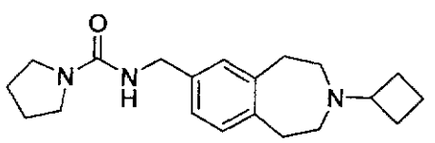


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-methoxynicotinamide

^{1}H NMR (400 MHz, DMSO) δ ppm 1.49 - 1.66 (m, 2 H) 1.69 - 1.86 (m, 2 H) 1.93 - 2.05 (m, 2 H) 2.20 - 2.43 (m, 4 H) 2.67 - 2.86 (m, 5 H) 3.97 (s, 3 H) 4.38 - 4.48 (m, 2 H) 7.02 - 7.08 (m, 3 H) 7.09 - 7.16 (m, 1 H) 8.09 - 8.16 (m, 1 H) 8.27 - 8.34 (m, 1 H) 8.67 - 8.81 (m, 1 H)

MS ES$^+$ 366

2.194 Example 194

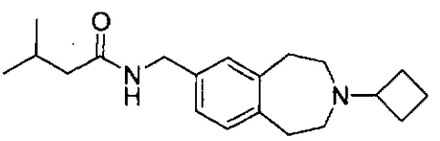


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)pyrrolidine-1-carboxamide

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.43 - 1.69 (m, 2 H) 1.79 (t, 5 H) 1.92 - 2.10 (m, 2 H) 2.13 - 2.47 (m, 4 H) 2.81 (br. s., 5 H) 3.22 (t, 4 H) 3.28 - 3.55 (m, 1 H) 4.16 (d, 2 H) 6.51 - 6.67 (m, 1 H) 7.00 (br. s., 3 H)

MS ES+ 328

2.195 Example 195

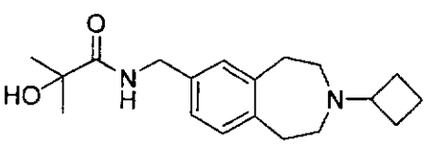


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3-methylbutanamide

^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 0.96 (d, 6 H) 1.55 - 1.81 (m, 2 H) 1.84 - 2.01 (m, 2 H) 2.03 - 2.19 (m, 5 H) 2.27 - 2.62 (m, 4 H) 2.72 - 3.03 (m, 5 H) 4.26 - 4.38 (m, 2 H) 7.05 (s, 3 H)

MS ES+ 315

2.196 Example 196

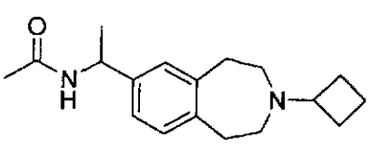


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-hydroxy-2-methylpropanamide

^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 1.15 (s, 6 H) 1.35 - 1.57 (m, 2 H) 1.61 - 1.79 (m, 2 H) 1.79 - 1.96 (m, 2 H) 2.06 - 2.38 (m, 4 H) 2.50 - 2.75 (m, 5 H) 4.05 - 4.14 (m, 2 H) 6.81 (d, 3 H)

MS ES+ 317

2.197 Example 197

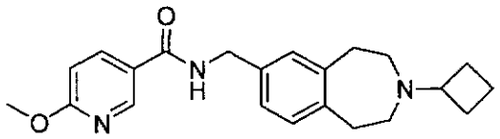


N-(1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethyl)acetamide

^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.01 - 7.11 (m, 3H), 2.79 - 2.97 (m, 5H), 2.36 - 2.58 (m, 4H), 2.06 - 2.18 (m, 3H), 1.89 - 2.01 (m, 5H), 1.61 - 1.78 (m, 2H), 1.37 - 1.46 (m, 3H)

MS ES$^+$ 287

2.198 Example 198

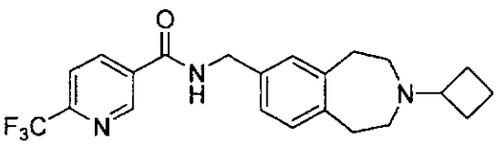


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-methoxynicotinamide

^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.72 (none, 2 H) 1.87 - 2.10 (m, 2 H) 2.08 - 2.28 (m, 2 H) 2.35 - 2.76 (m, 4 H) 2.95 (br. s., 5 H) 3.98 (s, 3 H) 4.53 (s, 2 H) 6.87 (d, 1 H) 7.05 - 7.21 (m, 3 H) 8.06 - 8.19 (m, 1 H) 8.67 (d, 1 H)

MS ES$^+$ 366

2.199 Example 199

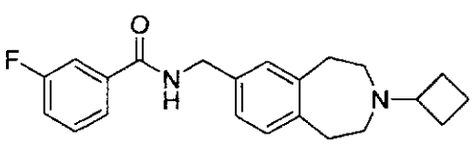


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(trifluoromethyl)nicotinamide

^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.55 (none, 2 H) 1.75 - 1.91 (m, 2 H) 1.93 - 2.12 (m, 2 H) 2.18 - 2.60 (m, 4 H) 2.82 (d, 5 H) 4.45 (s, 2 H) 7.01 (d, 3 H) 7.75 - 7.91 (m, 1 H) 8.26 - 8.44 (m, 1 H) 9.02 (s, 1 H)

MS ES$^+$ 404

2.200 Example 200

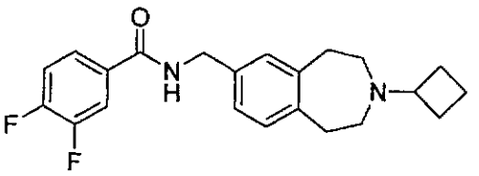


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3-fluorobenzamide

^{1}H NMR (400 MHz, DMSO) δ ppm 1.49 - 1.65 (m, 2 H) 1.69 - 1.84 (m, 2 H) 1.92 - 2.05 (m, 2 H) 2.17 - 2.44 (m, 4 H) 2.68 - 2.86 (m, 5 H) 4.34 - 4.49 (m, 2 H) 6.98 - 7.11 (m, 3 H) 7.34 - 7.43 (m, 1 H) 7.48 - 7.57 (m, 1 H) 7.64 - 7.72 (m, 1 H) 7.72 - 7.79 (m, 1 H) 9.02 - 9.15 (m, 1 H)

MS ES$^+$ 353

2.201 Example 201

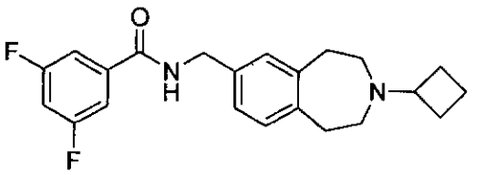


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3,4-difluorobenzamide

^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.69 (none, 2 H) 1.95 (br. s., 2 H) 2.11 (br. s., 2 H) 2.49 (br. s., 4 H) 2.93 (br. s., 5 H) 4.52 (s, 2 H) 7.11 (br. s., 3 H) 7.30 - 7.52 (m, 1 H) 7.65 - 7.88 (m, 2 H)

MS ES$^+$ 371

2.202 Example 202

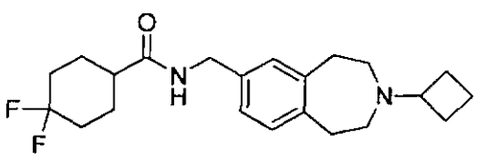


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3,5-difluorobenzamide

^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.55 - 1.86 (m, 2 H) 1.86 - 2.07 (m, 2 H) 2.07 - 2.27 (m, 2 H) 2.33 - 2.75 (m, 4 H) 2.95 (br. s., 5 H) 4.52 (s, 2 H) 7.04 - 7.27 (m, 4 H) 7.48 (dd, 2 H)

MS ES$^+$ 371

2.203 Example 203

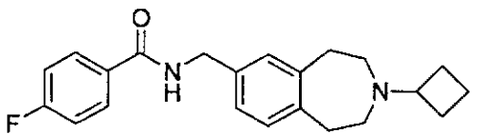


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-4,4-difluorocyclohexanecarboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61 (br. s., 4 H) 1.79 (t, 6 H) 2.01 (br. s., 4 H) 2.33 (d, 4 H) 2.80 (br. s., 5 H) 4.19 (d, 2 H) 6.87 - 7.00 (m, 2 H) 7.04 (d, *J*=7.33 Hz, 1 H) 8.30 (br. s., 1 H)

MS ES$^+$ 377

2.204 Example 204

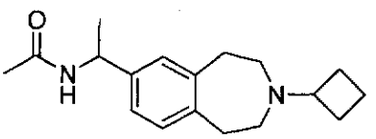


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-4-fluorobenzamide

^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.70 (none, 2 H) 1.83 - 2.04 (m, 2 H) 2.05 - 2.18 (m, 2 H) 2.34 - 2.65 (m, 4 H) 2.93 (br. s., 5 H) 4.53 (s, 2 H) 7.02 - 7.16 (m, 3 H) 7.16 - 7.26 (m, 2 H) 7.92 (d, 2 H)

MS ES$^+$ 353

2.205 Example 205

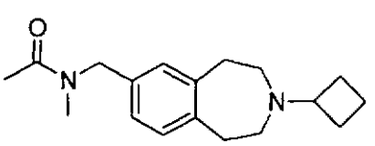


N-(1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethyl)acetamide

NMR: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.00 - 7.15 (m, 3H), 4.90 - 5.03 (m, 1H), 2.81 - 2.98 (m, 5H), 2.42 - 2.57 (m, 4H), 2.05 - 2.19 (m, 2H), 1.90 - 2.03 (m, 5H), 1.62 - 1.79 (m, 2H), 1.37 - 1.48 (m, 3H)

MS ES$^+$ 287

2.206 Example 206

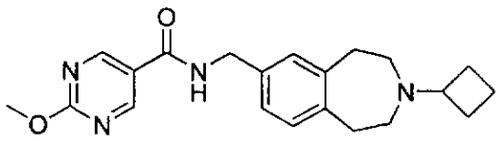


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-N-methylacetamide

NMR: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.04 - 7.17 (m, 1H), 6.92 - 7.04 (m, 2H), 4.49 - 4.60 (m, 2H), 2.80 - 3.01 (m, 8H), 2.38 - 2.57 (m, 4H), 2.07 - 2.20 (m, 5H), 1.88 - 2.03 (m, 2H), 1.60 - 1.80 (m, 2H)

MS ES$^+$ 287

2.207 Example 207

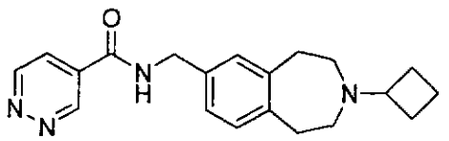


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-methoxypyrimidine-5-carboxamide

NMR: ^{1}H NMR (400 MHz, DMSO)δ 9.11 (t, 1H), 9.03 (s, 2H), 7.03-7.10 (m, 3H), 4.43 (d, 2H), 3.98 (s, 3H), 2.70-2.85 (m, 5H), 2.28-2.40 (m, 4H), 1.96-2.04 (m, 2H), 1.72-1.84 (m, 2H), 1.48-1.66 (m, 2H)

MS ES$^+$ 367

2.208 Example 208

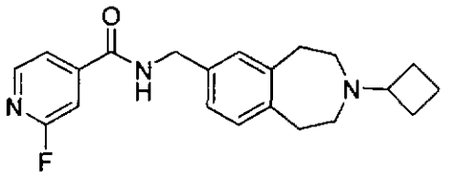


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)pyridazine-4-carboxamide

^{1}H NMR (400 MHz, DMSO)δ 9.56-9.60 (m, 1H), 9.41-9.50 (m, 2H), 8.03 (dd, 1H), 7.04-7.11 (m, 3H), 4.46 (d, 2H), 2.70-2.87 (m, 5H), 2.26-2.42 (m, 4H), 1.95-2.05 (m, 2H), 1.71-1.84 (m, 2H), 1.48-1.66 (m, 2H)

MS ES$^+$ 337

2.209 Example 209

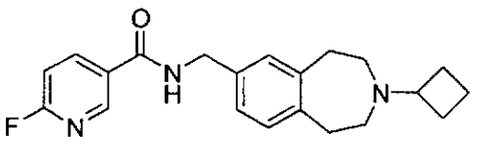


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-fluoroisonicotinamide

^{1}H NMR (400 MHz, DMSO)δ 9.40 (s, 1H), 8.47 (d, 1H), 7.84 (d, 1H), 7.63 (s, 1H), 7.09-7.17 (m, 3H), 4.50 (d, 2H), 2.87 (bs, 4H), 2.76-2.86 (m, 1H), 2.32-2.47 (bs, 4H), 2.02-2.12 (m, 2H), 1.77-1.90 (m, 2H), 1.57-1.72 (m, 2H)

MS ES$^+$ 354

2.210 Example 210

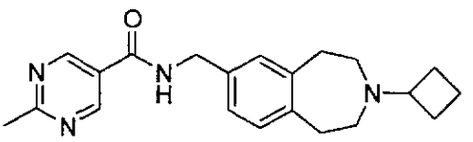


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-fluoronicotinamide

^{1}H NMR (400 MHz, DMSO)δ 9.12-9.21 (m, 1H), 8.74 (d, 1H), 8.42 (td, 1H), 7.31 (dd, 1H), 7.03-7.09 (m, 3H), 4.43 (d, 2H), 2.70-2.84 (m, 5H), 2.28-2.39 (bs, 4H), 1.95-2.04 (m, 2H), 1.72-1.83 (m, 2H), 1.50-1.66 (m, 2H)

MS ES$^+$ 354

2.211 Example 211

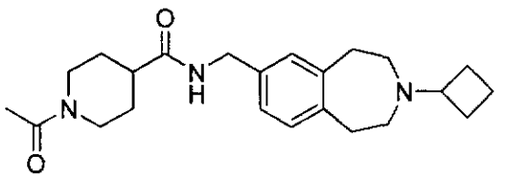


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-methylpyrimidine-5-carboxamide

^{1}H NMR (400 MHz, DMSO)δ 9.23 (t, 1H), 9.09 (s, 2H), 7.03-7.11 (m, 3H), 4.44 (d, 2H), 2.71-2.86 (m, 5H), 2.68 (s, 3H), 2.27-2.42 (m, 4H), 1.95-2.05 (m, 2H), 1.72-1.85 (m, 2H), 1.48-1.66 (m, 2H)

MS ES$^+$ 351

2.212 Example 212

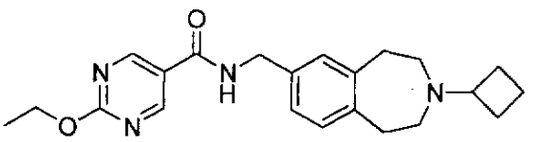


1-acetyl-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)piperidine-4-carboxamide

^{1}H NMR (400 MHz, DMSO)δ 8.10-8.18 (m, 1H), 7.00-7.06 (m, 1H), 6.91-7.00 (m, 2H), 4.28-4.40 (m, 1H), 4.20 (d, 2H), 3.76-3.87 (m, 1H), 2.99-3.09 (m 1H), 2.73-2.86 (m, 5H), 2.53-2.64 (m, 1H), 2.29-2.48 (m, 5H), 1.95-2.07 (m, 5H), 1.67-1.87 (m, 4H), 1.48-1.67 (m, 3H), 1.34-1.49 (m, 1H)

MS ES$^+$ 384

2.213 Example 213

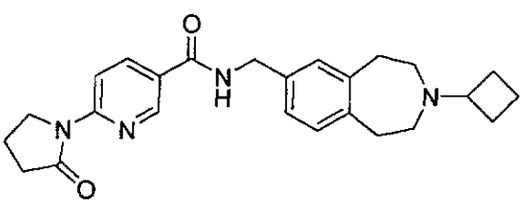


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-ethoxypyrimidine-5-carboxamide

^{1}H NMR (400 MHz, DMSO)δ 9.09 (t, 1H), 9.01 (s, 2H), 7.02-7.11 (m, 3H), 4.38-4.47 (m, 4H), 2.66-2.86 (m, 5H), 2.24-2.40 (m, 4H), 1.95-2.04 (m, 2H), 1.71-1.84 (m, 2H), 1.48-1.65 (m, 2H), 1.35 (t, 3H)

MS ES$^+$ 381

2.214 Example 214

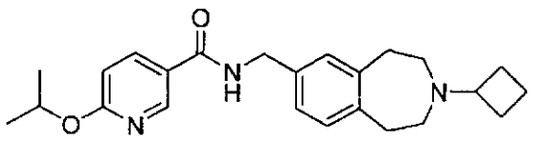


N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(2-oxopyrrolidin-1-yl)nicotinamide

^{1}H NMR (400 MHz, DMSO)δ 9.04 (t, 1H), 8.87 (d, 1H), 8.37 (d, 1H), 8.26 (dd, 1H), 7.01-7.10 (m, 3H), 4.43 (d, 2H), 4.03 (t, 2H), 2.66-2.85 (m, 5H), 2.61 (t, 2H), 2.25-2.41 (m, 4H), 1.93-2.12 (m, 4H), 1.70-1.83 (m, 2H), 1.48-1.66 (m, 2H)

MS ES$^+$ 419

2.215 Example 215



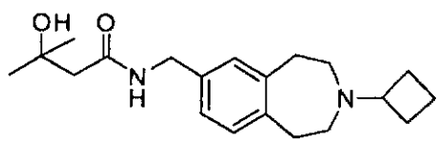
N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-isopropoxynicotinamide

^{1}H NMR (400 MHz, DMSO)δ 8.94 (t, 1H), 8.68 (d, 1H), 8.13 (dd, 1H), 7.00-7.09 (m, 3H), 6.80 (d, 1H), 5.31 (septet, 1H), 4.41 (d, 2H), 2.72-2.87 (m, 5H), 2.28-2.44 (m, 4H), 1.95-2.05 (m, 2H), 1.73-1.86 (m, 2H), 1.48-1.66 (m, 2H), 1.31 (d, 6H)

MS ES$^+$ 394

2.216 Example 216

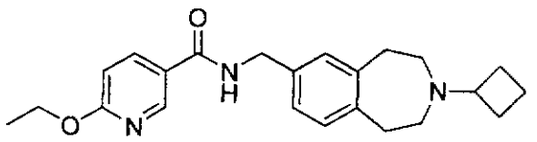
N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3-hydroxy-3-methylbutanamide



^{1}H NMR: (400 MHz, MeOD) δ 6.95 - 7.12 (m, 3 H) 4.34 (s, 2 H) 3.55 (s, 2 H) 2.88 - 2.94 (m, 4 H) 2.78 - 2.88 (m, 1 H) 2.46 (br. s., 4 H) 2.04 - 2.17 (m, 2 H) 1.87 - 2.01 (m, 2 H) 1.58 - 1.79 (m, 2 H) 1.14 - 1.19 (m, 6 H)

MS ES$^+$: 331

2.217 Example 217



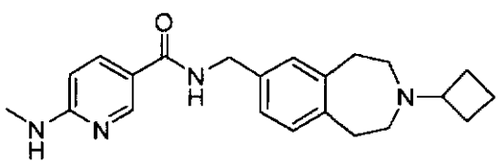
N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-ethoxynicotinamide

^{1}H NMR (400 MHz, DMSO)δ 8.95 (t, 1H), 8.68 (d, 1H), 8.14 (dd, 1H), 7.01-7.09 (m, 3H), 6.85 (d, 1H), 4.41 (d, 2H), 4.36 (quart, 2H), 2.71-2.86 (m, 5H), 2.26-2.45 (m, 4H), 1.94-2.05 (m, 2H), 1.70-1.86 (m, 2H), 1.47-1.67 (m, 2H), 1.33 (t, 3H)

MS ES$^+$ 380

2.218 Example 218

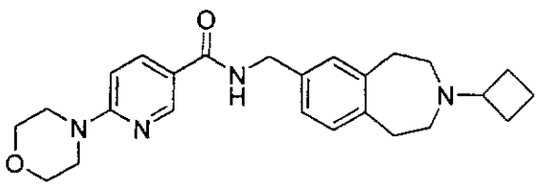
N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(methylamino)nicotinamide



^{1}H NMR: (400 MHz, DMSO-d_6) δ8.43 - 8.58 (m, 2 H), 7.77 (m, 1 H), 6.85 - 7.03 (m, 4 H), 6.36 (m, 1 H), 4.22 - 4.36 (m, 2 H), 2.73 (m, 8 H), 2.13 - 2.34 (m, 4 H), 1.85 - 2.01 (m, 2 H), 1.61 - 1.79 (m, 2 H), 1.49 (m, 2 H)

MS ES$^+$: 365

2.219 Example 219



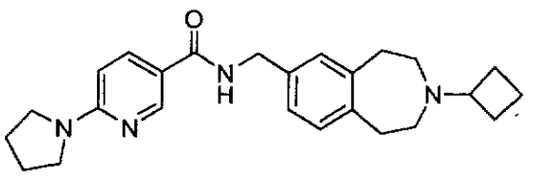
N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-morpholinonicotinamide

^{1}H NMR (400 MHz, DMSO) δ 8.72 - 8.85 (m, 1H), 8.67 (s, 1H), 7.92 - 8.11 (m, 1H), 6.95 - 7.14 (m, 3H), 6.79 - 6.92 (m, 1H), 4.17 - 4.77 (m, 2H), 3.64 - 3.81 (m, 4H), 3.46 - 3.62 (m, 4H), 2.67 - 2.90 (m, 5H), 2.19 - 2.44 (m, 4H), 1.90 - 2.09 (m, 2H), 1.68 - 1.89 (m, 2H), 1.46 - 1.68 (m, 2H)

MS ES$^+$ 421

2.220 Example 220

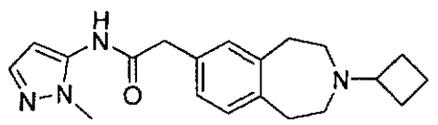
N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(pyrrolidin-1-yl)nicotinamide



^{1}H NMR: (400 MHz, DMSO-d_6) δ8.51 - 8.75 (m, 2 H), 7.95 (m, 1 H), 7.03 (br. s., 3 H), 6.45 (m, 1 H), 4.28 - 4.44 (m, 2 H), 3.38 - 3.53 (m, 4 H), 2.65 - 2.89 (m, 5 H), 2.19 - 2.42 (m, 4 H), 1.95 (br. s., 6 H), 1.66 - 1.85 (m, 2 H), 1.57 (m, 2 H)

MS ES$^+$: 404

2.221 Example 221

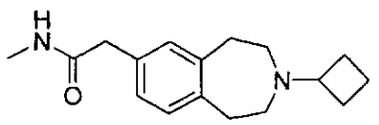


2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-N-(1-methyl-1H-pyrazol-5-yl)acetamide

^{1}H NMR (400 MHz, MeOD) δ ppm 1.60 - 1.81 (m, 2 H) 1.87 - 2.05 (m, 2 H) 2.06 - 2.20 (m, 2 H) 2.36 - 2.63 (m, 4 H) 2.81 - 3.02 (m, 5 H) 3.62 - 3.71 (m, 5 H) 6.21 (d, 1 H) 7.12 (d, 3 H) 7.34 - 7.44 (m, 1 H)

MS ES$^+$ 339

2.222 Example 222



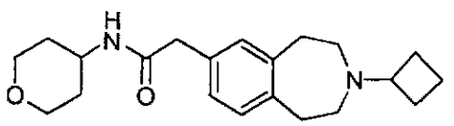
2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-N-methylacetamide

^{1}H NMR (400 MHz, MeOD) δ ppm 1.59 - 1.81 (m, 2 H) 1.86 - 2.03 (m, 2 H) 2.05 - 2.20 (m, 2 H) 2.35 - 2.60 (m, 4 H) 2.73 (s, 3 H) 2.80 - 2.99 (m, 5 H) 3.44 (s, 2 H) 7.04 (s, 3 H)

MS ES$^+$ 273

2.223 Example 223

2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-N-(tetrahydro-2H-pyran-4-yl)acetamide

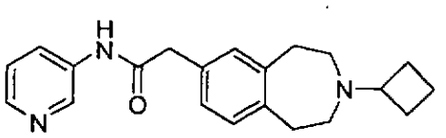


^{1}H NMR: (400 MHz, MeOD) δ 7.05 (s, 3 H), 3.79 - 4.00 (m, 3 H), 3.43 (s, 4 H), 2.77 - 2.98 (m, 5 H), 2.34 - 2.59 (m, 4 H), 2.03 - 2.19 (m, 2 H), 1.86 - 2.04 (m, 2 H), 1.59 - 1.88 (m, 4 H), 1.40 - 1.60 (m, 2 H)

MS ES$^+$: 365

2.224 Example 224

2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-*N*-(pyridin-3-yl)acetamide

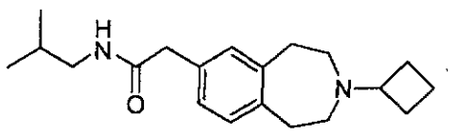


^{1}H NMR: (400 MHz, MeOD) δ 8.74 (m, 1 H), 8.22 - 8.30 (m, 1 H), 8.08 - 8.17 (m, 1 H), 7.35 - 7.44 (m, 1 H), 7.03 - 7.19 (m, 3 H), 3.67 (s, 2 H), 2.77 - 3.00 (m, 5 H), 2.30 - 2.66 (m, 4 H), 2.04 - 2.19 (m, 2 H), 1.85 - 2.04 (m, 2 H), 1.71 (m, 2 H)

MS ES$^+$: 336

2.225 Example 225

2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-*N*-isobutylacetamide

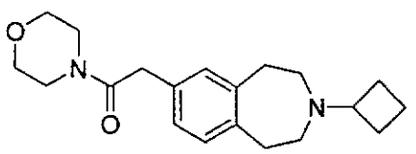


^{1}H NMR: (400 MHz, MeOD)δ 7.06 (s, 3 H), 3.42 - 3.48 (m, 2 H), 2.97 - 3.04 (m, 2 H), 2.79 - 2.96 (m, 5 H), 2.35 - 2.62 (m, 4 H), 2.06 - 2.19 (m, 2 H), 1.89 - 2.06 (m, 2 H), 1.60 - 1.86 (m, 3 H), 0.89 (m, 6 H)

MS ES$^+$: 337

2.226 Example 226

2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-morpholinoethanone

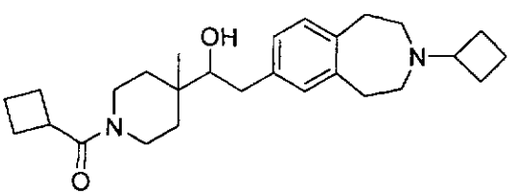


^{1}H NMR (400 MHz, MeOD) δ 6.95 - 7.15 (m, 3H), 3.74 (s, 2H), 3.57 - 3.68 (m, 4H), 3.45 - 3.56 (m, 4H), 2.77 - 2.98 (m, 5H), 2.48 (br. s., 4H), 2.06 - 2.23 (m, 2H), 1.87 - 2.05 (m, 2H), 1.60 - 1.85 (m, 2H)

MS ES$^+$: 329

2.227 Example 227

Cyclobutyl(4-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-hydroxyethyl)-4-methylpiperidin-1-yl)methanone

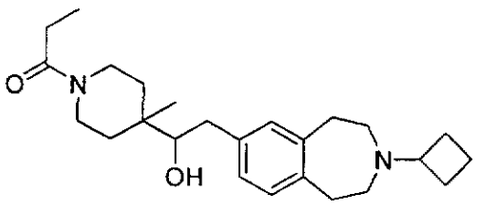


^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 6.93 (br. s., 3H), 4.13 - 4.32 (m, 1H), 3.46 - 3.59 (m, 1H), 3.36 - 3.46 (m, 1H), 3.06 - 3.33 (m, 2H), 2.66 - 3.02 (m, 7H), 2.21 - 2.51 (m, 7H), 1.83 (br. s., 8H), 1.42 - 1.76 (m, 6H), 1.30 - 1.43 (m, 1H), 1.05 (s, 3H)

MS ES$^+$: 425

2.228 Example 228 (Racemic)

1-(4-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-hydroxyethyl)-4-methylpiperidin-1-yl)propan-1-one

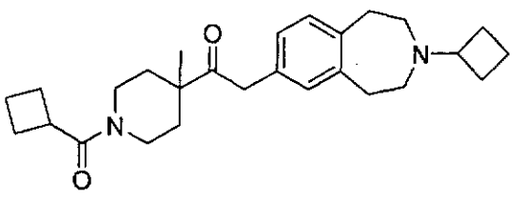


^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.09 (s, 3 H) 1.12 - 1.21 (m, 3 H) 1.35 - 1.46 (m, 1 H) 1.46 - 1.52 (m, 1 H) 1.52 - 1.79 (m, 7 H) 1.83 - 2.01 (m, 1 H) 2.02 - 2.18 (m, 2 H) 2.29 - 2.56 (m, 6 H) 2.72 - 3.04 (m, 6 H) 3.18 - 3.33 (m, 1 H) 3.39 - 3.48 (m, 1 H) 3.63 - 3.76 (m, 1 H) 4.29 - 4.42 (m, 1 H) 6.95 (br. s., 2 H) 7.03 - 7.09 (m, 1 H)

MS ES$^+$: 399

2.229 Example 229

1-(1-(cyclobutanecarbonyl)-4-methylpiperidin-4-yl)-2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)ethanone

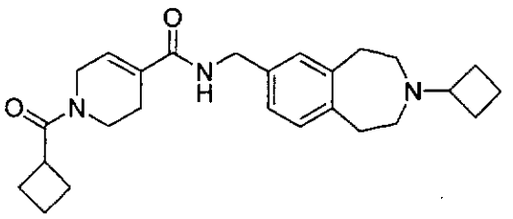


^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 7.00 - 7.05 (m, 1H), 6.85 - 6.91 (m, 2H), 3.77 - 3.86 (m, 1H), 3.66 - 3.76 (m, 2H), 3.31 - 3.41 (m, 1H), 3.22 (quin, *J* = 8.59 Hz, 1H), 3.06 - 3.17 (m, 2H), 2.71 - 2.92 (m, 5H), 2.39 (br. s., 4H), 2.18 - 2.33 (m, 2H), 2.00 - 2.16 (m, 6H), 1.74 - 1.99 (m, 3H), 1.53 - 1.73 (m, 2H), 1.42 - 1.53 (m, 1H), 1.31 - 1.42 (m, 1H), 1.22 (s, 3H)

MS ES$^+$: 423

2.230 Example 230

1-(cyclobutanecarbonyl)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-1,2,3,6-tetrahydropyridine-4-carboxamide

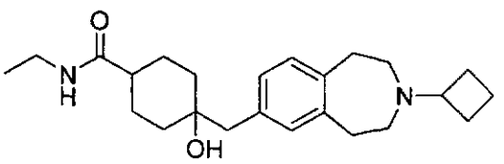


^{1}H NMR (400 MHz, DMSO-*d6*) δppm 8.24 - 8.44 (m, 1H), 6.90 - 7.06 (m, 3H), 6.46 - 6.58 (m, 1H), 4.20 - 4.30 (m, 2H), 3.93 - 4.08 (m, 2H), 3.48 - 3.58 (m, 1H), 3.33 - 3.44 (m, 2H), 2.64 - 2.86 (m, 5H), 2.20 - 2.40 (m, 6H), 2.04 - 2.20 (m, 4H), 1.83 - 2.04 (m, 3H), 1.67 - 1.83 (m, 3H), 1.49 - 1.66 (m, 2H)

MS ES$^+$: 422

2.231 Example 231

4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-N-ethyl-4-hydroxycyclohexanecarboxamide

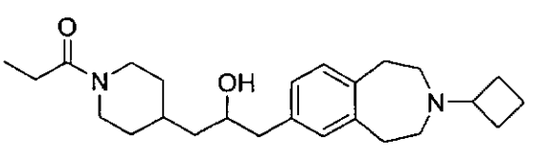


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.85 (m, 3 H) 0.98 - 1.08 (m, 2 H) 1.11 - 1.32 (m, 4 H) 1.33 - 1.74 (m, 7 H) 1.76 - 1.89 (m, 2 H) 2.05 - 2.23 (m, 4 H) 2.35 - 2.41 (m, 2 H) 2.48 - 2.68 (m, 5 H) 2.75 - 2.92 (m, 2 H) 3.73 - 3.82 (m, 1 H) 6.59 - 6.88 (m, 3 H) 7.29 - 7.45 (m, 1 H)

MS ES$^+$: 385

2.232 Example 232 (Enantiomer of Example 142)

1-(4-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)propan-1-one

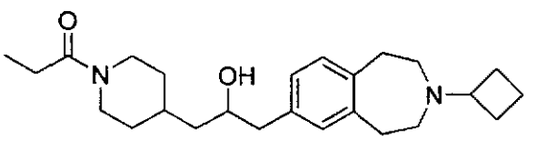


^{1}H NMR (400 MHz, MeOD) δ 6.92 - 7.09 (m, 3H), 4.38 - 4.54 (m, 1H), 3.81 - 3.96 (m, 2H), 3.01 - 3.17 (m, 1H), 2.81 - 2.98 (m, 5H), 2.38 - 2.76 (m, 7H), 2.05 - 2.18 (m, 5H), 1.90 - 2.04 (m, 2H), 1.61 - 1.89 (m, 5H), 1.28 - 1.48 (m, 2H), 0.83 - 1.27 (m, 2H)

MS ES$^+$: 385

2.233 Example 233 (Enantiomer of Example 142)

1-(4-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)propan-1-one

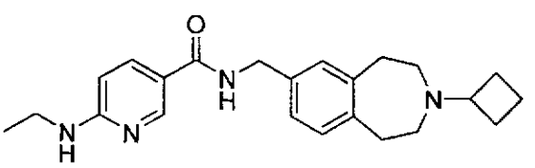


^{1}H NMR (400 MHz, MeOD) δ 6.92 - 7.09 (m, 3H), 4.38 - 4.54 (m, 1H), 3.81 - 3.96 (m, 2H), 3.01 - 3.17 (m, 1H), 2.81 - 2.98 (m, 5H), 2.38 - 2.76 (m, 7H), 2.05 - 2.18 (m, 5H), 1.90 - 2.04 (m, 2H), 1.61 - 1.89 (m, 5H), 1.28 - 1.48 (m, 2H), 0.83 - 1.27 (m, 2H)

MS ES$^+$: 385

2.234 Example 234

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(ethylamino)nicotinamide

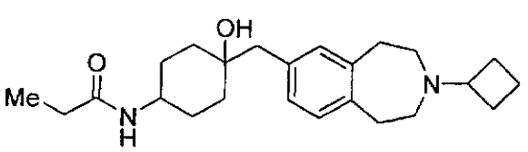


^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 8.56 - 8.66 (m, 1H), 8.49 - 8.56 (m, 1H), 7.75 - 7.87 (m, 1H), 6.92 - 7.08 (m, 4H), 6.37 - 6.46 (m, 1H), 4.29 - 4.42 (m, 2H), 3.23 - 3.29 (m, 2H), 2.64 - 2.88 (m, 5H), 2.32 (br. s., 4H), 1.91 - 2.06 (m, 2H), 1.67 - 1.84 (m, 2H), 1.45 - 1.66 (m, 2H), 1.03 - 1.19 (m, 3H)

MS ES$^+$: 379

2.235 Example 235

N-(4-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-4-hydroxycyclohexyl)propionamide

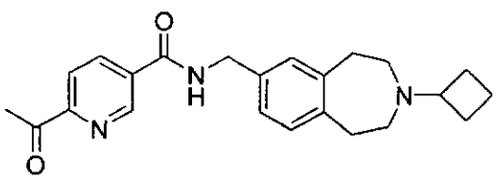


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.85 (m, 3 H) 1.08 - 1.20 (m, 2 H) 1.23 - 1.51 (m, 8 H) 1.57 - 1.70 (m, 2 H) 1.80 - 1.92 (m, 4 H) 2.12 - 2.26 (m, 4 H) 2.38 - 2.44 (m, 2 H) 2.53 - 2.70 (m, 5 H) 3.18 - 3.29 (m, 1 H) 3.85 (s, 1 H) 6.72 - 6.78 (m, 2 H) 6.79 - 6.87 (m, 1 H) 7.36 - 7.47 (m, 1 H)

MS ES$^+$: 385

2.236 Example 236

6-acetyl-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)nicotinamide

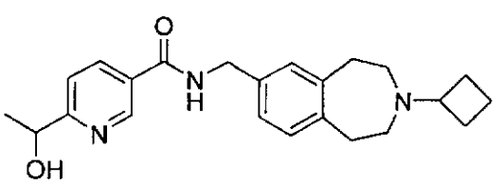


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.47 - 1.66 (m, 2 H) 1.69 - 1.88 (m, 2 H) 1.93 - 2.09 (m, 2 H) 2.23 - 2.41 (m, 4 H) 2.62 - 2.70 (m, 3 H) 2.71 - 2.92 (m, 5 H) 4.34 - 4.56 (m, 2 H) 6.98 - 7.17 (m, 3 H) 7.98 - 8.10 (m, 1 H) 8.32 - 8.45 (m, 1 H) 9.08 - 9.20 (m, 1 H) 9.26 - 9.40 (m, 1 H)

MS ES$^+$: 378

2.237 Example 237

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(1-hydroxyethyl)nicotinamide

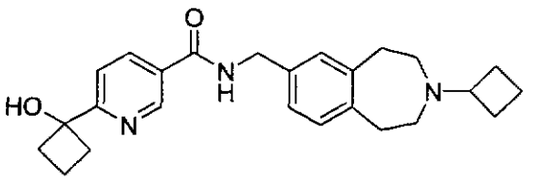


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 - 1.41 (m, 3 H) 1.51 - 1.65 (m, 2 H) 1.71 - 1.84 (m, 2 H) 1.94 - 2.06 (m, 2 H) 2.26 - 2.39 (m, 4 H) 2.71 - 2.84 (m, 5 H) 4.40 - 4.47 (m, 2 H) 4.73 - 4.83 (m, 1 H) 5.44 - 5.49 (m, 1 H) 7.02 - 7.10 (m, 3 H) 7.56 - 7.64 (m, 1 H) 8.19 - 8.27 (m, 1 H) 8.92 - 8.97 (m, 1 H) 9.03 - 9.16 (m, 1 H)

MS ES$^+$: 380

2.238 Example 238

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(1-hydroxycyclobutyl)nicotinamide

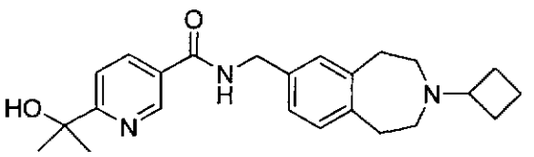


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 - 1.68 (m, 2 H) 1.72 - 2.06 (m, 6 H) 2.18 - 2.44 (m, 6 H) 2.52 - 2.60 (m, 2 H) 2.75 - 2.90 (m, 5 H) 4.39 - 4.48 (m, 2 H) 5.84 (s, 1 H) 7.02 - 7.10 (m, 3 H) 7.62 - 7.69 (m, 1 H) 8.15 - 8.23 (m, 1 H) 8.98 - 9.04 (m, 1 H) 9.06 - 9.15 (m, 1 H)

MS ES$^+$: 406

2.239 Example 239

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(2-hydroxypropan-2-yl)nicotinamide

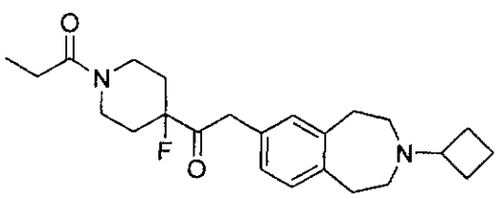


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (s, 6 H) 1.51 - 1.66 (m, 2 H) 1.68 - 1.84 (m, 2 H) 1.93 - 2.06 (m, 2 H) 2.23 - 2.42 (m, 4 H) 2.68 - 2.87 (m, 5 H) 4.36 - 4.50 (m, 2 H) 5.31 (s, 1 H) 7.00 - 7.11 (m, 3 H) 7.71 - 7.79 (m, 1 H) 8.15 - 8.25 (m, 1 H) 8.90 - 8.99 (m, 1 H) 9.02 - 9.15 (m, 1 H)

MS ES$^+$: 394

2.240 Example 240

1-(4-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)acetyl)-4-fluoropiperidin-1-yl)propan-1-one

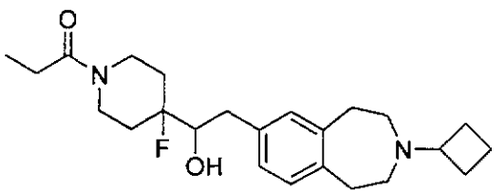


^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 0.96 - 1.07 (m, 3 H) 1.43 - 2.03 (m, 11 H) 2.20 - 2.42 (m, 5 H) 2.72 - 2.90 (m, 6 H) 3.17 - 3.34 (m, 1 H) 3.62 - 3.75 (m, 1 H) 3.79 - 3.89 (m, 2 H) 4.35 - 4.48 (m, 1 H) 6.78 - 6.89 (m, 2 H) 6.92 - 7.02 (m, 1 H)

MS ES$^+$: 401

2.241 Example 241

1-(4-(2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1-hydroxyethyl)-4-fluoropiperidin-1-yl)propan-1-one

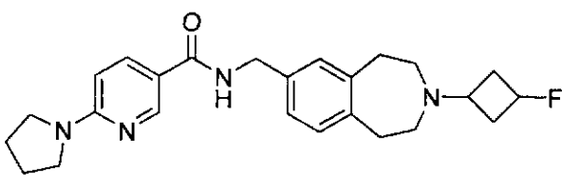


^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 1.09 - 1.19 (m, 3 H) 1.53 - 2.17 (m, 12 H) 2.30 - 2.51 (m, 5 H) 2.51 - 2.62 (m, 1 H) 2.72 - 3.00 (m, 6 H) 3.30 - 3.44 (m, 1 H) 3.66 - 3.90 (m, 2 H) 4.52 - 4.67 (m, 1 H) 6.95 - 7.15 (m, 3 H) 1H was not determined

MS ES$^+$: 403

2.242 Example 242

N-((3-(3-fluorocyclobutyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yl)methyl)-6-(pyrrolidin-1-yl)nicotinamide

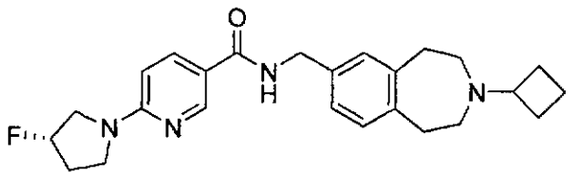


1H NMR (400 MHz, CD_3OD) δ 8.50 - 8.62 (m, 1 H) 7.89 - 8.02 (m, 1 H) 7.00 - 7.14 (m, 3 H) 6.43 - 6.56 (m, 1 H) 4.97 - 5.23 (m, 1 H) 4.49 (s, 2 H) 3.41 - 3.57 (m, 4 H) 3.11 - 3.25 (m, 1 H) 2.84 - 2.99 (m, 4 H) 2.48 (br. s., 4 H) 2.19 - 2.41 (m, 4 H) 1.97 - 2.12 (m, 4 H).

MS ES$^+$: 423.

2.243 Example 243

(*S*)-*N*-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(3-fluoropyrrolidin-1-yl)nicotinamide

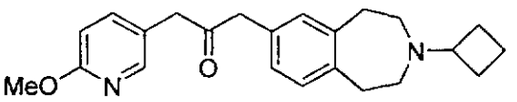


^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 - 8.83 (m, 2H), 7.84 - 8.07 (m, 1H), 6.88 - 7.20 (m, 3H), 6.27 - 6.65 (m, 1H), 5.27 - 5.58 (m, 1H), 4.24 - 4.50 (m, 2H), 3.40 - 3.98 (m, 4H), 2.66 - 2.90 (m, 5H), 1.91 (none, 12H)

MS ES$^+$: 423

2.244 Example 244

1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(6-methoxypyridin-3-yl)propan-2-one

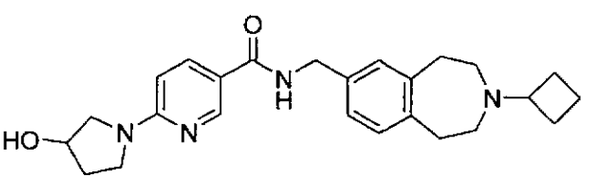


^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 1.52 - 1.82 (m, 2 H) 1.77 - 2.00 (m, 2 H) 2.01 - 2.21 (m, 2 H) 2.31 - 2.61 (m, 4 H) 2.74 - 3.02 (m, 5 H) 3.69 (s, 2 H) 3.73 (s, 2 H) 3.92 (s, 3 H) 6.67 - 6.76 (m, 1 H) 6.89 - 7.01 (m, 2 H) 7.04 - 7.14 (m, 1 H) 7.31 - 7.43 (m, 1 H) 7.87 - 7.96 (m, 1 H)

MS ES$^+$: 365

2.245 Example 245

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(3-hydroxypyrrolidin-1-yl)nicotinamide

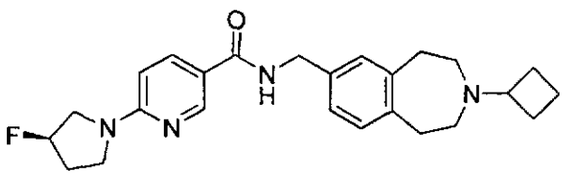


^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 - 8.78 (m, 2H), 7.84 - 8.12 (m, 1H), 6.83 - 7.15 (m, 3H), 6.22 - 6.58 (m, 1H), 4.81 - 5.08 (m, 1H), 4.17 - 4.54 (m, 3H), 3.33 - 3.65 (m, 4H), 2.64 - 2.90 (m, 5H), 2.16 - 2.41 (m, 4H), 1.76 (none, 9H)

MS ES$^+$: 421

2.246 Example 246

(*R*)-*N*-((3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-yl)methyl)-6-(3-fluoropyrrolidin-1-yl)nicotinamide

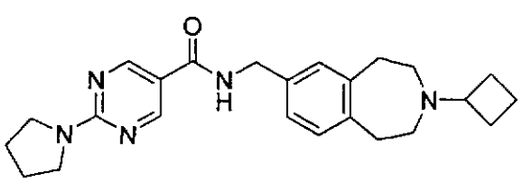


^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 - 8.83 (m, 2H), 7.84 - 8.07 (m, 1H), 6.88 - 7.20 (m, 3H), 6.27 - 6.65 (m, 1H), 5.27 - 5.58 (m, 1H), 4.24 - 4.50 (m, 2H), 3.40 - 3.98 (m, 4H), 2.66 - 2.90 (m, 5H), 1.91 (none, 12H)

MS ES$^+$: 423

2.247 Example 247

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-(pyrrolidin-1-yl)pyrimidine-5-carboxamide

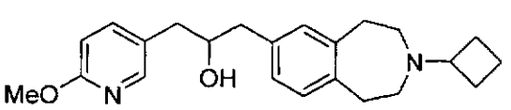


^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 3H), 6.82 - 7.23 (m, 3H), 4.24 - 4.59 (m, 2H), 3.41 - 3.65 (m, 4H), 2.63 - 3.04 (m, 4H), 2.6-2.4 (6H, overlapped by solvent peak) 2.13 - 2.42 (m, 2H), 1.77 (none, 7H)

MS ES$^+$: 407

2.248 Example 248

1-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-3-(6-methoxypyridin-3-yl)propan-2-ol

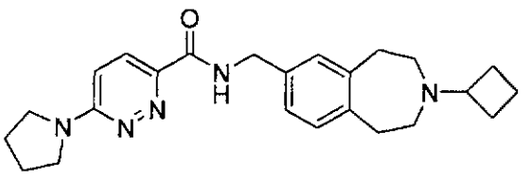


^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 1.59 - 1.78 (m, 5 H) 2.00 - 2.21 (m, 2 H) 2.29 - 2.57 (m, 4 H) 2.60 - 2.95 (m, 9 H) 3.92 (s, 3 H) 3.95 - 4.06 (m, 1 H) 6.68 - 6.76 (m, 1 H) 6.95 - 7.11 (m, 3 H) 7.47 - 7.57 (m, 1 H) 7.97 - 8.09 (m, 1 H)

MS ES$^+$: 367

2.249 Example 249

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(pyrrolidin-1-yl)pyridazine-3-carboxamide

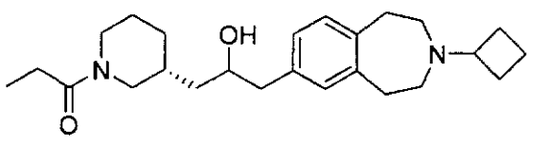


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.47 - 1.66 (m, 2 H) 1.69 - 1.85 (m, 2 H) 1.91 - 2.08 (m, 6 H) 2.22 - 2.42 (m, 4 H) 2.66 - 2.85 (m, 5 H) 3.42 - 3.62 (m, 4 H) 4.36 - 4.49 (m, 2 H) 6.91 - 6.98 (m, 1 H) 7.00 - 7.11 (m, 3 H) 7.77 - 7.88 (m, 1 H) 9.11 - 9.26 (m, 1 H)

MS ES$^+$: 406

2.250 Example 250 (Diastereomer of Example 325)

1-((3R)-3-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)propan-1-one

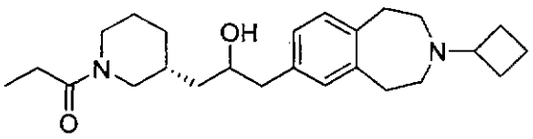


1H NMR (400 MHz, CD3OD) δ 6.89 - 7.06 (m, 3 H) 4.20 - 4.32 (m, 1 H) 3.69 - 3.97 (m, 2 H) 3.01 - 3.15 (m, 1 H) 2.77 - 2.97 (m, 5 H) 2.56 - 2.75 (m, 3 H) 2.21 - 2.56 (m, 6 H) 2.03 - 2.19 (m, 2 H) 1.88 - 2.03 (m, 2 H) 1.76 - 1.88 (m, 1 H) 1.56 - 1.76 (m, 4 H) 1.18 - 1.57 (m, 4 H) 1.02 - 1.16 (m, 3 H).

MS ES$^+$: 399

2.251 Example 251 (Diastereomer of Example 325)

1-((3R)-3-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)propan-1-one

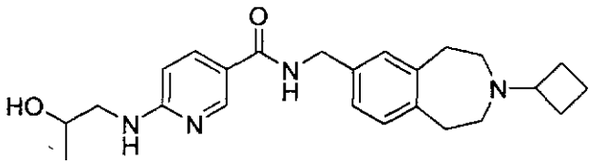


1H NMR (400 MHz, CD_3OD) δ 6.87 - 7.07 (m, 3 H) 4.20 - 4.35 (m, 1 H) 3.71 - 3.91 (m, 2 H) 2.98 - 3.11 (m, 1 H) 2.57 - 2.94 (m, 8 H) 2.28 - 2.54 (m, 6 H) 2.01 - 2.18 (m, 2 H) 1.81 - 2.01 (m, 3 H) 1.53 - 1.78 (m, 4 H) 1.25 - 1.53 (m, 3 H) 1.02 - 1.17 (m, 4 H).

MS ES^+: 399

2.252 Example 252

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(2-hydroxypropylamino)nicotinamide

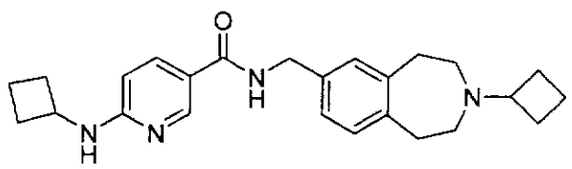


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 - 1.12 (m, 3 H) 1.48 - 1.67 (m, 2 H) 1.69 - 1.86 (m, 2 H) 1.91 - 2.08 (m, 2 H) 2.23 - 2.42 (m, 4 H) 2.67 - 2.85 (m, 5 H) 3.16 - 3.29 (m, 2 H) 3.71 - 3.86 (m, 1 H) 4.32 - 4.44 (m, 2 H) 4.70 - 4.79 (m, 1 H) 6.47 - 6.58 (m, 1 H) 6.97 - 7.08 (m, 4 H) 7.77 - 7.86 (m, 1 H) 8.49 - 8.55 (m, 1 H) 8.56 - 8.66 (m, 1 H)

MS ES^+: 409

2.253Example 253

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(cyclobutylamino)nicotinamide

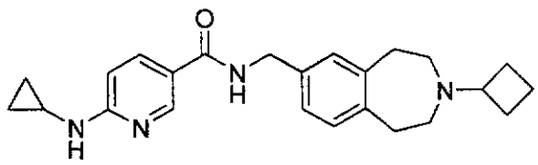


^{1}H NMR (400 MHz, MeOD-d_4)δ 8.44 - 8.52 (m, 1 H), 7.78 - 7.89 (m, 1 H), 6.99 - 7.14 (m, 3 H), 6.40 - 6.51 (m, 1 H), 4.42 - 4.53 (m, 2 H), 4.24 - 4.38 (m, 1 H), 2.71 - 2.99 (m, 5 H), 2.33 - 2.55 (m, 6 H), 2.04 - 2.17 (m, 2 H), 1.85 - 2.04 (m, 4 H), 1.54 - 1.85 (m, 4 H)

MS ES$^+$: ES$^+$

2.254 Example 254

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(cyclopropylamino)nicotinamide

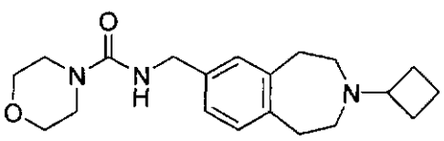


^{1}H NMR (400 MHz, MeOD-d_4) δ 8.48 - 8.60 (m, 1 H), 7.91 - 8.01 (m, 1 H), 7.03 - 7.15 (m, 3 H), 6.69 - 6.79 (m, 1 H), 4.51 (s, 2 H), 2.93 (br. s., 5 H), 2.30 - 2.67 (m, 4 H), 2.06 - 2.18 (m, 2 H), 1.86 - 2.07 (m, 2 H), 1.60 - 1.81 (m, 2 H), 0.76 - 0.91 (m, 2 H), 0.47 - 0.62 (m, 2 H)

MS ES$^+$: ES$^+$

2.255 Example 255

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)morpholine-4-carboxamide

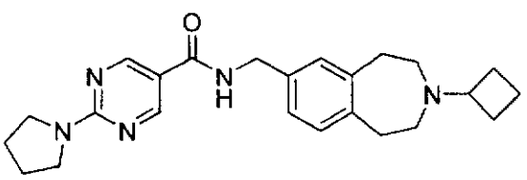


^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.85 (s, 3H), 4.33 - 4.67 (m, 1H), 4.05 - 4.31 (m, 2H), 3.37 - 3.62 (m, 4H), 3.03 - 3.28 (m, 4H), 1.66 - 3.01 (m, 16H).

MS ES$^+$: 345

2.256 Example 256

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-(pyrrolidin-1-yl)pyrimidine-5-carboxamide

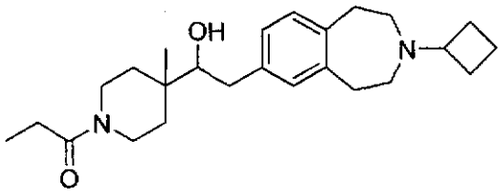


NMR: ^{1}H NMR (400 MHz, DMSO)δ 8.65 (t, 1H), 8.53 (s, 1H), 7.82 (s, 1H), 6.90-7.01 (m, 3H), 4.30 (d, 2H), 3.37-3.49 (m, 4H), 2.57-2.79 (m, 5H), 2.11-2.33 (m, 4H), 1.82-1.98 (m, 6H), 1.61-1.78 (m, 2H), 1.39-1.57 (m, 2H)

MS ES$^+$: 406

2.257 Example 257 (Enantiomer of Example 228)

1-{4-[2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-hydroxyethyl]-4-methylpiperidin-1-yl}propan-1-one

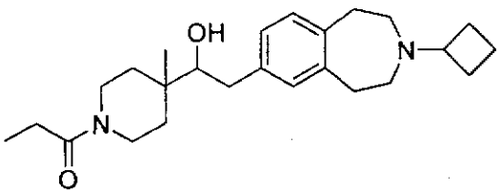


1H NMR (400 MHz, CHLOROFORM-d) d ppm 1.09 (s, 3 H) 1.12 - 1.21 (m, 3 H) 1.35 - 1.46 (m, 1 H) 1.46 - 1.52 (m, 1 H) 1.52 - 1.79 (m, 7 H) 1.83 - 2.01 (m, 1 H) 2.02 - 2.18 (m, 2 H) 2.29 - 2.56 (m, 6 H) 2.72 - 3.04 (m, 6 H) 3.18 - 3.33 (m, 1 H) 3.39 - 3.48 (m, 1 H) 3.63 - 3.76 (m, 1 H) 4.29 - 4.42 (m, 1 H) 6.95 (br. s., 2 H) 7.03 - 7.09 (m, 1 H)

MS ES$^+$: 399

2.258 Example 258 (Enantiomer of Example 228)

1-{4-[2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-hydroxyethyl]-4-methylpiperidin-1-yl}propan-1-one

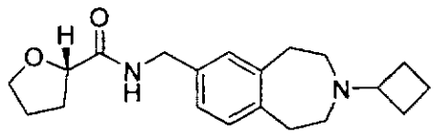


1H NMR (400 MHz, CHLOROFORM-d) d ppm 1.09 (s, 3 H) 1.12 - 1.21 (m, 3 H) 1.35 - 1.46 (m, 1 H) 1.46 - 1.52 (m, 1 H) 1.52 - 1.79 (m, 7 H) 1.83 - 2.01 (m, 1 H) 2.02 - 2.18 (m, 2 H) 2.29 - 2.56 (m, 6 H) 2.72 - 3.04 (m, 6 H) 3.18 - 3.33 (m, 1 H) 3.39 - 3.48 (m, 1 H) 3.63 - 3.76 (m, 1 H) 4.29 - 4.42 (m, 1 H) 6.95 (br. s., 2 H) 7.03 - 7.09 (m, 1 H)

MS ES$^+$: 399

2.259 Example 259

(S)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)tetrahydrofuran-2-carboxamide hydrochloride

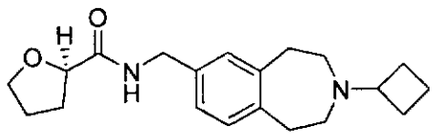


^{1}H NMR (400 MHz, DMSO-d_6)δ 10.60 - 10.88 (m, 1 H), 8.20 - 8.38 (m, 1 H), 7.07 (s, 3 H), 4.23 (m, 3 H), 3.84 - 3.99 (m, 1 H), 3.71 - 3.84 (m, 1 H), 3.55 - 3.72 (m, 1 H), 3.43 - 3.56 (m, 2 H), 3.19 - 3.30 (m, 2 H), 2.87 - 3.02 (m, 2 H), 2.64 - 2.83 (m, 2 H), 2.28 - 2.45 (m, 2 H), 2.04 - 2.26 (m, 3 H), 1.73 (m, 5 H)

MS ES$^-$:327

2.260 Example 260

(R)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)tetrahydrofuran-2-carboxamide hydrochloride

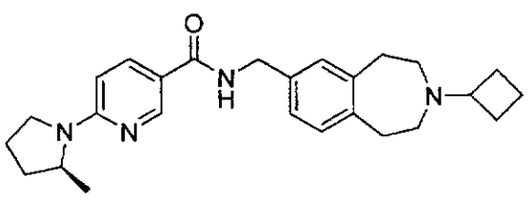


^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 - 10.90 (m, 1 H), 8.21 - 8.38 (m, 1 H), 7.07 (s, 3 H), 4.23 (s, 3 H), 3.83 - 3.98 (m, 1 H), 3.72 - 3.84 (m, 1 H), 3.55 - 3.72 (m, 1 H), 3.43 - 3.55 (m, 2 H), 3.20 - 3.29 (m, 2 H), 2.85 - 3.03 (m, 2 H), 2.62 - 2.84 (m, 2 H), 2.29 - 2.45 (m, 2 H), 2.03 - 2.27 (m, 3 H), 1.51 - 1.95 (m, 5 H)

MS ES$^+$:329

2.261 Example 261

(S)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(2-methylpyrrolidin-1-yl)nicotinamide

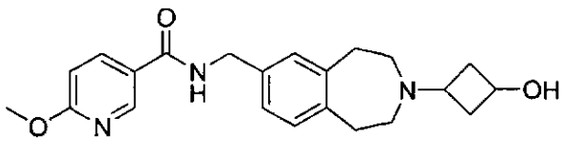


NMR: ^{1}H NMR (400 MHz, DMSO)δ 8.60-8.72 (m, 2H), 7.95 (d, 1H), 6.96-7.09 (m, 3H), 6.45 (d, 1H), 4.39 (d, 2H), 4.13-4.24 (m, 1H), 3.45-3.56 (m, 1H), 3.25-3.35 (m, 1H), 2.61-2.87 (m, 5H), 2.20-2.40 (m, 4H), 1.86-2.11 (m, 5H), 1.39-1.85 (m, 5H), 1.15 (d, 3H)

MS ES$^+$: 419

2.262 Example 262

N-((3-(3-hydroxycyclobutyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yl)methyl)-6-methoxynicotinamide

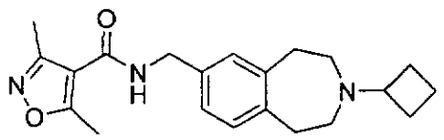


1H NMR (400 MHz, CD_3OD) δ 8.60 - 8.69 (m, 1 H) 8.04 - 8.14 (m, 1 H) 7.02 - 7.19 (m, 3 H) 6.78 - 6.89 (m, 1 H) 4.50 (s, 2 H) 3.94 (s, 3 H) 3.86 - 3.95 (m, 1 H) 2.94 (br. s., 4 H) 2.41 - 2.73 (m, 7 H) 1.76 - 1.92 (m, 2 H).

MS ES$^+$: 382.

2.263 Example 263

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-3,5-dimethyl-1,2-oxazole-4-carboxamide

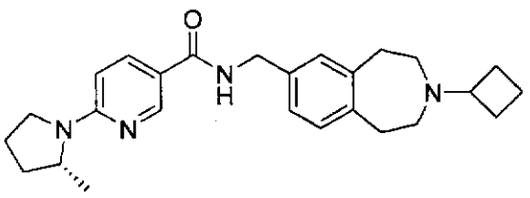


NMR: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.03 - 7.18 (m, 3H), 5.69 - 5.89 (m, 1H), 4.48 - 4.65 (m, 2H), 2.86 - 3.02 (m, 4H), 2.71 - 2.86 (m, 1H), 2.55 - 2.68 (m, 4H), 2.33 - 2.55 (m, 6H), 2.02 - 2.17 (m, 2H), 1.83 - 2.00 (m, 2H), 1.59 - 1.79 (m, 2H)

MS ES$^+$: 353

2.264 Example 264

(R)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(2-methylpyrrolidin-1-yl)nicotinamide

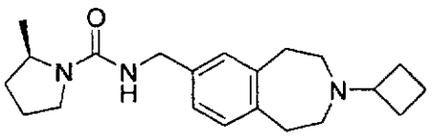


NMR: ^{1}H NMR (400 MHz, DMSO)δ 8.57-8.69 (m, 2H), 7.94 (dd, 1H), 6.98-7.07 (m, 3H), 6.46 (d, 1H), 4.38 (d, 2H), 4.15-4.24 (m, 1H), 3.47-3.55 (m, 1H), 3.25-3.35 (m, 1H), 2.63-2.85 (m, 5H), 2.24-2.40 (m, 4H), 1.89-2.11 (m, 5H), 1.48-1.84 (m, 5H), 1.16 (d, 3H)

MS ES$^+$: 419

2.265 Example 265

(*R*)-*N*-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-methylpyrrolidine-1-carboxamide

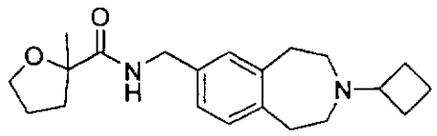


^{1}H NMR (400 MHz, METHANOL-d_4) δ 6.97 - 7.22 (m, 3H), 6.34 - 6.72 (m, 1H), 4.11 - 4.44 (m, 2H), 3.85 - 4.04 (m, 1H), 3.47 - 3.78 (m, 1H), 3.31 - 3.45 (m, 1H), 3.25 (1H, under solvent peak) 2.84 - 3.19 (m, 4H), 2.09 - 2.42 (m, 5H), 1.45 - 2.09 (m, 8H), 1.14 (none, 4H)

MS ES$^+$: 342

2.266 Example 266

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-methyltetrahydrofuran-2-carboxamide hydrochloride

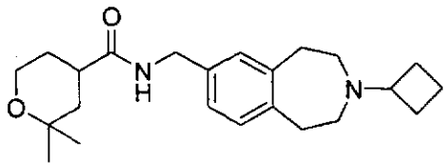


^{1}H NMR (400 MHz, DMSO-d_6)δ 10.69 - 10.97 (m, 1 H), 8.06 - 8.26 (m, 1 H), 7.07 (s, 3 H), 4.23 (m, 2 H), 3.80 - 3.97 (m, 2 H), 3.58 - 3.79 (m, 1 H), 3.42 - 3.58 (m, 2 H), 3.27 - 3.42 (m, 2 H), 2.87 - 3.03 (m, 2 H), 2.63 - 2.85 (m, 2 H), 2.30 - 2.46 (m, 2 H), 2.08 - 2.30 (m, 3 H), 1.83 - 1.97 (m, 1 H), 1.56 - 1.83 (m, 4 H), 1.33 (s, 3 H)

MS ES$^+$: ES$^+$

2.267 Example 267

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2,2-dimethyltetrahydro-2H-pyran-4-carboxamide

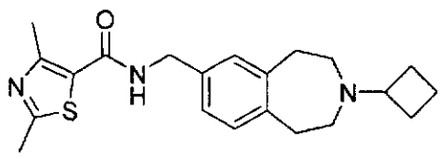


^{1}H NMR (400 MHz, MeOD-d_4) δ 6.80 - 6.94 (m, 3 H), 4.13 (s, 2 H), 3.49 - 3.62 (m, 2 H), 2.60 - 2.80 (m, 5 H), 2.43 - 2.59 (m, 1 H), 2.31 (br. s., 4 H), 1.94 (m, 2 H), 1.78 (br. s., 2 H), 1.48 (m, 6 H), 1.07 (m, 6 H)

MS ES$^+$: 371

2.268 Example 268

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2,4-dimethylthiazole-5-carboxamide

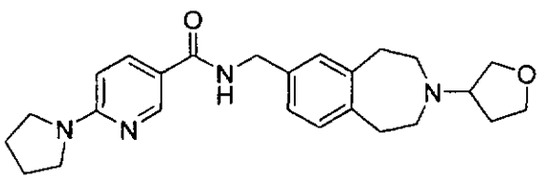


^{1}H NMR (400 MHz, MeOD-d_4) δ 6.87 - 6.99 (m, 3 H), 4.30 (s, 2 H), 2.62 - 2.83 (m, 5 H), 2.51 (s, 3 H), 2.41 (s, 3 H), 2.21 - 2.39 (m, 4 H), 1.90 - 2.01 (m, 2 H), 1.71 - 1.85 (m, 2 H), 1.54 (m, 2 H)

MS ES$^+$: 370

2.269 Example 269

6-(pyrrolidin-1-yl)-N-((3-(tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)nicotinamide

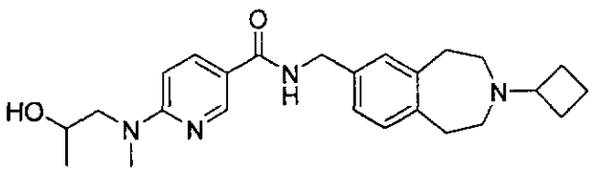


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 - 1.82 (m, 1 H) 1.86 - 2.03 (m, 5 H) 2.53 - 2.64 (m, 2 H) 2.75 - 2.89 (m, 4 H) 3.13 - 3.25 (m, 1 H) 3.38 - 3.47 (m, 4 H) 3.47 - 3.55 (m, 1 H) 3.56 - 3.66 (m, 1 H) 3.69 - 3.86 (m, 2 H) 4.31 - 4.45 (m, 2 H) 6.41 - 6.50 (m, 1 H) 6.97 - 7.09 (m, 3 H) 7.90 - 8.02 (m, 1 H) 8.58 - 8.72 (m, 2 H) 2H were overlapping with residual DMSO

MS ES$^+$: 421

2.270 Example 270

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-((2-hydroxypropyl)(methyl)amino)nicotinamide

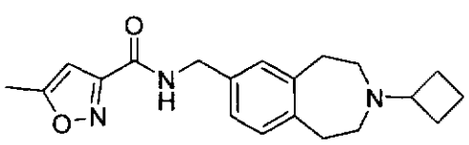


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.10 (m, 3 H) 1.50 - 1.68 (m, 2 H) 1.71 - 1.85 (m, 2 H) 1.94 - 2.09 (m, 2 H) 2.24 - 2.43 (m, 4 H) 2.68 - 2.86 (m, 5 H) 3.11 (s, 3 H) 3.37 - 3.48 (m, 1 H) 3.51 - 3.62 (m, 1 H) 3.85 - 4.00 (m, 1 H) 4.34 - 4.45 (m, 2 H) 4.69 - 4.76 (m, 1 H) 6.60 - 6.70 (m, 1 H) 6.97 - 7.11 (m, 3 H) 7.91 - 8.00 (m, 1 H) 8.59 - 8.63 (m, 1 H) 8.64 - 8.73 (m, 1 H)

MS ES$^+$: 423

2.271 Example 271

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-5-methylisoxazole-3-carboxamide

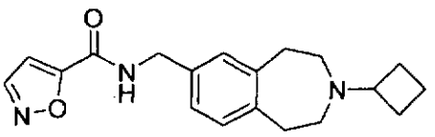


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 - 1.66 (m, 2 H) 1.69 - 1.84 (m, 2 H) 1.93 - 2.07 (m, 2 H) 2.21 - 2.41 (m, 4 H) 2.43 - 2.48 (m, 3 H) 2.69 - 2.85 (m, 5 H) 4.27 - 4.43 (m, 2 H) 6.50 - 6.58 (m, 1 H) 6.96 - 7.10 (m, 3 H) 9.08 - 9.22 (m, 1 H)

MS ES$^+$: 340

2.272 Example 272

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)isoxazole-5-carboxamide

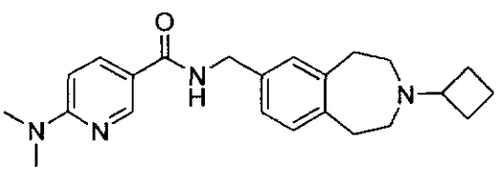


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 - 1.61 (m, 2 H) 1.62 - 1.79 (m, 2 H) 1.85 - 2.01 (m, 2 H) 2.26 (br. s., 4 H) 2.62 - 2.80 (m, 5 H) 4.24 - 4.39 (m, 2 H) 6.91 - 7.08 (m, 4 H) 8.61 - 8.74 (m, 1 H) 9.24 - 9.46 (m, 1 H)

MS ES$^+$: 326

2.273 Example 273

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-(dimethylamino)pyridine-3-carboxamide

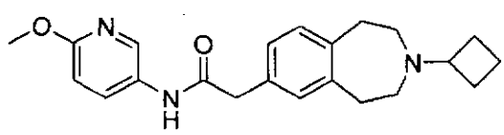


NMR: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.40 - 8.54 (m, 1H), 7.72 - 7.86 (m, 1H), 6.92 - 7.02 (m, 3H), 6.34 - 6.44 (m, 1H), 5.95 - 6.11 (m, 1H), 4.47 (d, 2H), 2.97 - 3.11 (m, 6H), 2.74 - 2.87 (m, 4H), 2.61 - 2.73 (m, 1H), 2.23 - 2.45 (m, 4H), 1.89 - 2.03 (m, 2H), 1.73 - 1.86 (m, 2H), 1.50 - 1.65 (m, 2H)

MS ES$^+$: 379, ES$^-$:377

2.274 Example 274

2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-N-(6-methoxypyridin-3-yl)acet amide

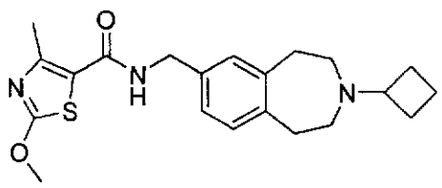


^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.31 - 8.39 (m, 1H), 7.84 - 7.95 (m, 1H), 7.05 (br. s., 3H), 6.74 - 6.82 (m, 1H), 3.81 (s, 3H), 3.55 (s, 2H), 2.82 (br. s., 5H), 2.34 (br. s., 4H), 2.00 (d, J = 5.81 Hz, 2H), 1.79 (br. s., 2H), 1.48 - 1.69 (m, 2H)

MS ES$^+$: 366

2.275 Example 275

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-methoxy-4-methylthiazole-5-carboxamide

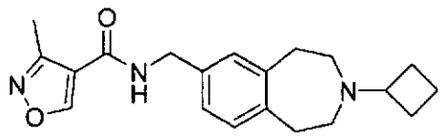


^{1}H NMR (400 MHz, MeOD) δ 6.94 (s, 3 H), 4.30 (s, 2 H), 3.94 (s, 3 H), 2.79 (br. s., 5 H), 2.35 (s, 7 H), 1.91 - 2.06 (m, 2 H), 1.71 - 1.91 (m, 2 H), 1.44 - 1.66 (m, 2 H)

MS ES$^+$: 386

2.276 Example 276

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3-methylisoxazole-4-carboxamide

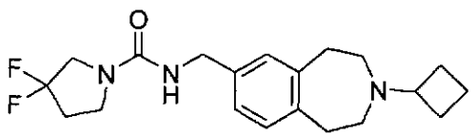


^{1}H NMR (400 MHz, MeOD)δ 9.14 (s, 1 H), 7.23 (s, 3 H), 4.59 (s, 2 H), 2.90 - 3.14 (m, 5 H), 2.60 (s, 7 H), 2.25 (m, 2 H), 2.09 (br. s., 2 H), 1.70 - 1.96 (m, 2 H)

MS ES$^+$: 340

2.277Example 277

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3,3-difluoropyrrolidine-1-carboxamide

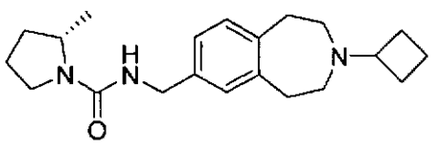


^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.07 (s, 3H), 4.21 (s, 2H), 3.42 - 3.67 (m, 7H), 3.06 - 3.17 (m, 2H), 2.90 - 3.04 (m, 2H), 2.61 - 2.76 (m, 2H), 2.12 - 2.39 (m, 6H), 1.60 - 1.91 (m, 2H)

MS ES$^+$: 364

2.278 Example 278

(*S*)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-methylpyrrolidine-1-carboxamide

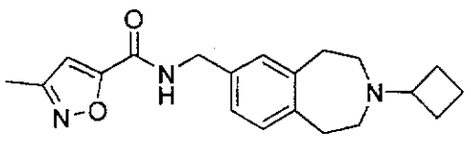


^{1}H NMR (400 MHz, METHANOL-d_4) δ 6.97 - 7.22 (m, 3H), 6.34 - 6.72 (m, 1H), 4.11 - 4.44 (m, 2H), 3.85 - 4.04 (m, 1H), 3.47 - 3.78 (m, 1H), 3.31 - 3.45 (m, 1H), 3.25 (1H, under solvent peak) 2.84 - 3.19 (m, 4H), 2.09 - 2.42 (m, 5H), 1.45 - 2.09 (m, 8H), 1.14 (none, 4H)

MS ES$^+$: 342

2.279 Example 279

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3-methylisoxazole-5-carboxamide

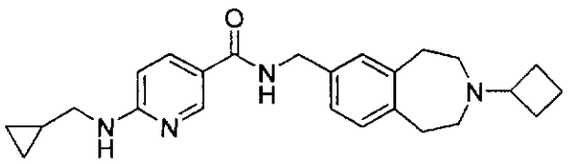


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.43 - 1.61 (m, 2 H) 1.64 - 1.79 (m, 2 H) 1.89 - 2.01 (m, 2 H) 2.19 - 2.34 (m, 7 H) 2.62 - 2.81 (m, 5 H) 4.27 - 4.36 (m, 2 H) 6.86 - 6.91 (m, 1 H) 6.93 - 7.05 (m, 3 H) 9.24 - 9.37 (m, 1 H)

MS ES$^+$: 340

2.280 Example 280

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-[(cyclopropylmethyl)amino]pyridine-3-carboxamide

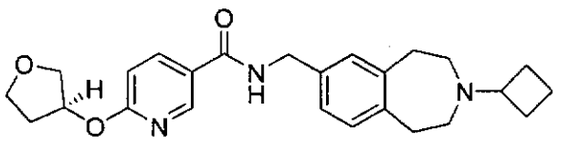


NMR: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.25 - 8.31 (m, 1H), 7.61 - 7.69 (m, 1H), 6.82 - 6.91 (m, 3H), 6.10 - 6.19 (m, 1H), 5.83 - 5.94 (m, 1H), 4.70 - 4.80 (m, 1H), 4.30 - 4.38 (m, 2H), 2.91 - 2.99 (m, 2H), 2.61 - 2.75 (m, 4H), 2.48 - 2.62 (m, 1H), 2.11 - 2.30 (m, 4H), 1.79 - 1.90 (m, 2H), 1.59 - 1.77 (m, 2H), 1.37 - 1.52 (m, 2H), 0.81 - 0.93 (m, 1H), 0.29 - 0.38 (m, 2H), -0.01 - 0.10 (m, 2H)

MS ES$^+$: 405, ES$^-$: 403

2.281 Example 281

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-[(3S)-tetrahydrofuran-3-yloxy]pyridine-3-carboxamide

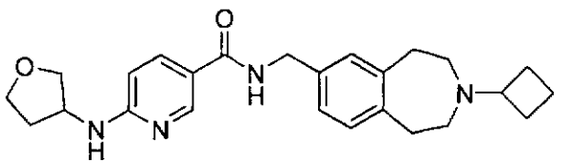


NMR: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.55 - 8.61 (m, 1H), 7.95 - 8.06 (m, 1H), 7.08 - 7.15 (m, 3H), 6.74 - 6.83 (m, 1H), 6.16 - 6.26 (m, 1H), 5.58 - 5.66 (m, 1H), 4.55 - 4.64 (m, 2H), 3.97 - 4.10 (m, 2H), 3.86 - 3.97 (m, 2H), 2.88 - 3.01 (m, 4H), 2.73 - 2.85 (m, 1H), 2.37 - 2.55 (m, 4H), 2.21 - 2.36 (m, 1H), 2.04 - 2.20 (m, 3H), 1.85 - 2.00 (m, 2H), 1.62 - 1.79 (m, 2H)

MS ES$^+$: 422, ES$^-$: 420

2.282 Example 282

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-(tetrahydrofuran-3-ylamino)pyridine-3-carboxamide

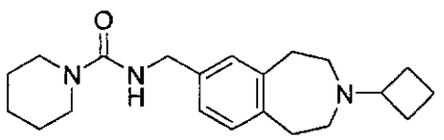


NMR: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.39 - 8.49 (m, 1H), 7.74 - 7.86 (m, 1H), 6.94 - 7.09 (m, 3H), 6.24 - 6.36 (m, 1H), 5.96 - 6.12 (m, 1H), 4.76 - 4.88 (m, 1H), 4.44 - 4.56 (m, 2H), 4.33 - 4.44 (m, 1H), 3.84 - 3.94 (m, 2H), 3.70 - 3.82 (m, 1H), 3.58 - 3.68 (m, 1H), 2.76 - 2.87 (m, 4H), 2.59 - 2.76 (m, 1H), 2.18 - 2.46 (m, 5H), 1.90 - 2.06 (m, 2H), 1.70 - 1.91 (m, 3H), 1.52 - 1.68 (m, 2H)

MS ES$^+$: 421, ES$^-$: 419

2.283 Example 283

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)piperidine-1-carboxamide

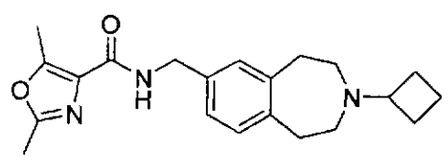


^{1}H NMR (400 MHz, METHANOL-d$_4$)δ 7.11 - 7.24 (m, 3H), 4.32 (s, 2H), 3.59 - 3.81 (m, 3H), 3.37 - 3.46 (m, 4H), 3.18 - 3.30 (m, 2H), 3.02 - 3.13 (m, 2H), 2.73 - 2.86 (m, 2H), 2.27 - 2.47 (m, 4H), 1.75 - 2.00 (m, 2H), 1.62 - 1.72 (m, 2H), 1.51 - 1.60 (m, 4H)

MS ES$^+$: 342

2.284 Example 284

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2,5-dimethyloxazole-4-carboxamide

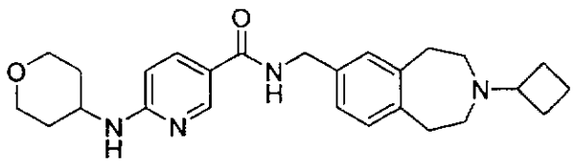


^{1}H NMR (400 MHz, MeOD) δ7.09 (m 3 H), 4.47 (s, 2 H), 2.93 (br. s., 5 H), 2.34 - 2.64 (m, 10 H), 2.05 - 2.20 (m, 2 H), 1.86 - 2.04 (m, 2 H), 1.58 - 1.84 (m, 2 H)

MS ES$^+$: 354

2.285 Example 285

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-(tetrahydro-2H-pyran-4-ylamino)pyridine-3-carboxamide

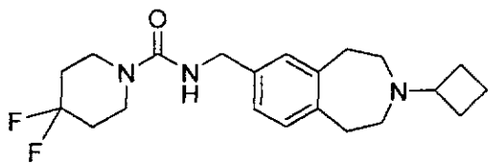


NMR: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.36 - 8.44 (m, 1H), 7.70 - 7.78 (m, 1H), 6.94 - 7.04 (m, 3H), 6.38 - 6.47 (m, 1H), 4.38 (s, 2H), 3.81 - 3.95 (m, 3H), 3.40 - 3.50 (m, 2H), 2.75 - 2.92 (m, 5H), 2.31 - 2.59 (m, 4H), 1.97 - 2.09 (m, 2H), 1.78 - 1.93 (m, 4H), 1.52 - 1.71 (m, 2H), 1.37 - 1.52 (m, 2H)

MS ES$^+$: 435

2.286 Example 286

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-4,4-difluoropiperidine-1-carboxamide

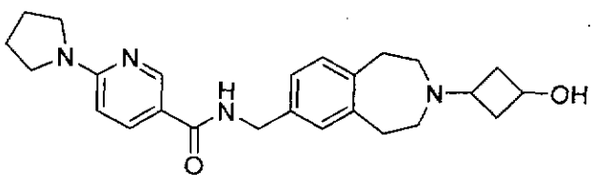


NMR: ^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.17 - 7.30 (m, 3H), 4.41 - 4.50 (m, 2H), 3.65 - 3.76 (m, 4H), 3.05 - 3.33 (m, 5H), 2.67 - 2.97 (m, 4H), 2.28 - 2.41 (m, 2H), 2.03 - 2.26 (m, 6H), 1.81 - 1.99 (m, 2H)

MS ES$^+$: 378

2.287 Example 287

N-((3-(3-hydroxycyclobutyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yl)methyl)-6-(pyrrolidin-1-yl)nicotinamide

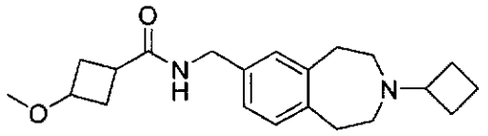


^{1}H NMR (400 MHz, CD_3OD) δ 8.55 - 8.59 (m, 1 H) 7.91 - 7.98 (m, 1 H) 7.03 - 7.12 (m, 3 H) 6.48 - 6.53 (m, 1 H) 4.49 (s, 2 H) 3.85 - 3.96 (m, 1 H) 3.44 - 3.55 (m, 4 H) 2.87 - 2.97 (m, 4 H) 2.30 - 2.60 (m, 7 H) 2.01 - 2.08 (m, 4 H) 1.75 - 1.87 (m, 2 H).

MS ES^+: 421.

2.288 Example 288

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3-methoxycyclobutanecarboxamide

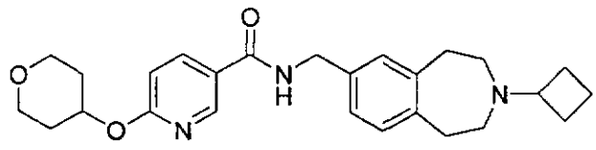


^{1}H NMR (400 MHz, MeOD) δ 6.96 - 7.15 (m, 3 H), 4.31 (m, 2 H), 4.05 - 4.19 (m, 0.3 H), 3.73 - 3.89 (m, 0.7 H), 3.25 (s, 3 H), 2.97 - 3.10 (m, 0.3 H), 2.92 (m, 5 H), 2.56 - 2.70 (m, 0.7 H), 2.33 - 2.56 (m, 6 H), 2.04 - 2.25 (m, 4 H), 1.84 - 2.05 (m, 2 H), 1.55 - 1.82 (m, 2 H)

MS ES^+: 343 (Two peaks cis and trans isomers)

2.289 Example 289

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(tetrahydro-2H-pyran-4-yloxy)nicotinamide

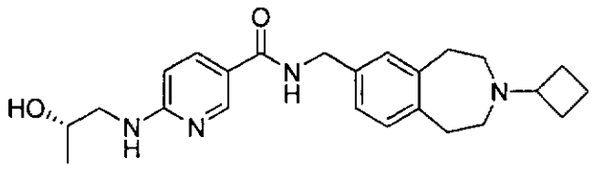


^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1 H), 8.62 - 8.72 (m, 1 H), 8.08 - 8.21 (m, 1 H), 7.05 (br. s., 3 H), 6.80 - 6.93 (m, 1 H), 5.18 - 5.32 (m, 1 H), 4.41 (m, 2 H), 3.79 - 3.88 (m, 2 H), 3.45 - 3.61 (m, 2 H), 2.81 (br. s., 5 H), 2.34 (m, 4 H), 1.92 - 2.09 (m, 4 H), 1.71 - 1.91 (m, 2 H), 1.46 - 1.71 (m, 4 H)

MS ES^+: 436

2.290 Example 290

(S)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(2-hydroxypropylamino)nicotinamide

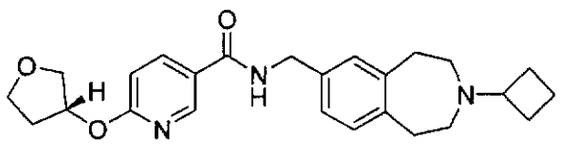


^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 0.92 (m, 3 H) 1.25 - 1.47 (m, 2 H) 1.47 - 1.67 (m, 2 H) 1.70 - 1.89 (m, 2 H) 1.99 - 2.23 (m, 4 H) 2.45 - 2.75 (m, 5 H) 2.95 - 3.09 (m, 2 H) 3.50 - 3.65 (m, 1 H) 4.11 - 4.22 (m, 2 H) 4.49 - 4.59 (m, 1 H) 6.27 - 6.36 (m, 1 H) 6.71 - 6.97 (m, 4 H) 7.54 - 7.68 (m, 1 H) 8.28 - 8.34 (m, 1 H) 8.35 - 8.49 (m, 1 H)

MS ES$^+$: 409

2.291 Example 291

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-[(3R)-tetrahydrofuran-3-yloxy]pyridine-3-carboxamide

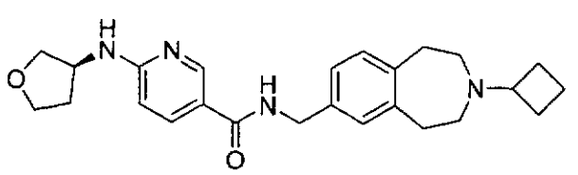


NMR: NMR: ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ 8.80 - 8.87 (m, 1H), 8.27 - 8.33 (m, 1H), 7.24 - 7.34 (m, 3H), 6.99 - 7.08 (m, 1H), 5.77 - 5.84 (m, 1H), 4.66 - 4.75 (m, 2H), 4.03 - 4.25 (m, 4H), 2.97 - 3.16 (m, 5H), 2.57 - 2.74 (m, 4H), 2.43 - 2.57 (m, 1H), 2.24 - 2.37 (m, 3H), 2.06 - 2.22 (m, 2H), 1.81 - 1.97 (m, 2H)

MS ES$^+$: 422, ES$^-$: 420

2.292 Example 292

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-[(3S)-tetrahydrofuran-3-ylamino]pyridine-3-carboxamide

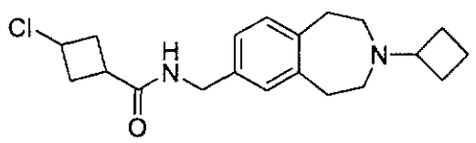


1H NMR (400 MHz, METHANOL-d4) d 8.51 - 8.60 (m, 1H), 7.84 - 7.92 (m, 1H), 7.05 - 7.18 (m, 3H), 6.53 - 6.60 (m, 1H), 4.45 - 4.56 (m, 3H), 3.94 - 4.03 (m, 2H), 3.79 - 3.91 (m, 1H), 3.64 - 3.72 (m, 1H), 2.86 - 3.04 (m, 5H), 2.44 - 2.72 (m, 4H), 2.25 - 2.37 (m, 1H), 2.10 - 2.21 (m, 2H), 1.88 - 2.07 (m, 3H), 1.64 - 1.81 (m, 2H)

MS ES$^+$: 421

2.293 Example 293

3-chloro-N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]cyclobutanecarboxamide

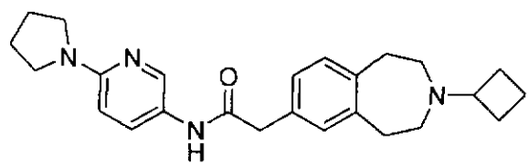


1H NMR (400 MHz, MeOD) d 6.97 - 7.11 (m, 3 H), 4.57 - 4.69 (m, 0.3 H), 4.34 - 4.46 (m, 0.7 H), 4.31 (m, 2 H), 3.23 - 3.30 (m, 0.3 H), 2.62 - 3.00 (m, 7.7 H), 2.31 - 2.65 (m, 6 H), 2.05 - 2.19 (m, 2 H), 1.86 - 2.04 (m, 2 H), 1.57 - 1.83 (m, 2 H)

MS ES$^+$: 347

2.294Example 294

2-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-[6-(pyrrolidin-1-yl)pyridin-3-yl]acetamide

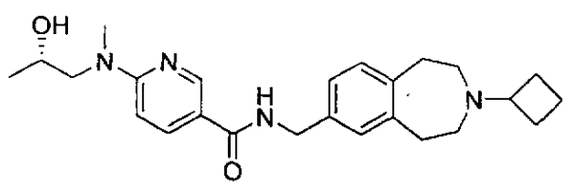


1H NMR (400 MHz, MeOD) d 8.11 - 8.20 (m, 1 H), 7.65 - 7.76 (m, 1 H), 7.05 - 7.18 (m, 3 H), 6.42 - 6.53 (m, 1 H), 3.61 (s, 2 H), 3.42 (m, 4 H), 2.96 (m, 5 H), 2.57 (br. s., 4 H), 2.15 (m, 2 H), 1.90 - 2.10 (m, 6 H), 1.75 (br. s., 2 H)

MS ES$^+$: 405

2.295 Example 295

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-{[(2S)-2-hydroxypropyl](methyl)amino}pyridine-3-carboxamide

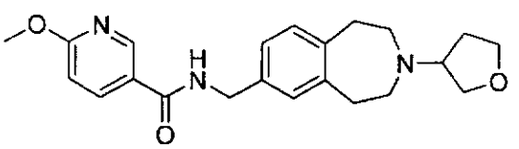


1H NMR (400 MHz, DMSO-d6) d ppm 1.03 - 1.17 (m, 3 H) 1.52 - 1.70 (m, 2 H) 1.73 - 1.90 (m, 2 H) 1.96 - 2.13 (m, 2 H) 2.21 - 2.48 (m, 4 H) 2.71 - 2.89 (m, 5 H) 3.15 (s, 3 H) 3.41 - 3.50 (m, 1 H) 3.54 - 3.66 (m, 1 H) 3.89 - 4.05 (m, 1 H) 4.36 - 4.50 (m, 2 H) 4.71 - 4.81 (m, 1 H) 6.64 - 6.74 (m, 1 H) 6.98 - 7.15 (m, 3 H) 7.93 - 8.06 (m, 1 H) 8.62 - 8.67 (m, 1 H) 8.67 - 8.76 (m, 1 H)

MS ES^+: 423

2.296 Example 296

6-methoxy-N-{[3-(tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]methyl}pyridine-3-carboxamide

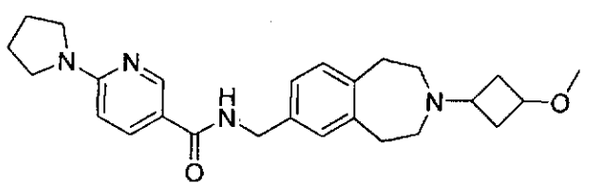


1H NMR (400 MHz, CHLOROFORM-d) d 8.56 - 8.63 (m, 1H), 7.97 - 8.05 (m, 1H), 7.06 - 7.15 (m, 3H), 6.74 - 6.82 (m, 1H), 6.14 - 6.28 (m, 1H), 4.55 - 4.65 (m, 2H), 3.91 - 4.04 (m, 4H), 3.83 - 3.91 (m, 1H), 3.67 - 3.81 (m, 2H), 3.23 - 3.33 (m, 1H), 2.86 - 2.99 (m, 4H), 2.66 - 2.78 (m, 2H), 2.50 - 2.65 (m, 2H), 1.99 - 2.11 (m, 1H), 1.82 - 1.96 (m, 1H)

MS ES^+: 382

2.297 Example 297

N-{[3-(3-methoxycyclobutyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]methyl}-6-(pyrrolidin-1-yl)pyridine-3-carboxamide

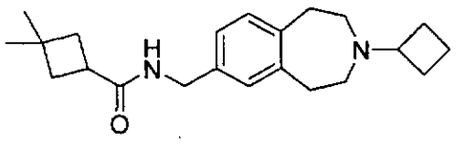


1H NMR (400 MHz, CD3OD) δ 1H NMR (400 MHz, METHANOL-d4) d ppm 8.52 - 8.63 (m, 1 H) 7.88 - 8.00 (m, 1 H) 6.99 - 7.13 (m, 3 H) 6.48 - 6.55 (m, 1 H) 4.49 (s, 2 H) 3.54 - 3.67 (m, 1 H) 3.45 - 3.54 (m, 4 H) 3.24 (s, 3 H) 2.85 - 2.96 (m, 4 H) 2.37 - 2.58 (m, 7 H) 1.97 - 2.10 (m, 4 H) 1.70 - 1.86 (m, 2 H)

MS ES^+: 435

2.298 Example 298

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-3,3-dimethylcyclobutanecarboxamide

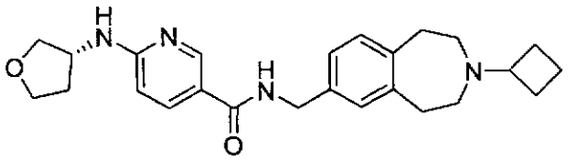


1H NMR (400 MHz, MeOD) d 6.96 - 7.13 (m, 3 H), 4.30 (s, 2 H), 2.99 - 3.14 (m, 1 H), 2.92 (m, 5 H), 2.23 - 2.66 (m, 4 H), 1.84 - 2.21 (m, 8 H), 1.58 - 1.81 (m, 2 H), 1.20 (s, 3 H), 1.10 (s, 3 H)

MS ES^+: 341

2.299 Example 299

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-[(3R)-tetrahydrofuran-3-ylamino]pyridine-3-carboxamide

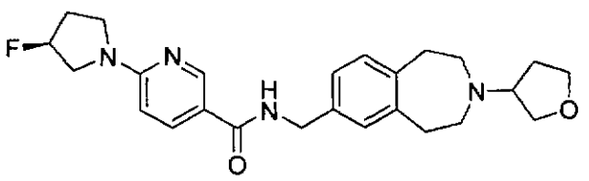


1H NMR (400 MHz, METHANOL-d4) d 8.49 - 8.59 (m, 1H), 7.81 - 7.92 (m, 1H), 7.05 - 7.15 (m, 3H), 6.51 - 6.61 (m, 1H), 4.44 - 4.56 (m, 3H), 3.94 - 4.03 (m, 2H), 3.81 - 3.91 (m, 1H), 3.65 - 3.74 (m, 1H), 2.80 - 2.99 (m, 5H), 2.40 - 2.60 (m, 4H), 2.26 - 2.37 (m, 1H), 2.06 - 2.17 (m, 2H), 1.88 - 2.03 (m, 3H), 1.63 - 1.79 (m, 2H)

MS ES^+: 421

2.300 Example 300

6-((S)-3-fluoropyrrolidin-1-yl)-N-((3-(tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)nicotinamide

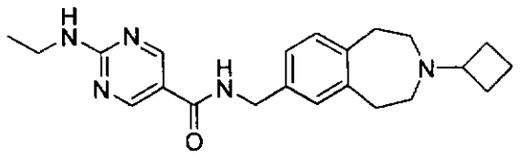


1H NMR (400 MHz, CD3OD-d4) δ 8.49 - 8.59 (m, 1H), 7.81 - 7.92 (m, 1H), 7.05 - 7.15 (m, 3H), 6.51 - 6.61 (m, 1H), 4.44 - 4.56 (m, 3H), 3.94 - 4.03 (m, 2H), 3.81 - 3.91 (m, 1H), 3.65 - 3.74 (m, 1H), 2.80 - 2.99 (m, 5H), 2.40 - 2.60 (m, 4H), 2.26 - 2.37 (m, 1H), 2.06 - 2.17 (m, 2H), 1.88 - 2.03 (m, 3H), 1.63 - 1.79 (m, 2H)

MS ES$^+$: 439

2.301Example 301

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-(ethylamino)pyrimidine-5-carboxamide

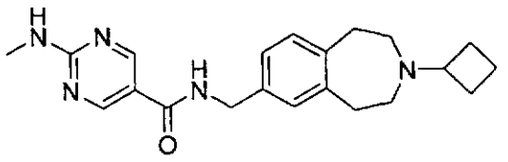


1H NMR (400 MHz, CD3OD) δ 8.34 - 8.94 (m, 2H), 6.73 - 7.32 (m, 3H), 4.12 - 4.45 (m, 2H), 3.23 - 3.48 (m, 2H), 2.53 - 2.88 (m, 5H), 1.34 - 2.49 (m, 10H), 1.12 (m, 3H)

MS ES$^+$: 380

2.302 Example 302

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-(methylamino)pyrimidine-5-carboxamide

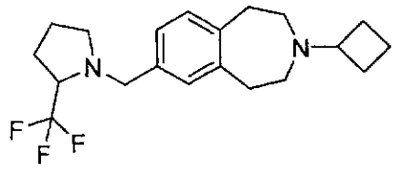


1H NMR (400 MHz, CD3OD) δ 8.28 - 8.88 (m, 2H), 6.73 - 7.26 (m, 3H), 4.10 - 4.45 (m, 2H), 2.52 - 2.93 (m, 8H), 1.88 (m, 10H)

MS ES$^+$: 365

2.303 Example 303

3-cyclobutyl-7-((2-(trifluoromethyl)pyrrolidin-1-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine

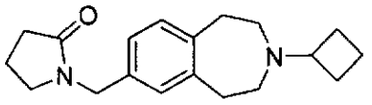


1H NMR (400 MHz, CDCl3-d) δ 7.07 (s, 3H), 4.01 - 4.28 (m, 1H), 3.49 - 3.71 (m, 1H), 3.17 - 3.41 (m, 1H), 2.69 - 3.11 (m, 6H), 2.25 - 2.66 (m, 5H), 1.88 (none, 10H)

MS ES$^+$: 354

2.304 Example 304

1-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)pyrrolidin-2-one

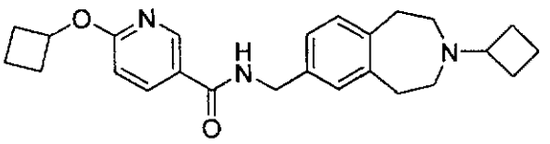


1H NMR (400 MHz, CDCl3-d) δ 6.94 - 7.15 (m, 3H), 4.31 - 4.52 (m, 2H), 3.19 - 3.40 (m, 2H), 2.84 - 3.00 (m, 4H), 2.69 - 2.84 (m, 1H), 2.33 - 2.58 (m, 5H), 1.81 - 2.19 (m, 6H), 1.68 (none, 3H)

MS ES^+: 299

2.305 Example 305

6-cyclobutoxy-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)nicotinamide

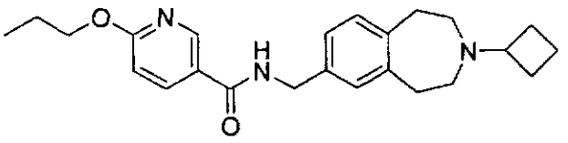


NMR: 1H NMR (400 MHz, DMSO) d 8.94 (t, 1H), 8.66 (d, 1H), 8.14 (dd, 1H), 7.00-7.07 (m, 3H), 6.84 (dd, 1H), 5.18 (quint, 1H), 4.41 (d, 2H), 2.68-2.84 (m, 5H), 2.23-2.46 (m, 6H), 1.94-2.13 (m, 4H), 1.70-1.84 (m, 3H), 1.48-1.70 (m, 3H)

MS ES^+: 406

2.306 Example 306

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-propoxynicotinamide

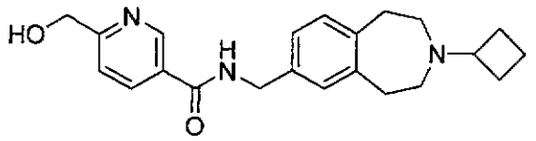


NMR: 1H NMR (400 MHz, DMSO) d 8.84 (s, 1H), 8.69 (s, 1H), 8.15 (dd, 1H), 7.05 (s, 3H), 6.85 (dd, 1H), 4.35-4.51 (m, 2H), 4.16-4.35 (m, 2H), 2.70-2.92 (m, 5H), 2.25-2.45 (m, 4H), 1.91-2.10 (m, 2H), 1.68-1.90 (m, 4H), 1.48-1.68 (m, 2H), 0.78-1.16 (m, 3H)

MS ES^+: 394

2.307 Example 307

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(hydroxymethyl)nicotinamide

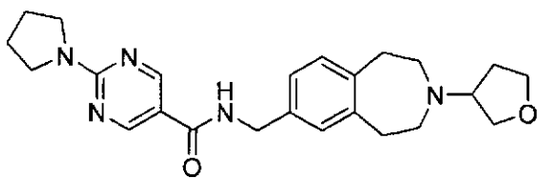


1H NMR (400 MHz, CHLOROFORM-d) d 8.72 - 9.13 (m, 1H), 7.90 - 8.28 (m, 1H), 7.31 - 7.48 (m, 1H), 7.01 - 7.20 (m, 3H), 6.19 - 6.51 (m, 1H), 4.73 - 5.03 (m, 2H), 4.46 - 4.73 (m, 2H), 3.41 - 3.65 (m, 1H), 2.69 - 3.07 (m, 5H), 2.25 - 2.68 (m, 3H), 1.87 (none, 6H)

MS ES^+: 366

2.308 Example 308

2-(pyrrolidin-1-yl)-N-((3-(tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)pyrimidine-5-carboxamide

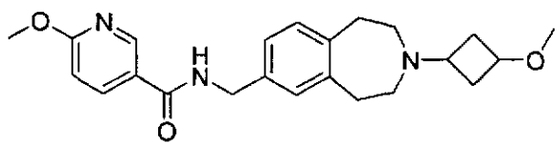


NMR: 1H NMR (400 MHz, CHLOROFORM-d) d 8.64 - 8.82 (m, 2H), 7.03 - 7.17 (m, 3H), 6.05 - 6.19 (m, 1H), 4.51 - 4.67 (m, 2H), 3.93 - 4.03 (m, 1H), 3.84 - 3.92 (m, 1H), 3.69 - 3.82 (m, 2H), 3.56 - 3.69 (m, 4H), 3.22 - 3.35 (m, 1H), 2.85 - 3.02 (m, 4H), 2.66 - 2.79 (m, 2H), 2.51 - 2.65 (m, 2H), 1.97 - 2.12 (m, 5H), 1.83 - 1.97 (m, 1H)

MS ES^+: 422

2.309 Example 309

6-methoxy-N-((3-(3-methoxycyclobutyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)nicotinamide

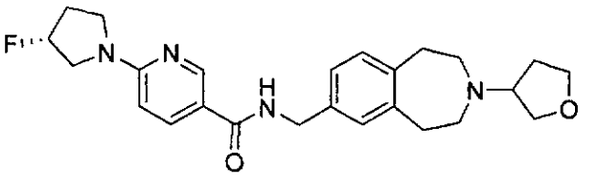


1H NMR (400 MHz, CD3OD) δ 8.61 - 8.70 (m, 1 H) 8.05 - 8.13 (m, 1 H) 7.02 - 7.12 (m, 3 H) 6.79 - 6.87 (m, 1 H) 4.50 (s, 2 H) 3.96 (s, 3 H) 3.62 (m, 1 H) 3.24 (s, 3 H) 2.87 - 2.96 (m, 4 H) 2.34 - 2.62 (m, 7 H) 1.72 - 1.86 (m, 2 H).

MS ES^+: 396

2.310 Example 310

6-((R)-3-fluoropyrrolidin-1-yl)-N-((3-(tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)nicotinamide

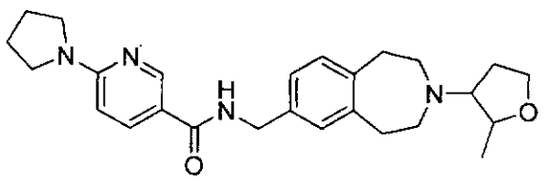


1H NMR (400 MHz, METHANOL-d4) δ 8.57 - 8.69 (m, 1H), 7.94 - 8.05 (m, 1H), 7.03 - 7.16 (m, 3H), 6.54 - 6.62 (m, 1H), 5.31 - 5.52 (m, 1H), 4.45 - 4.56 (m, 2H), 3.92 - 4.00 (m, 1H), 3.82 - 3.91 (m, 2H), 3.65 - 3.80 (m, 5H), 3.52 - 3.63 (m, 1H), 2.87 - 3.00 (m, 4H), 2.54 - 2.79 (m, 4H), 2.06 - 2.45 (m, 3H), 1.83 - 1.96 (m, 1H)

MS ES$^+$: 439

2.311 Example 311

N-((3-(2-methyltetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(pyrrolidin-1-yl)nicotinamide

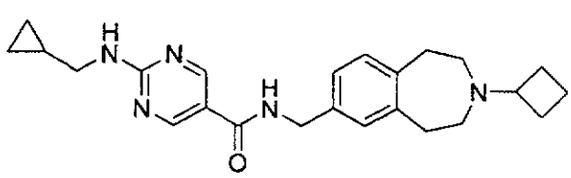


1H NMR (400 MHz, DMSO-d6) δ ppm 1.06 - 1.19 (m, 3 H) 1.79 - 2.03 (m, 6 H) 2.54 - 2.67 (m, 2 H) 2.77 - 2.89 (m, 4 H) 2.93 - 3.03 (m, 1 H) 3.37 - 3.49 (m, 4 H) 3.54 - 3.69 (m, 1 H) 3.79 - 3.89 (m, 1 H) 3.93 - 4.05 (m, 1 H) 4.34 - 4.44 (m, 2 H) 6.40 - 6.52 (m, 1 H) 6.97 - 7.10 (m, 3 H) 7.89 - 8.01 (m, 1 H) 8.57 - 8.73 (m, 2 H), 2H was hidden with the residure of DMSO.

MS ES$^+$: 435

2.312 Example 312

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-2-[(cyclopropylmethyl)amino]pyrimidine-5-carboxamide

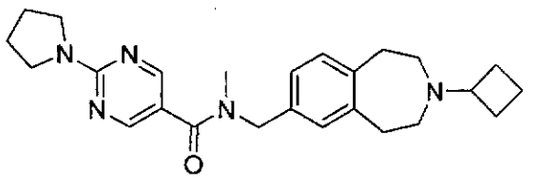


1H NMR (400 MHz, CHLOROFORM-d) δ 8.70 (br. s., 2H), 7.02 - 7.17 (m, 3H), 6.12 (br. s., 1H), 5.58 (br. s., 1H), 4.57 (d, J = 5.31 Hz, 2H), 3.33 (t, J = 6.32 Hz, 2H), 1.43 - 3.11 (m, 15H), 0.98 - 1.19 (m, 1H), 0.49 - 0.67 (m, 2H), 0.27 (q, J = 4.88 Hz, 2H)

MS ES$^+$: 406

2.313 Example 313

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-N-methyl-2-(pyrrolidin-1-yl)pyrimidine-5-carboxamide

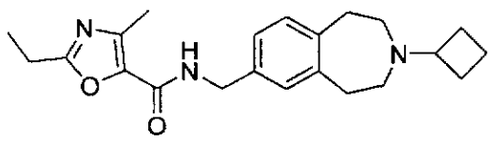


1H NMR (400 MHz, DICHLOROMETHANE-d2) δ 8.38 (s, 2H), 6.83 - 7.11 (m, 3H), 4.51 (s, 2H), 3.30 - 3.59 (m, 5H), 2.90 (s, 8H), 2.34 (br. s., 3H), 1.36 - 2.14 (m, 10H)

MS ES$^+$: 421

2.314 Example 314

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide

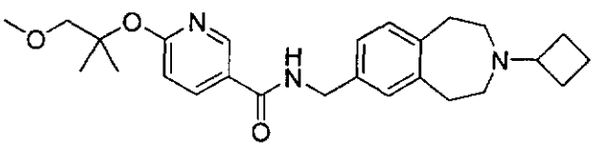


1H NMR (400 MHz, METHANOL-d4) δ 6.98 - 7.16 (m, 3H), 4.45 (s, 2H), 2.74 - 3.00 (m, 7H), 2.30 - 2.59 (m, 7H), 2.03 - 2.15 (m, 2H), 1.85 - 2.01 (m, 2H), 1.58 - 1.84 (m, 2H), 1.25 - 1.48 (m, 3H)

MS ES$^+$: 368

2.315 Example 315

N-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)methyl]-6-[(1-methoxy-2-methylpropan-2-yl)oxy]pyridine-3-carboxamide

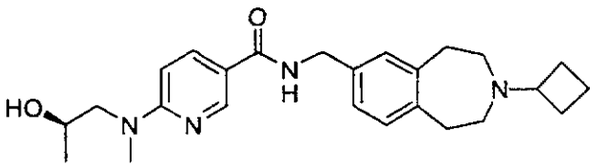


1H NMR (400 MHz, CD3OD) δ 8.55 - 8.67 (m, 1 H) 7.98 - 8.07 (m, 1 H) 7.00 - 7.13 (m, 3 H) 6.69 - 6.78 (m, 1 H) 4.50 (s, 2 H) 3.72 (s, 2 H) 3.36 (s, 3 H) 2.88 - 2.95 (m, 4 H) 2.76 - 2.87 (m, 1 H) 2.46 (br. s., 4 H) 2.04 - 2.15 (m, 2 H) 1.86 - 2.00 (m, 2 H) 1.61 - 1.77 (m, 2 H) 1.57 (s, 6 H).

MS ES$^+$: 438

2.316 Example 316

(R)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-((2-hydroxypropyl)(methyl)amino)nicotinamide

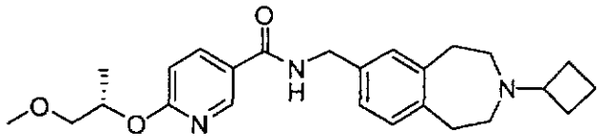


1H NMR (400 MHz, DMSO-d6) δ ppm 0.98 - 1.12 (m, 3 H) 1.47 - 1.66 (m, 2 H) 1.69 - 1.85 (m, 2 H) 1.93 - 2.08 (m, 2 H) 2.21 - 2.42 (m, 4 H) 2.66 - 2.86 (m, 5 H) 3.10 (s, 3 H) 3.36 - 3.46 (m, 1 H) 3.49 - 3.61 (m, 1 H) 3.85 - 3.98 (m, 1 H) 4.32 - 4.45 (m, 2 H) 4.67 - 4.76 (m, 1 H) 6.58 - 6.70 (m, 1 H) 6.96 - 7.09 (m, 3 H) 7.90 - 7.99 (m, 1 H) 8.58 - 8.62 (m, 1 H) 8.62 - 8.72 (m, 1 H)

MS ES$^+$: 423

2.317 Example 317

(S)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(1-methoxypropan-2-yloxy)nicotinamide

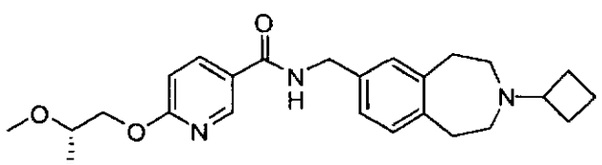


1H NMR (400 MHz, CD3OD) δ 8.61 - 8.64 (m, 1 H) 8.06 - 8.10 (m, 1 H) 7.04 - 7.12 (m, 3 H) 6.77 - 6.82 (m, 1 H) 5.38 - 5.48 (m, 1 H) 4.50 (s, 2 H) 3.50 - 3.64 (m, 2 H) 3.37 (s, 3 H) 2.87 - 2.95 (m, 4 H) 2.77 - 2.87 (m, 1 H) 2.46 (br. s., 4 H) 2.04 - 2.15 (m, 2 H) 1.87 - 1.99 (m, 2 H) 1.60 - 1.77 (m, 2 H) 1.29 - 1.34 (m, 3 H).

MS ES$^+$: 424

2.318 Example 318

(S)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-6-(2-methoxypropoxy)nicotinamide

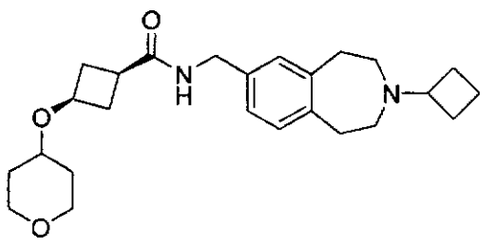


1H NMR (400 MHz, CD3OD) δ 8.61 - 8.67 (m, 1 H) 8.07 - 8.14 (m, 1 H) 7.02 - 7.13 (m, 3 H) 6.83 - 6.89 (m, 1 H) 4.50 (s, 2 H) 4.27 - 4.39 (m, 2 H) 3.71 - 3.80 (m, 1 H) 3.41 (s, 3 H) 2.88 - 2.96 (m, 4 H) 2.78 - 2.88 (m, 1 H) 2.46 (br. s., 4 H) 2.05 - 2.15 (m, 2 H) 1.87 - 2.00 (m, 2 H) 1.60 - 1.77 (m, 2 H) 1.20 - 1.27 (m, 3 H).

MS ES$^+$: 424

2.319 Example 319

cis-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3-(tetrahydro-2H-pyran-4-yloxy)cyclobutanecarboxamide

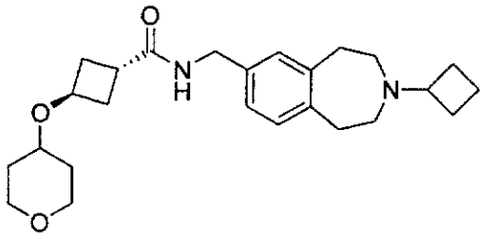


1H NMR (400 MHz, DICHLOROMETHANE-d2) Shift 6.84 - 7.06 (m, 3H), 5.68 (br. s., 1H), 4.19 - 4.31 (m, 2H), 3.72 - 3.94 (m, 3H), 3.39 (tt, J = 4.23, 8.91 Hz, 1H), 3.22 - 3.34 (m, 2H), 2.79 (br. s., 4H), 1.32 - 2.52 (m, 20H)

MS ES$^+$: 413

2.320 Example 320

trans-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-3-(tetrahydro-2H-pyran-4-yloxy)cyclobutanecarboxamide

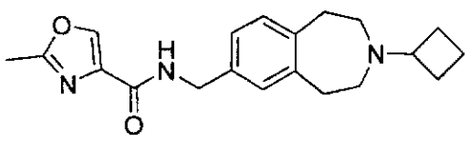


1H NMR (400 MHz, DICHLOROMETHANE-d2) Shift 6.94 - 7.18 (m, 3H), 5.77 (br. s., 1H), 4.28 - 4.49 (m, 3H), 3.81 - 3.99 (m, 2H), 3.44 - 3.61 (m, 1H), 3.32 - 3.46 (m, 2H), 2.65 - 3.11 (m, 5H), 2.28 - 2.59 (m, 5H), 2.15 - 2.28 (m, 2H), 2.01 - 2.15 (m, 2H), 1.31 - 2.01 (m, 10H)

MS ES$^+$: 413

3.321 Example 321

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-methyloxazole-4-carboxamide

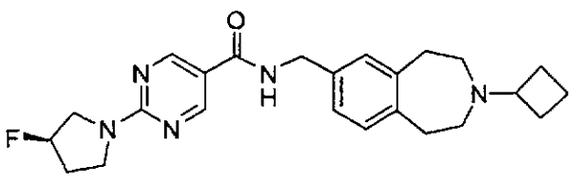


1H NMR (400 MHz, MeOD) d 8.21 - 8.31 (m, 1 H), 7.04 - 7.13 (m, 3 H), 4.49 (s, 2 H), 2.76 - 2.99 (m, 5 H), 2.48 (s, 7 H), 2.05 - 2.19 (m, 2 H), 1.87 - 2.03 (m, 2 H), 1.58 - 1.82 (m, 2 H)

MS ES$^+$: 340

3.322 Example 322

(R)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-(3-fluoropyrrolidin-1-yl)pyrimidine-5-carboxamide

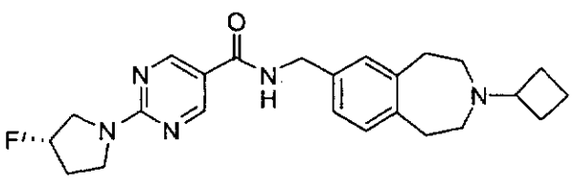


1H NMR (400 MHz, CD3OD / CD2Cl2) δ 8.79 (s, 2 H) 7.00 - 7.14 (m, 3 H) 5.26 - 5.48 (m, 1 H) 4.49 (s, 2 H) 3.58 - 4.05 (m, 4 H) 2.75 - 2.98 (m, 5 H) 2.17 - 2.60 (m, 6 H) 2.03 - 2.17 (m, 2 H) 1.84 - 2.01 (m, 2 H) 1.57 - 1.77 (m, 2 H).

MS ES$^+$: 424

3.323 Example 323

(S)-N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-(3-fluoropyrrolidin-1-yl)pyrimidine-5-carboxamide

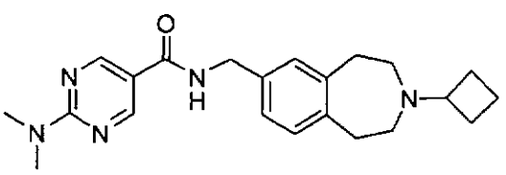


1H NMR (400 MHz, CD3OD / CD2Cl2) δ 8.79 (s, 2 H) 7.01 - 7.13 (m, 3 H) 5.29 - 5.48 (m, 1 H) 4.49 (s, 2 H) 3.58 - 4.03 (m, 4 H) 2.75 - 3.01 (m, 5 H) 2.16 - 2.67 (m, 6 H) 2.03 - 2.14 (m, 2 H) 1.86 - 2.03 (m, 2 H) 1.58 - 1.78 (m, 2 H).

MS ES$^+$: 424

3.324 Example 324

N-((3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)methyl)-2-(dimethylamino)pyrimidine-5-carboxamide

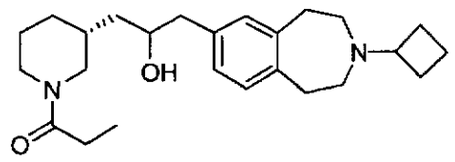


1H NMR (400 MHz, CD3OD) δ 8.76 (s, 2 H) 7.02 - 7.15 (m, 3 H) 4.48 (s, 2 H) 3.23 (s, 6 H) 2.76 - 2.98 (m, 5 H) 2.48 (br. s., 4 H) 2.03 - 2.18 (m, 2 H) 1.85 - 2.01 (m, 2 H) 1.56 - 1.80 (m, 2 H).

MS ES$^+$: 380

3.325 Example 325

1-((3R)-3-(3-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-2-hydroxypropyl)piperidin-1-yl)propan-1-one



1H NMR (400 MHz, CD3OD) δ 6.85 - 7.11 (m, 3 H) 4.19 - 4.43 (m, 1 H) 3.68 - 3.98 (m, 2 H) 2.58 - 3.19 (m, 9 H) 2.28 - 2.57 (m, 5 H) 1.55 - 2.18 (m, 9 H) 1.01 - 1.55 (m, 8 H)

MS ES^+: 399

3. Biological efficacy of compounds of the invention

3.1 In Vitro H3 Binding Assay

The ability of compounds to bind to the H3 receptor was determined by measuring the reduction in tritiated N-α-methyl-histamine (^{3}H-NαMH) binding in a competition binding assay. Changes in the levels of bound radio-label were monitored by scintillation counting with a Trilux Microbeta (Perkin Elmer).

Membranes were prepared from CHO-K1 cells stably expressing human H3 receptor; routinely grown as monolayers in Ham's F12 medium (Invitrogen) supplemented with 10% Foetal Clone III (Hyclone), 500μg/ml G418 (Invitrogen), 5 μg/ml blasticidine S (Invivogen) and 50 μg/ml Gentamicin (Sigma) in 5% CO_2 at 37°C. Cells were grown to 80-95% confluency, rinsed once with 1x PBS (Invitrogen) and detached by incubating with 1x PBS containing 0.02% EDTA (Sigma) for 10 minutes at room temperature. Cells were collected by centrifugation at 900 xg, 4°C for 10 minutes. Cells were rinsed once with 1x PBS and re-suspended in ice cold homogenisation buffer (50mM Tris-HCl (pH 7.4), 2.5mM EDTA, 5mM $MgCl_2$, 200mM Sucrose) at $1x10^7$ cells/ml and kept on ice. Cells were homogenised on ice and debris removed by centrifugation at 500 x g, 4°C for 5 minutes. The resulting supernatant was centrifuged at 75,600 xg, 4°C for 60 minutes. Membranes were suspended in homogenisation buffer, protein concentration was determined (BCA Protein Assay kit (Pierce)), diluted to 2.2 mg/ml, dispensed into 1ml aliquots and stored at -80 °C.

Membranes were thawed on ice, sonicated with 4 cycles of 20 pulses (50% amplitude, 0.5 pulse) (UP200S Hielscher) on ice, diluted in assay buffer (50mM Tris-HCl (pH7.4), 5mM $MgCl_2$) to 62.5 μg/ml. Compound was serially diluted in DMSO before being diluted 1:10 with assay buffer. 5μg of membrane in 80 μl of assay buffer was added per well of a 96 well polystyrene plate (Corning). 10 μl of compound was added per well. The assay was initiated by the addition of 10 μl of 20nM ^{3}H-NαMH per well and incubated for one hour at room temperature with shaking. Total binding was determined in the presence of 1% DMSO and non-specific binding was determined by the inclusion of 1 μM R-α-methyl-histamine (RαMH). Incubations were then

filtered through filtermat A (Perkin Elmer) and washed three times with assay buffer. Filtermats were dried at 42°C for two hours, scintillant added and the level of bound radioactivity determined.

IC50 values for compounds were determined from seven point log scale dose-response studies and represent the concentration of compound required to inhibit 50% of the specific binding of 2nM ^{3}H-NαMH (difference between total and non-specific binding). Curves were generated using the average of duplicate wells for each data point and analyzed using nonlinear regression of sigmoidal dose response (variable slope).

3.2 In Vitro H3 Functional Assay

The functional activity of compounds at the H3 receptor was determined by measuring changes in the level of intracellular cAMP using a cAMP response element driven luciferase reporter assay. The changes in luciferase expression were monitored by a luminescence plate reader, Analyst HT (MDS Analytical). Increases in intracellular cAMP were readily detected upon activation of protein kinase A by forskolin (Sigma) and suppression of this response observed with the application of the H3 receptor agonist RαMH (Sigma).

CHO(dhfr$^+$)-cre-luc cells stably expressing human H3 receptor were routinely grown as monolayers in Minimal Essential Medium α (MEMα) (Invitrogen) supplemented with 10% dialysed FBS (Hyclone), in 5% CO_2 at 37°C. 48 hours prior to assay, cells were seeded in clear-base white walled 384-well plates (Corning) at a density of 5000 cells/well. On the day of assay, growth media was removed and replaced with 15 µl of assay buffer (MEMα, 5 mg/ml fatty acid free BSA (Sigma)) per well. Cells were then incubated for 30 minutes at 37°C, 5% CO_2. Compound was serially diluted in DMSO before being diluted 1:10 with assay buffer. 2.5 µl of compound diluted in assay buffer was added and cells incubated for 5 minutes at 37°C, 5% CO_2. 2.5 µl of each reagent was then added in the following order: RαMH (10 nM), isobutylmethylxanthine (1-methyl-3-(2-methylpropyl)-7H-purine-2,6-dione; IBMX) (500 µM) (Sigma) and forskolin (1 µM). Cells were then incubated for 90 minutes at 37°C, 5% CO_2, followed by 30 minutes at room temperature. At the end of incubation 25 µl of Steadylite reagent (Perkin Elmer) was added, plates were sealed and placed on a shaker for 5 minutes. The level of light output to determine the level of luciferase expression was then measured.

IC50 values for compounds were determined from ten point half log scale dose-response studies and represent the concentration of compound required to prevent 50% inhibition of forskolin stimulated cells in the presence of RαMH alone. Curves were generated using the average of duplicate wells for each data point and analyzed using nonlinear regression of four parameter dose response.

3.3 Results

The results of the biological assays carried out in 3.1 and 3.2 above were as follows:

Example Compound	hH3 binding IC_{50}/nM	hH3 functional IC_{50}/nM
Example 1	1	0.7
Example 5	22	31

Example 11	30	
Example 19	20	
Example 20	11	3
Example 21	13	
Example 23	11	2
Example 24	44	16
Example 25	37	
Example 26	36	
Example 27	21	
Example 29	13	8
Example 30	5	
Example 34	26	5
Example 35	11	1
Example 36	12	2
Example 38	9	
Example 40	3	2
Example 42	9	30
Example 44	14	3
Example 45	13	
Example 49	34	
Example 50	24	
Example 53	51	6
Example 54	10	
Example 55	12	
Example 57	12	
Example 59	6	3
Example 63	6	
Example 65	4	
Example 67	11	
Example 68	1	3
Example 69	2	0.5
Example 70	5	3
Example 72	1	2
Example 73	12	1

Example 74	3	1
Example 75	15	
Example 77	3	1
Example 78	4	2
Example 79	6	3
Example 81	0.4	0.8
Example 84	10	
Example 85	14	
Example 86	3	1
Example 87	4	
Example 88	5	2
Example 89	18	
Example 90	10	
Example 91	6	
Example 92	4	1
Example 93	29	
Example 95	18	
Example 96	18	
Example 97	9	2
Example 98	15	
Example 99	18	
Example 100	2	0.5
Example 102	18	
Example 103	11	1
Example 106	13	
Example 107	9	4
Example 108	1	4
Example 109	2	
Example 110	17	
Example 111	7	7
Example 113	13	
Example 114	12	19
Example 120	1	
Example 131	30	

Example 132	6	
Example 134	13	1
Example 137	26	
Example 143	24	7
Example 146	10	10
Example 155	24	
Example 164	10	5
Example 167	22	71
Example 171	14	4
Example 181	21	4
Example 191	13	2
Example 194	26	7
Example 211	6	9
Example 216	41	20
Example 221	11	3
Example 224	2	4
Example 231	23	15
Example 233	2	16
Example 239	16	1
Example 242	0.6	3
Example 244	10	6
Example 251	11	6
Example 253	1	4
Example 256	0.3	3
Example 257	25	7
Example 262	25	10
Example 263	18	6
Example 265	6	4
Example 268	4	
Example 269	2.5	
Example 274	9	
Example 275	7	
Example 276	19	
Example 280	0.3	

Example 281	0.8	
Example 282	1	
Example 287	1	
Example 290	3	
Example 294	8	
Example 300	5	
Example 302	3	
Example 304	61	34
Example 306	18	2
Example 313	1	
Example 315	2	
Example 316	0.9	
Example 319	62	

These results indicate that compounds of the invention have potent antagonist or inverse agonist activity at the H3 receptor, both in terms of binding and in terms of inhibition of the functional response caused by receptor activation. The compounds tested above exhibit IC_{50} values of less than 1 μM, and several compounds show low nanomolar affinity at the H3 receptor. Accordingly, the compounds of the invention are expected to have usefulness in the prevention or treatment of conditions, such as those discussed above, in which H3 receptor activity is implicated.

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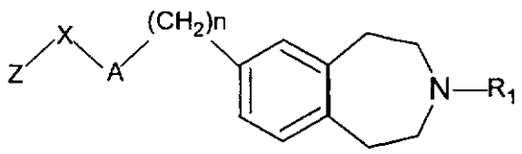
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Claims

1. A compound having the formula:



wherein:

R1 is a group selected from C_{3-8} cycloalkyl, C_{1-6} alkyl, C_{1-6} alkylene-C_{3-8} cycloalkyl, each of which groups may optionally be substituted with C_{1-6} alkyl, halogen, haloC_{1-6} alkyl or OR15, or R1 is heterocyclyl, optionally substituted with C_{1-6} alkyl, haloC_{1-6} alkyl or OR15;

n is 0, 1, 2, 3 or 4, the alkylene group -$(CH_2)_n$- formed thereby being optionally substituted with a group selected from C_{1-4} alkyl, C_{3-8} cycloalkyl and arylsulfonyl;

A is a group selected from -N(R2)CO-, -CON(R2)-, -OC(O)-, -C(O)O-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cycloalkylene-, -C(R2)(haloC_{1-6} alkyl)-, C_{1-4} alkylene and -C(OR3)(haloC_{1-6} alkyl)-;

R2 and R3 are each independently selected from H, C_{1-6} alkyl, and C_{3-8} cycloalkyl, or, when A is -N(R2)CO- and X is absent, R2 may form, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group, which may optionally be substituted;

X is absent or is C_{1-4} alkylene or C_{2-4} alkenylene, each of which may optionally be substituted with one or more C_{1-4} alkyl groups, OR16, halogen or haloC_{1-6} alkyl;

Z is selected from aryl, heteroaryl, C_{3-8} cycloalkyl, and heterocyclyl, each of which may optionally be substituted by a group selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl, or, when X is present, Z may be H, or, when X is absent and A is -C(R2)(OR3)- or -N(R2)CO-, Z may be H, or, when A is -N(R2)CO- and X is absent, Z may form, together with the adjacent nitrogen atom and R2, an N-containing heterocyclyl group which may optionally be substituted, wherein, when A is -CO-, Z is linked to X or A via a carbon atom and wherein, when A is –N(R2)CO- and Z is H, R1 is C_{3-8} cycloalkyl; and

Y represents a bond, C_{1-6} alkylene, CO, NR14, COC_{2-6} alkenylene, O, SO_2 or $NHCOC_{1-6}$ alkylene;

wherein said cycloalkyl, aryl, heteroaryl and heterocyclyl groups Z may be optionally substituted by one or more substituents which may be the same or different, and which are selected from halogen, haloC_{1-6} alkyl, hydroxy, cyano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alkyl-NR5R6, -C_{3-8} cycloalkyl-NR5R6, -CONR12R13, -NR12COR13, -NR5SO_2R6, -OCONR5R6, -NR5CO_2R6, -NR4CONR5R6 or -SO_2NR5R6-SHR8, -alkyl-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, -alkyl-SO_2R9, -alkyl-CONHR9, -alkyl-SONHR9, -alkyl-COR10, -CO-alkyl-R10, -O-alkyl-R11 (wherein R4, R5 and R6 independently represent hydrogen, C_{1-6} alkyl, -C_{3-8} cycloalkyl, -C_{1-6} alkylene-C_{3-8} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein R8 represents C_{1-6}

alkyl, wherein R9 represents C_{1-6} alkyl or aryl, wherein R10 represents aryl, wherein R11 represents C_{3-8} cycloalkyl or aryl, R12, R13, R14, R15 and R16 each independently represent H or C_{1-6} alkyl, and wherein -NR5R6 and -NR12R13 may represent a nitrogen containing heterocyclyl group); wherein said R4, R5, R6 R8, R9, R10 and R11 groups may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl;

and wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8} cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen, haloC_{1-6} alkyl and C_{1-6} alkyl;

and wherein, when A is C_{1-4} alkylene, said cycloalkyl, aryl, heteroaryl or heterocyclyl group Z (such as a heterocyclyl group Z) is substituted at least with hydroxy, CF_3, or =O;

and wherein, when A is CON(R2) n is 1;

or a pharmaceutically acceptable salt or ester thereof,

provided that: when A is -CO-, R1 is CH_3, C_{3-8} cycloalkyl-substituted C_{1-6} alkylene or n-butyl, n is 0 and X is -CH_2CH_2-, Z is not N-benzyl substituted 4-piperidinyl, N-(3-fluorobenzyl)-substituted 4-piperidinyl or N-acetyl substituted 4-piperidinyl;

when A is -OC(O)-, R1 is cyclobutyl, n is 0 and X is -CH_2CH_2-, Z is not H;

when A is -OC(O)-, R1 is n-propyl, n is 0 and X is -CH_2-, Z is not H; and

when A is –CO-, R1 is CH_3, n is 0 and X is CH_2, Z is not H.

2. A compound according to claim 1, wherein: R1 is C_{1-6} alkyl, C_{3-8} cycloalkyl-C_{1-6} alkylene, or C_{3-8} cycloalkyl, each of which may optionally be substituted by one or two halogens, hydroxy or C_{1-6} alkoxy (such as methoxy), or R1 is heterocyclyl, optionally substituted by hydroxy, C_{1-6} alkoxy or C_{1-6} alkyl;

n is 0, 1 or 2;

A is -N(R2)CO-, -OC(O)-, -CON(R2)-, -CO-, -C(R2)(OR3)-, C_{1-4}alkylene, -C(=N-O-R3)- or -C(=CHR3)-;

R2 and R3 are each independently H or C_{1-6} alkyl;

or, when A is -N(R2)CO- and X is absent, R2 may form, together with the adjacent nitrogen atom and Z, an N-containing heterocyclyl group which may optionally be substituted by one to three halogen atoms or carbamoyl groups;

X is absent or is C_{1-4} alkylene or C_{2-4} alkenylene, each of which may optionally be substituted with a C_{1-4} alkyl group; and

Z is aryl, heteroaryl, C_{3-8} cycloalkyl or heterocyclyl,

each of which may optionally be substituted by

(1) a group selected from -Y-aryl, -Y-heteroaryl, -Y-heterocyclyl, and -Y-C_{3-8} cycloalkyl,

wherein Y represents a bond, O, NR14, or C_{1-6} alkylene, and said aryl is selected from phenyl, said heteroaryl is selected from triazolyl, thiazolyl, thienyl and pyrazolyl, said heterocyclyl is selected from morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrrolidinyl, and said C_{3-8} cycloalkyl is selected from cyclobutyl or cyclopropyl; or

(2) one to three substituents selected from

C_{1-6} alkyl, halogen, haloC_{1-6} alkyl, cyano, amino, C_{1-6} alkoxy, C_{1-6} alkyl-carbonyl, hydroxy-substituted C_{1-6} alkyl-carbonyl, C_{3-8} cycloalkyl-carbonyl, carboxyl, C_{1-6} alkoxy-carbonyl, carbamoyl, C_{1-6} alkyl-carbamoyl; C_{1-6} alkylamino, and =O; or

Z may be H when X is present, or Z may be H when X is absent and A is -C(R2)(OR3)- or -N(R2)CO-,

wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8}cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen, haloC_{1-6} alkyl and C_{1-6} alkyl;

wherein, when A is C_{1-4} alkylene, said cycloalkyl, aryl, heteroaryl or heterocyclyl group Z (such as a heterocyclyl group Z) is substituted at least with hydroxy, CF_3 or =O;

and wherein, when A is CON(R2), n is 1.

3. A compound according to claim 1, wherein: R1 is C_{1-6} alkyl or C_{3-8} cycloalkyl, optionally substituted with halogen or C_{1-6} alkoxy, or R1 is heterocyclyl, optionally substituted with C_{1-6} alkyl;

n is 1;

A is –CON(R2)- or -N(R2)CO-;

R2 is selected from H and C_{1-6} alkyl;

X is absent or is C_{1-4} alkylene, which may be optionally substituted with one or more C_{1-4} alkyl or hydroxy groups;

Z is aryl, heteroaryl, C_{3-8} cycloalkyl or heterocyclyl,

each of which may optionally be substituted by

(1) a group selected from -Y-aryl, -Y-heteroaryl, Y-heterocyclyl, and -Y-C_{3-8} cycloalkyl,

wherein Y represents a bond, O, NR14, or C_{1-6} alkylene, and said aryl is selected from phenyl, said heteroaryl is selected from triazolyl, thiazolyl, thienyl and pyrazolyl, said heterocyclyl is selected from morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, and pyrrolidinyl, and said C_{3-8} cycloalkyl is selected from cyclopropyl and cyclobutyl; or

(2) one to three substituents selected from

C_{1-6} alkyl, halogen, haloC_{1-6} alkyl), cyano, amino, C_{1-6} alkylamino, N,N-C_{1-6} dialkylamino, C_{1-6} alkoxy, C_{1-6} alkyl-carbonyl, carboxyl, C_{1-6} alkoxy-carbonyl, carbamoyl, C_{1-6} alkyl-carbamoyl, hydroxy C_{1-6} alkyl and =O; or

Z may be H when X is present,

wherein substituents of Z selected from -Y-aryl, -Y-heteroaryl, -Y-C_{3-8}cycloalkyl and -Y-heterocyclyl may be optionally substituted by one or more substituents selected from =O, hydroxy, cyano, nitro, halogen, haloC_{1-6} alkyl and C_{1-6} alkyl.

4. A compound according to claim 1, wherein: R1 is C_{1-6} alkyl or C_{3-8} cycloalkyl;

n is 1;

A is -C(R2)(OR3)-;

R2 and R3 are each independently H or C_{1-6} alkyl;

X is absent or is C_{1-4} alkylene;

Z is heteroaryl, or heterocyclyl,

each of which may optionally be substituted by one to three substituents selected from

C_{1-6} alkyl, halogen, haloC_{1-6} alkyl, cyano, hydroxy, amino, C_{1-6} alkoxy, C_{1-6} alkyl-carbonyl, hydroxy-substituted C_{1-6} alkyl-carbonyl, carboxyl, C_{1-6} alkoxy-carbonyl, C_{3-8} cycloalkyl-carbonyl, carbamoyl, C_{1-6} alkyl-carbamoyl.

5. A compound according to claim 1, wherein: R1 is C_{1-6} alkyl or C_{3-8} cycloalkyl;

n is 0;

A is C_{1-4} alkylene;

R2 and R3 are each independently H or C_{1-6} alkyl;

X is absent or is C_{1-4} alkylene;

Z is heteroaryl, or heterocyclyl,

each of which may optionally be substituted by one to three substituents selected from

C_{1-6} alkyl, halogen), haloC_{1-6} alkyl, cyano, hydroxy, amino, C_{1-6} alkoxy, C_{1-6} alkyl-carbonyl, hydroxy-substituted C_{1-6} alkyl-carbonyl, carboxyl, C_{1-6} alkoxy-carbonyl, C_{3-8} cycloalkyl-carbonyl, carbamoyl, C_{1-6} alkyl-carbamoyl,

wherein said heteroaryl or heterocyclyl group Z is substituted at least with hydroxy, CF_3 or =O.

6. A compound according to claim 1 or claim 2, wherein R1 is C_{1-3} alkyl, heterocyclyl or C_{3-8} cycloalkyl.

7. A compound according to claim 1 or claim 2, wherein R1 is C_{1-3} alkyl substituted with C_{3-8} cycloalkyl.

8. A compound according to claim 1 or claim 2, wherein R1 is cyclopropylethyl or cyclopropylmethyl.

9. A compound according to claim 1 or claim 2, wherein R1 is selected from methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, tetrahydrofuranyl and cyclopentyl.

10. A compound according to claim 1, wherein R1 is further substituted with a group selected from F, methyl, hydroxy, C_{1-6} alkoxy and CH_2F.

11. A compound according to any preceding claim, wherein R2 is H.

12. A compound according to any preceding claim, wherein R3 is H.

13. A compound according to any preceding claim, wherein X is a straight chain C_{1-4} alkylene group, optionally having one or more methyl or ethyl substituents.

14. A compound according to claim 13, wherein X is methylene or ethylene.

15. A compound according to claim 1, wherein Z is aryl, heteroaryl, C_{3-8} cycloalkyl or heterocyclyl, each of which may be substituted with one or more substituents selected from C_{1-6} alkyl, halogen, haloC_{1-6} alkyl, cyano, amino, C_{1-6} alkoxy, -COR4, -CONR12R13, aryl, and heteroaryl.

16. A compound according to claim 1, wherein Z is heteroaryl, said heteroaryl being selected from thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, imidazopyridyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indolizinyl, indazolyl, purinyl, pyrrolopyridinyl, fluropyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, and benzothiadiazolyl groups.

17. A compound according claim 1 or 2, wherein Z is aryl, said aryl being selected from phenyl, naphthyl and tetrahydronaphthalenyl groups.

18. A compound according claim 1, wherein Z is heterocyclyl, said heterocyclyl being selected from pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl, indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1H-3-benzazepine, and tetrahydroisoquinolinyl groups.

19. A compound according to claim 1, wherein Z is cycloalkyl, said cycloalkyl being selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups.

20. A compound according to any of claims 1 to 3, wherein A is –CON(R2)-, and n is 0, 1 or 2.

21. A compound according to claim 1 or 2, wherein A is -OC(O)- or -C(O)O-, and n is 0, 1 or 2.

22. A compound according to claim 1 or 2, wherein A is -C(R2)(OR3)- or -CO-, and n is 0, 1 or 2.

23. A compound according to claim 20 or claim 22, wherein R2 is H.

24. A compound according to claim 22 or claim 23, wherein R3 is H or C_{1-4} alkyl.

25. A pharmaceutical composition comprising a compound according to any preceding claim, together with one or more pharmaceutically acceptable excipients.

26. A compound according to any of claims 1 to 24, or a composition according to claim 25, for use in therapy.

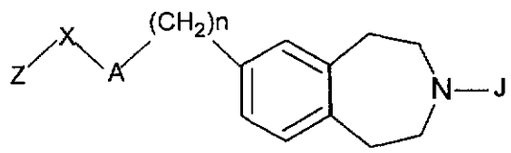
27. A compound according to any of claims 1 to 24, or a composition according to claim 25, for use in the treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, wherein the provisos to claim 1 do not apply.

28. A method of treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, the method comprising the administration, to a subject in need of such treatment or prevention, of a therapeutically effective amount of a compound according to any of claims 1 to 24, wherein the provisos to claim 1 do not apply.

29. A compound according to claim 27, or a method according to claim 28, wherein the condition is a disorder of the central nervous system.

30. A compound or a method according to claim 29, wherein the disorder is selected from schizophrenia, neurodegenerative disorders (such as Alzheimer's Disease), cognitive disorders (such as dementia), sleep disorders, pain, obesity, attentional disorders and epilepsy.

31. An intermediate compound having the formula:



wherein n, A, X and Z have the same meaning as in claim 1, or Z-X-A- together represents C_{1-6} alkylsulfonyloxy, nitro, halogen (such as Br), carbaldehyde O-C_{1-6} alkyl oxime, amino, amino attached to an amino protecting group or arylsulfonyl, and wherein J is an amino protecting group or H, provided that Z is joined to X or A via a carbon atom when Z contains a piperazinyl moiety, and provided that:

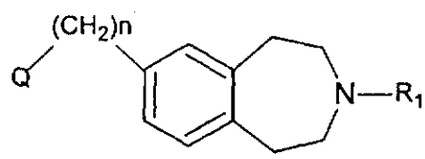
when A is -OC(O)-, J is H, n is 0 and X is -CH_2CH_2-, Z is not H;

when A is -OC(O)-, J is tert-butoxycarbonyl, n is 0 and X is -CH_2-, Z is not H;

when A is -NHCO-, J is tert-butoxycarbonyl, n is 0 and X is -isopropyl, Z is not H; and

when A is -NHCO-, J is tert-butoxycarbonyl, aminoiminomethyl or H, n is 0 and X is -CH_2- or -CH_2CH_2-, Z is not pyrrolidin-2-yl substituted with oxo, phenylpropyl and acetic acid substituents.

32. An intermediate compound having the formula:

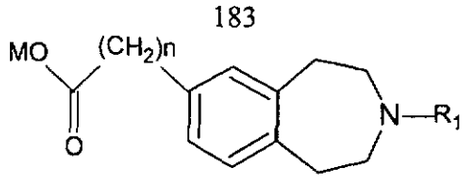


wherein n and R1 have the same meaning as in claim 1, and wherein Q is selected from cyano, amino, amino attached to an amino protecting group, arylsulfonyl and halogen (such as Br).

33. Use of an intermediate compound according to claim 31 or claim 32 in the synthesis of a compound according to any of claims 1 to 24, wherein the provisos to claim 31 do not apply.

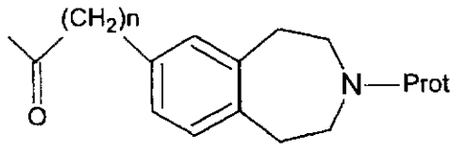
34. A method of synthesis of a compound according to claim 1, wherein A is -N(R2)CO-, the method comprising the reaction of an intermediate having the formula:

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with an amine (Z-X)(R2)NH in the presence of a catalyst, wherein n, Z, X, R1 and R2 have the same meaning as in claim 1, and wherein M represents H or a monovalent metal cation.

35. A method of synthesis of a compound according to claim 1, wherein A is -CO- or -C(R2)(OR3)- and X is present, the method comprising the reaction of a protected intermediate:



with an aldehyde Z-CHO in the presence of a catalyst, followed by deprotection of the protected amine and substitution thereof with R1 and, optionally, by catalytic hydrogenation, wherein n, Z, X, R1, R2 and R3 have the same meaning as in claim 1, and wherein Prot represents an amine protecting group.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/001774

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D223/16 C07D401/06 C07D401/12 C07D401/14 C07D403/12
C07D405/12 C07D405/14 C07D409/12 C07D409/14 C07D413/12
C07D417/12 A61K31/55 A61P25/18

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)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	B PECHERER ET. AL.: "The Synthesis of Some 7- and 7,8-Substituted 2,3,4,5-Tetrahydro-1H-3-benzazepines" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 8, 1971, pages 779-783, XP002545446 page 779, compound no. 3c.	32
X	A. HALL ET. AL.: "Discovery of Brain Penetrant, Soluble, Pyrazole Amide EP1 Receptor Antagonists." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 18, 15 July 2008 (2008-07-15), pages 4027-4032, XP002545447 page 4029, compounds 8a and 8b	1,6, 9-12,16, 25,26, 31,33

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[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 document 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
14 September 2009	29/09/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/001774

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	page 1, line 1 - page 2, line 6; claims; examples; table 3	1-31, 33-35
Y	WO 2006/018260 A (GLAXO GROUP LTD.) 23 February 2006 (2006-02-23) cited in the application page 1, line 1 - page 2, line 10; claims; examples	1-35
Y	WO 2005/123723 A (GLAXO GROUP LTD.) 29 December 2005 (2005-12-29) cited in the application page 1, line 1 - page 2, line 10; claims; examples	1-35
Y	WO 2005/058837 A (GLAXO GROUP LTD.) 30 June 2005 (2005-06-30) cited in the application page 1, line 25 - line 41; claims; examples	1-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/001774

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DERIVADOS DE BENZAZEPINA Y SU USO COMO ANTAGONISTAS DE HISTAMINA H3

La presente invención se refiere a los compuestos y sus usos, y en particular a los compuestos que tienen un esqueleto de benzazepina y su uso terapéutico en el tratamiento o prevención de las condiciones que tengan una asociación con el receptor H3 de histamina.

El receptor H3 fue identificado por primera vez farmacológicamente en 1983 como un autoreceptor que regula la producción de histamina (1). El receptor luego fue clonado en 1999 (2). Es un receptor constitutivamente activo acoplado a la proteína G, que se expresa predominantemente en el sistema nervioso central (SNC) y modula una variedad de funciones del SNC, ambas, central y periféricamente. Se expresa en los terminales presinápticos de las neuronas del SNC y actúa como un modulador negativo de liberación de neurotransmisores, como la histamina, acetilcolina, norepinefrina, serotonina y dopamina (3). Como consecuencia, la habilidad del receptor H3 para regular la liberación de un amplio rango de neurotransmisores, ha impulsado la investigación del desarrollo de antagonistas / agonistas inversos, los cuales tienen potencial en las condiciones del comportamiento y fisiológicas y, por ejemplo los desórdenes del SNC, tales como la narcolepsia, trastornos del sueño, desórdenes de cognición o atención, dolor y la supresión de la ingesta de alimentos.

Las neuronas histaminérgicas están localizadas en el núcleo tuberomamilar del hipotálamo posterior y proyectan sus axones a regiones del cerebro incluyendo el hipotálamo, tálamo, corteza cerebral, amígdalas y tabique. La actividad de las neuronas histaminérgicas está estrechamente ligada con el ciclo de sueño / vigilia y numerosos informes en la literatura han establecido que el receptor H3 juega un rol en los procesos

relacionados con la cognición y el sueño / vigilia, basados en estudios con antagonistas de los receptores H3 conocidos y sus efectos en modelos animales (**4**, **5**, **6**). El compuesto antagonista de H3 A-349821, actualmente está en desarrollo preclínico y ha sido probado en demostrar los efectos de aumento de cognición en la rata (7).

El sistema histaminérgico es uno de los objetivos de la señalización de leptina en el hipotálamo. El conocido antagonista de H3 clobenpropit, aumenta la liberación de histamina en el hipotálamo de ratones y tiene el efecto de reducir el consumo de energía en ratones delgados y obesos (8). El rol del receptor H3 en la obesidad ha sido además sustentado a través de estudios con los antagonistas tioperamida y ciproxifan y más recientemente con compuestos sin imidazol **(10).**

El antagonista no selectivo tioperamida tiene un efecto antinociceptivo en una cantidad de modelos de dolor agudo **(11)**. Los antagonistas de H3 han sido sugeridos para el tratamiento del dolor neuropático **(12).** Adicionalmente, GSK207040 y GSK334429 son compuestos antagonistas de H3 selectivos sin imidazol que muestran gran afinidad por ambos receptores H3, de rata y humanos. Ambos compuestos reducen la alodinia táctil en la rata, lo que sugiere que los antagonistas de H3 tienen potencial terapéutico en el tratamiento de dolor neuropático **(13).**

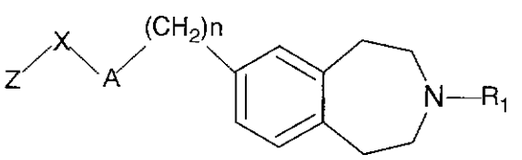
En un intento por identificar compuestos con propiedades farmacológicas mejoradas, los compuestos sin imidazol han estado al frente de las investigaciones, por ejemplo A-349821 (**7**) y GSK207040 / GSK334429 (**13**). ABT-239 está actualmente siendo investigado para el uso en el trastorno de déficit de atención e hiperactividad, la enfermedad de Alzheimer y la esquizofrenia (14).

WO05/123723, WO06/018260 y WO05/058837 divulgan derivados de benzazepina antagonistas de H3 reivindicados como útiles en el tratamiento de desórdenes psiquiátricos y neurológicos. WO05/058328 divulga receptores D3 de dopamina derivados de benzazepina, reivindicados para ser útiles en el tratamiento de los desórdenes del

SNC, tales como la esquizofrenia y depresión. WO02/40471 también divulga derivados de benzazepina útiles como moduladores del receptor D3 de dopamina. US2003/0158177 divulga antagonistas de hormona que concentra la melanina, reivindicados como en el tratamiento de la obesidad.

Existe una necesidad clínica de generar más clases de antagonista de H3 y/o compuestos agonista inverso, que demuestren las propiedades farmacológicas mejoradas (9).

De acuerdo a un primer aspecto de la presente invención, se proporciona un compuesto que tiene la Fórmula 1:



Fórmula 1

en donde:

R1 es un grupo seleccionado de C_{3-8} cicloalquilo, C_{1-6} alquilo, y C_{3-8} cicloalquilo-sustituido C_{1-6} alquileno, cada uno de los grupos puede ser opcionalmente sustituido con C_{1-6} alquilo (tal como metilo), halógeno (tal como F), haloC_{1-6} alquilo (tal como CH_2F) o OR15, o R1 es heterociclilo, opcionalmente sustituido con C_{1-6} alquilo (como metilo), haloC_{1-6} alquilo (como CH_2F) o OR15;

n es 0, 1, 2, 3 o 4, el grupo alquileno $-(CH_2)_n-$ formado de ese modo es opcionalmente sustituido con un grupo seleccionado de C_{1-4} alquilo, C_{3-8} cicloalquilo y arilsulfonilo;

A es un grupo seleccionado de -N(R2)CO-, -OC(O)-, -C(O)O-, -CON(R2)-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cicloalquileno-, -C(R2)(haloC_{1-6} alquilo)-, C_{1-4} alquileno y -C(OR3)(haloC_{1-6} alquilo);

R2 y R3 cada uno son seleccionados independientemente de H, C_{1-6} alquilo (el cual puede ser de cadena recta o de cadena ramificada) y C_{3-8} cicloalquilo, o, cuando A es -N(R2)CO-

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y X está ausente, R2 puede formar, junto con el átomo de nitrógeno adyacente y Z, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido;

X está ausente o es C_{1-4} alquileno o C_{2-4} alquenileno, opcionalmente sustituido con uno o más grupos alquilo C_{1-4}, OR16, halógeno (tales como F), o haloC_{1-6} alquilo (tales como CF_3);

Z es seleccionado de arilo, heteroarilo, C_{3-8} cicloalquilo, y heterociclilo, cada uno de los cuales puede ser opcionalmente sustituido por un grupo seleccionado de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo, o cuando X está presente, Z puede ser H, o cuando X está ausente y A es -C(R2)(OR3)- o -N(R2)CO-, Z puede ser H, o cuando A es -N(R2)CO- y X está ausente, Z puede formar, junto con el átomo de nitrógeno adyacente y R2, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido, en donde, cuando A es -CO-, Z está ligado a X o A via un átomo de carbono y en donde A es –N(R2)CO- y Z es H, R1 es C_{3-8} cicloalquilo; y

Y representa un enlace, C_{1-6} alquileno, CO, COC_{2-6} alquenileno, O, SO_2, NR14, o $NHCOC_{1-6}$ alquileno;

en donde dichos grupos Z cicloalquilo, arilo, heteroarilo y heterociclilo, pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes, y los cuales son seleccionados de halógeno, haloC_{1-6} alquilo, tales como halometilo, hidroxi, ciano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alquilo-NR5R6, -C_{3-8} cicloalquilo-NR5R6, -CONR12R13, -NR12COR13, -NR5SO_2R6, -OCONR5R6, -NR5CO_2R6, -NR4CONR5R6 o -SO_2NR5R6-SHR8, -C_{1-6} alquilo-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, -C_{1-6} alquilo-SO_2R9, -C_{1-6} alquilo-CONHR9, -C_{1-6} alquilo-SONHR9, -C_{1-6} alquilo-COR10, -CO-C_{1-6} alquilo-R10, -O-C_{1-6} alquilo-R11 (en donde R4, R5 y R6 independientemente representan hidrógeno, C_{1-6} alquilo, -C_{3-8} cicloalquilo, -C_{1-6} alquileno-C_{3-8} cicloalquilo, arilo, heterociclilo o heteroarilo, en donde R8 representa -C_{1-6} alquilo, en donde R9 representa C_{1-6} alquilo o arilo, en donde R10 representa arilo, en donde R11

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representa C_{3-8} cicloalquilo o arilo, R12, R13, R14, R15 y R16 cada uno independientemente representa H o C_{1-6} alquilo, y en donde -NR5R6 y -NR12R13 pueden representar un grupo heterociclilo que contiene nitrógeno); en donde dichos grupos R4, R5, R6, R8, R9, R10 y R11 pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes, y los cuales son seleccionados del grupo consistente de halógeno, hidroxi, C_{1-6} alquilo, C_{1-6} alcoxi, ciano, amino, =O o trifluorometilo;

en donde los sustituyentes de Z seleccionados de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes seleccionados de =O, hidroxi, ciano, nitro, halógeno, haloC_{1-6} alquilo (tales como halometilo) y C_{1-6} alquilo;

en donde, cuando A es C_{1-4} alquileno, dicho grupo Z cicloalquilo, arilo, heteroarilo o heterociclilo (como un grupo heterociclilo Z) es sustituido al menos con hidroxi, CF_3 o =O;

y en donde, cuando A es CON(R2), n es 1;

o una sal aceptable para uso farmacéutico o un éster de la misma,

siempre que: cuando A es -CO-, R1 is CH_3, C_{3-8} cicloalquilo-sustituido C_{1-6} alquileno o n-butil, n es 0 y X es -CH_2CH_2-, Z no sea N-benzil sustituido 4-piperidinil, N-(3-fluorobenzil)-sustituido 4-piperidinil o N-acetil sustituido 4-piperidinil;

cuando A es -OC(O)-, R1 es ciclobutilo, n es 0 y X es -CH_2CH_2-, Z no sea H;

cuando A es -OC(O)-, R1 es n-propilo, n es 0 y X es -CH_2-, Z no sea H; y

cuando A es –CO-, R1 es CH_3, n es 0 y X es CH_2, Z no sea H.

Se ha descubierto que los compuestos de la invención modulan el receptor H3 de histamina. En particular, los compuestos poseen propiedades de antagonista o agonista inverso en este receptor. Basados en la alta afinidad por el receptor, los compuestos pueden tener el potencial de exhibir selectividad útil por el receptor H3. Ha sido descubierto que los compuestos de la invención donde n es al menos 1, particularmente

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aquellos en los cuales A es -CON(R2)-, y particularmente aquellos en los cuales n es 1, poseen propiedades de permeabilidad de la barrera de la sangre que va al cerebro, haciéndolos potencialmente apropiados para el tratamiento de los desórdenes del SNC.

El término 'C_{x-y} alquilo', según se usa en el presente documento, se refiere a un grupo hidrocarburo saturado lineal o ramificado, que contiene de x a y átomos de carbono. Por ejemplo, C_{1-6} alquilo se refiere a un grupo de hidrocarbono saturado lineal o raminificado, que contiene de 1 a 6 átomos de carbono. Ejemplos de grupos C_{1-6} alquilo incluyen metilo, etilo, n-propilo, isopropilo, n- butilo, isobutilo, sec-butilo, tert butilo, n-pentilo, isopentilo, neopentilo y hexilo.

El término 'C_{x-y} alquileno', según se usa en el presente documento, se refiere a un grupo hidrocarburo divalente obtenido removiendo un átomo de hidrógeno del 'C_{x-y} alquilo' mencionado anteriormente. Ejemplos de los grupos C_{1-6} alquileno incluyen metileno, etileno y propileno.

El término 'C_{x-y} alquenilo', según se usa en el presente documento, se refiere a un grupo hidrocarburo lineal o ramificado que contiene uno o más enlaces doble carbono-carbono y que tiene de x a y átomos de carbono. Ejemplos de dichos grupos incluyen etenilo, propenilo, butenilo, pentenilo y hexenilo.

El término 'C_{x-y} alquenileno', según se usa en el presente documento, se refiere a un grupo hidrocarburo divalente obtenido removiendo un átomo de hidrógeno de 'C_{x-y} alquenilo' antes mencionado. Ejemplos de grupos C_{2-6} alquenileno incluyen vinileno y propenileno.

El término 'C_{x-y} alcoxi', según se usa en el presente documento, se refiere a un grupo -O-C_{x-y} alquilo en donde -O-C_{x-y} alquilo es según se define en el presente documento. Ejemplos de dichos grupos incluyen metoxi, etoxi, propoxi, butoxi, pentoxi y hexoxi.

El término 'C_{x-y} cicloalquilo', según se usa en el presente documento, se refiere a un anillo de hidrocarbono monocíclico saturado de x a y átomos de carbono. Por ejemplo, C_{3-8}

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cicloalquilo se refiere a un anillo de hidrocarbono monocíclico saturado de 3 a 8 átomos de carbono. Los ejemplos de grupos de C_{3-8} cicloalquilo incluyen ciclopropil, ciclobutilo, ciclopentilo, ciclohexil, cicloheptil y ciclooctil.

El término 'C_{x-y} cicloalquileno', según se usa en el presente documento, se refiere a un grupo hidrocarburo divalente obtenido removiendo un átomo de hidrógeno de 'C_{x-y} cicloalquilo' anterior. Ejemplos de los grupos C_{3-8} cicloalquileno incluyen ciclopropileno y ciclobutileno.

El término 'halógeno', según se usa en el presente documento, se refiere a un floruro, cloruro, bromuro o a un yoduro, a menos que se especifique lo contrario.

El término 'haloC_{1-6} alquilo', según se usa en el presente documento, se refiere al grupo C_{1-6} alquilo, según es definido por el presente documento, en donde al menos un átomo de hidrógeno es reemplazado por halógeno. Ejemplos de dichos grupos incluyen fluoroetil, trifluorometilo y trifluoroetilo.

El término "arilo", según se usa en el presente documento, se refiere a un anillo de hidrocarbono monocíclico o bicíclico, en donde al menos un anillo es aromático. Ejemplos de dichos grupos incluyen fenilo, naftilo y tetrahidronaftalenilo.

El término "heteroarilo", según se usa en el presente documento, se refiere a un anillo aromático monocíclico de 5-6 miembros o a un anillo aromático bicíclico fusionado de 8-10 miembros, el anillo bíciclico o monocíclico contiene 1 a 4 héteroatomos seleccionados de oxígeno, nitrógeno y azufre. Ejemplos de dichos anillos aromáticos monocíclicos incluyen tienilo, furilo, furazanilo, pirrolilo, triazolilo, tetrazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, isotiazolilo, isoxazolilo, tiadiazolilo, piranilo, pirazolilo, pirimidilo, piridazinilo, pirazinilo, piridilo, triazinilo, tetrazinilo y similares. Ejemplos de dichos anillos aromáticos bicíclicos incluyen quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, pteridinilo, cinnolinilo, ftalazinilo, naftiridinilo, indolilo, isoindolilo, azaindolilo, indolizinilo, indazolilo, purinilo, pirrolopiridinilo, furopiridinilo, benzofuranilo, isobenzofuranilo,

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benzotienilo, benzoimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzoxadiazolilo, benzotiadiazolilo y imidazopiridilo.

El término "heterociclilo" se refiere a un anillo monocíclico de 4-7 miembros o a un anillo bicíclico fusionado de 8-12 miembros, los cuales pueden ser saturados o parcialmente no saturados, cuyo anillo monocíclico o bicíclico contiene 1 a 4 heteroátomos seleccionados de oxígeno, nitrógeno, silicio o azufre. Ejemplos de dichos anillos monocíclicos incluyen pirrolidinilo, azetidinilo, pirazolidinilo, oxazolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, hidantoinilo, valerolactamilo, oxiranilo, oxetanilo, dioxolanilo, dioxanilo, oxatiolanilo, oxatianilo, ditianilo, dihidrofuranilo, tetrahidrofuranilo, dihidropiranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidropirimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo, diazepanilo y azepanilo. Ejemplos de dichos anillos bicíclicos incluyen indolinilo, isoindolinilo, benzopiranilo, quinuclidinilo, 2,3,4,5-tetrahidro-1H-3-benzazepina y tetrahidroisoquinolinilo.

El término "heterociclilo que contiene N" se refiere a un anillo que contiene al menos un átomo de nitrógeno y seleccionado de entre los grupos 'heterociclilo' mencionados anteriormente. Ejemplos preferidos de dichos anillos incluyen pirrolidinilo, azetidinilo, piperidinilo, piperazinilo, morfolinilo y tiomorfolinilo.

"Las sales aceptables para uso farmacéutico" de los compuestos de la Fórmula I de la presente invención, incluyen sales con bases inorgánicas, sales con bases orgánicas, sales con ácidos inorgánicos, sales con ácidos orgánicos y sales con aminoácidos básicos o ácidos. En particular, las sales con ácido pueden ser empleadas en algunas instancias. El compuesto de la Fórmula I de la presente invención puede estar en forma de hidrato o no hidrato.

"Los ésteres aceptables para uso farmacéutico" de los compuestos de la Fórmula I son derivados en los cuales, uno o más grupos carboxilo (es decir grupos -C(O)OH) de dichos compuestos son modificados por reacción con una fracción alcohólica W-OH, de manera

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de producir grupos -C(O)OW, en donde W puede ser C_{1-18} alquilo (por ejemplo C_{1-6} alquilo), arilo, heteroarilo, C_{3-8} cicloalquilo o combinaciones de los mismos.

Métodos generales para la preparación de las sales y ésteres son bien conocidos por los expertos. La aceptabilidad farmacéutica de las sales y ésteres dependerá de una variedad de factores, incluyendo las características de procesamiento de la formulación y el comportamiento *in vivo*, y el experto podría rápidamente ser capaz de evaluar dichos factores en relación a la presente divulgación.

Cuando los compuestos de la invención existen en diferentes formas enantioméricas y/o diastereoisoméricas (incluyendo isomerismo geométrico alrededor de un enlace doble), estos compuestos se pueden preparar como mezclas isoméricas o racémicas, aunque la invención se refiere a todos dichos enantiómeros o isómeros, ya sea si están presentes en una forma ópticamente pura o como mezclas con otros isómeros. Los enantiómeros o isómeros individuales se pueden obtener mediante métodos conocidos en el arte, tales como la resolución óptica de productos o intermediarios (por ejemplo separación cromatográfica quiral (como la HPLC quiral)), o un enfoque de síntesis enantiomérica. Semejantemente, cuando los compuestos de la invención puedan existir como una forma alternativa tautomérica (por ejemplo, keto/enol, ácido imídico/amida), la invención se refiere a los tautómeros individuales en aislación, y a mezclas de los tautómeros en todas las proporciones.

En modalidades específicas del primer aspecto de la invención, cuando A es NHCO, R1 es ciclobutilo, etilo, n-propilo o isobutilo, n es 0 y X está ausente, Z no es 1-[[5-cloro-2(2-metilopropoxi)fenil]metil]-5-metil-1H-pirazol-3-il, y/o, cuando A es C_2 alquileno, R1 es CH_3, n es 0 y X está ausente, Z no es N-(4-carboxiciclohexil)- imidazolidinonilo sustituido.

En ciertas modalidades del primer aspecto de la invención: R1 es un grupo seleccionado de C_{3-8} cicloalquilo, C_{1-6} alquilo, y C_{3-8} cicloalquilo-sustituido C_{1-6} alquileno, cada uno de los

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grupos puede ser opcionalmente sustituido con halógeno (como F), haloC_{1-6} alquilo (como CF_3) o OR2;

n es 0, 1, 2, 3 o 4, el grupo alquileno $-(CH_2)_n$ formado de ese modo, siendo opcionalmente sustituido con un grupo seleccionado de C_{1-4} alquilo y C_{3-8} cicloalquilo;

A es un grupo seleccionado de -N(R2)CO-, -OC(O)-, -C(O)O-, -CON(R2)-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cicloalquileno-, -C(R2)(haloC_{1-6} alquil)- y -C(OR3)(haloC_{1-6} alquil)-;

R2 y R3 cada uno son independientemente seleccionados de H, C_{1-6} alquilo (el cual puede ser una cadena recta o una cadena ramificada), y C_{3-8} cicloalquilo, o cuando A es -N(R2)CO- y X está ausente, R2 puede formar, junto con el átomo de nitrógeno adyacente y Z, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido;

X está ausente o es C_{1-4} alquileno o C_{2-4} alquenileno, opcionalmente sustituido con uno o más grupos C_{1-4} alquilo, OR2, halógeno (como F) o haloC_{1-6} alquilo (como CF_3);

Z es seleccionado de arilo, heteroarilo, C_{3-8} cicloalquilo, y heterociclilo, cada uno de los cuales puede ser opcionalmente sustituido por un grupo seleccionado de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo, o, cuando X está presente, Z puede ser H, o, cuando A es -N(R2)CO- y X está ausente, Z puede formar, junto con el átomo de nitrógeno adyacente y R2, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido, siempre que A sea -CO-, Z esté ligado a X o A via un átomo de carbono; y

Y representa un enlace, C_{1-6} alquileno, CO, CONH, COC_{2-6} alquenileno, O, SO_2 o $NHCOC_{1-6}$ alquileno;

en donde dichos grupos Z alquileno, cicloalquilo, arilo, heteroarilo y heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes, y los cuales son seleccionados de halógeno, haloC_{1-6} alquilo, tales como halometilo, hidroxi, ciano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alquilo-

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NR5R6, -C_{3-8} cicloalquilo-NR5R6, -CONR5R6, -NR5CR6, -$NR5SO_2R6$, -OCONR5R6 , -$NR5CO_2R6$, -NR4CONR5R6 o -SO_2NR5R6-SHR8, C_{1-6} alquilo-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, C_{1-6} alquilo-SO_2R9, C_{1-6} alquilo-CONHR9, C_{1-6} alquilo-SONHR9, C_{1-6} alquilo-COR10, -CO-C_{1-6} alquilo-R10, -O-C_{1-6} alquilo-R11 (en donde R4, R5 y R6 independientemente representan hidrógeno, C_{1-6} alquilo, -C_{3-8} cicloalquilo, -C_{1-6} alquilo-C_{3-8} cicloalquilo, arilo, heterociclilo o heteroarilo, en donde R8 representa C_{1-6} alquilo, en donde R9 representa C_{1-6} alquilo o arilo, en donde R10 representa arilo, en donde R11 representa C_{3-8} cicloalquilo o arilo, y en donde -NR5R6 puede representar un grupo heterociclilo que contiene nitrógeno); en donde dichos grupos R4, R5, R6, R8, R9, R10 y R11 pueden ser opcionalmente sustituidos, los cuales pueden ser los mismos o diferentes, y los cuales son seleccionados del grupo consistente en halógeno, hidroxi, C_{1-6} alquilo, C_{1-6} alcoxi, ciano, amino, =O o trifluorometilo;

y en donde las condiciones del primer aspecto, aplican.

En modalidades adicionales del primer aspecto de la invención, R1 es un grupo seleccionado de C_{3-8} cicloalquilo, C_{1-6} alquilo, y C_{3-8} cicloalquilo-sustituido C_{1-6} alquileno, cada uno de los grupos puede ser opcionalmente sustituido con halógeno (como F), haloC_{1-6} alquilo (como CF_3) o OR2;

n es 0, 1, 2, 3 o 4, el grupo alquileno -$(CH_2)_n$- formado de ese modo, siendo opcionalmente sustituido con un grupo seleccionado de C_{1-4} alquilo y C_{3-8} cicloalquilo;

A es un grupo seleccionado de -N(R2)CO-, -OC(O)-, -C(O)O-, -CON(R2)-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cicloalquileno-, -C(R2)(haloC_{1-6} alquil)-, C_{1-4} alquileno y -C(OR3)(haloC_{1-6} alquil)-;

R2 y R3 son cada uno independientemente seleccionados de H, C_{1-6} alquilo (el cual puede ser una cadena recta o una cadena ramificada), y C_{3-8} cicloalquilo o, cuando A es -N(R2)CO- y X está ausente, R2 puede formar, junto con el átomo de nitrógeno y Z, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido;

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X está ausente o es C_{1-4} alquileno o C_{2-4} alquenileno, opcionalmente sustituido con uno o más grupos C_{1-4} alquilo, OR2, halógeno (tal como F), o halo C_{1-6} alquilo (tal como CF_3);

Z es seleccionado de arilo, heteroarilo, C_{3-8} cicloalquilo, y heterociclilo, cada uno de los cuales puede ser opcionalmente sustituido por un grupo seleccionado de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo, o cuando X está presente, Z puede ser H o, cuando X está ausente y A es -C(R2)(OR3)- o -N(R2)CO-, Z puede ser H, o cuando A es -N(R2)CO- y X está ausente, Z puede formar, junto con el átomo de nitrógeno adyacente y R2, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido, siempre y cuando A sea -CO-, Z esté ligado a X o A via un átomo de carbono; y

Y representa un enlace, C_{1-6} alquileno, CO, CONH, COC_{2-6} alquenileno, O, SO_2 o $NHCOC_{1-6}$ alquileno;

en donde dichos grupos cicloalquilo, arilo, heteroarilo y heterociclilo de Z pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes, y los cuales son seleccionados de halógeno, haloC_{1-6} alquilo, tales como halometilo, hidroxi, ciano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alquilo-NR5R6, -C_{3-8} cicloalquilo-NR5R6, -CONR5R6, -NR5CR6, -NR5SO_2R6, -OCONR5R6 , -NR5CO_2R6, -NR4CONR5R6 o -SO_2NR5R6-SHR8, C_{1-6} alquilo-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, C_{1-6} alquilo-SO_2R9, C_{1-6} alquilo-CONHR9, C_{1-6} alquilo-SONHR9, C_{1-6} alquilo-COR10, -CO-C_{1-6} alquilo-R10, -O-C_{1-6} alquilo-R11 (en donde R4, R5 y R6 independientemente representan hidrógeno, C_{1-6} alquilo, -C_{3-8} cicloalquilo, -C_{1-6} alquil-C_{3-8} cicloalquilo, arilo, heterociclilo o heteroarilo, en donde R8 representa C_{1-6} alquilo, en donde R9 representa C_{1-6} alquilo o arilo, en donde R10 representa arilo, en donde R11 representa C_{3-8} cicloalquilo o arilo, y en donde -NR5R6 puede representar un grupo heterociclilo que contiene nitrógeno); en donde dichos grupos R4, R5, R6, R8, R9, R10 y R11 pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos

o diferentes, y los cuales son seleccionados del grupo consistente en halógeno, hidroxi, C_{1-6} alquilo, C_{1-6} alcoxi, ciano, amino, =O o trifluorometilo;

en donde los sustituyentes de Z seleccionados de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes seleccionados de =O, hidroxi, ciano, nitro, halógeno, haloC_{1-6} (alquilo como halometilo) y C_{1-6} alquilo;

y en donde, cuando A es C_{1-4} alquileno, dicho grupo Z cicloalquilo, arilo, heteroarilo o heterociclilo (como un grupo Z heterociclilo) es sustituido al menos con hidroxi;

Y en donde las condiciones del primer aspecto, aplican.

En ciertos compuestos de la invención, en los cuales Z es seleccionado de arilo, heteroarilo, C_{3-8} cicloalquilo, heterociclilo, -C_{3-8} cicloalquil-Y-C_{3-8} cicloalquilo, -C_{3-8} cicloalquil-Y-arilo, -C_{3-8} cicloalquil-Y-heteroarilo, -C_{3-8} cicloalquil-Y-heterociclilo, -aril-Y-C_{3-8} cicloalquilo, -aril-Y-arilo, -aril-Y-heteroarilo, -aril-Y-heterociclilo, -heteroaril-Y-C_{3-8} cicloalquilo, -heteroaril-Y-arilo, -heteroaril-Y-heteroarilo, -heteroaril-Y-heterociclilo, -heterociclil-Y-C_{3-8} cicloalquilo, -heterociclil-Y-arilo, -heterociclil-Y-heteroarilo, y -heterociclil-Y-heterociclilo, Z puede estar ligado a A o X via un átomo de carbono (esto es, un átomo de carbono del grupo Z). Cuando A es -CO-, de modo que Z esté ligado a A o X via un átomo de carbono, esto significa que Z está ligado a A o X via un átomo de carbono de Z.

En ciertas modalidades de la invención, Y representa un enlace o C_{1-6} alquileno (por ejemplo metileno).

En ciertas modalidades de la invención, cuando A es -CO-, n es 0, R1 es C_{1-6} alquilo (como CH_3), y X está presente (y puede ser C_{1-4} alquilo, tal como -CH_2CH_2-), Z no es un grupo -heterociclil-Y-aril- que contiene un grupo piperidinilo. En modalidades específicas dentro de este grupo, Z no es -heterociclil-Y-aril-

En modalidades específicas, Z puede ser H cuando A es -CONH-(o -CON(R2)-) o -NHCO-(o -N(R2)CO-).

En otras modalidades, por ejemplo, cuando A es -NHCO- (o -N(R2)CO-), y n es 0, Z puede ser cualquiera de los grupos que contienen arilo, cicloalquilo, heterociclilo o heteroarilo, definidas anteriormente, particularmente fracciones que contienen una combinación de dos o más de dichos grupos. Dichos grupos de Z, en ciertas instancias, no son sustituidos con halógeno y/o alcoxi (como butiloxi). En ciertas instancias, cuando Z comprende dos o más dichos grupos, uno o ninguno de los grupos arilo, cicloalquilo, heterociclilo o heteroarilo de Z es además sustituido. En ciertas modalidades, Z no es aril-Y-heteroarilo, particularmente no aril-CH_2-heteroarilo.

En compuestos específicas de la invención, A es seleccionado de -N(R2)CO-, -OC(O)-, -C(O)O-, -CON(R2)-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cicloalquileno-, CO-, C_{1-4} alquileno, -C(R2)(haloC_{1-6} alquil)- y -C(OR3)(haloC_{1-6} alquil)-.

En aquellas modalidades en las cuales A es -N(R2)CO- y X está ausente, con R2 formando, junto con el átomo de nitrógeno adyacente y Z, un grupo heterociclilo que contiene N, los posibles sustituyentes en el grupo heterociclilo que contiene N, incluyen halógeno y carbamoilo.

En ciertos compuestos de la invención, R1 es C_{1-6} alquilo (como C_{1-3} alquilo), C_{3-8} cicloalquilo (como C_{3-7} cicloalquilo) o heterociclilo (preferentemente tetrahidrofuranilo). Los grupos específicas C_{1-6} alquilo o C_{3-8} de R1 incluyen metilo, etilo, isopropilo, ciclopropilo, ciclobutilo y ciclopentilo.

Alternativamente, R1 puede ser C_{1-6} alquilo (tal como C_{1-3} alquilo) sustituido con C_{3-8} cicloalquilo (como C_{3-7} cicloalquilo). In dichas modalidades, R1 puede por ejemplo, ser ciclopropiletilo o ciclopropilmetilo.

En todo caso, C_{1-6} alquilo, C_{3-8} cicloalquileno-C_{1-6} alquilo y C_{3-8} cicloalquilo para R1 pueden ser además sustituidos con uno o más grupos (por ejemplo 1 a 3) seleccionados de hidroxi, C_{1-6} alcoxi (como metoxi), C_{1-6} alquilo (como metilo), halógeno (como F o Cl) y

haloC_{1-6} alquilo, por ejemplo halometilo (como CH_2F), particularmente seleccionado de F y CH_2F.

En modalidades específicas de la invención, R1 es C_{3-8} cicloalquilo sustituido con hidroxi o metoxi.

En ciertas modalidades de la invención, n es 0, 1 o 2.

En modalidades específicas n es 0.

En modalidades específicas n es 1.

En ciertas modalidades de la invención, A es -N(R2)CO-, -OC(O)-, -CON(R2)-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)- o -C(=CR2R3)-.

En modalidades específicas de la invención, A es -C(R2)(OR3)-, C_{1-4}alquileno, -N(R2)CO-, o -CON(R2)-.

En ciertas modalidades de la invención, A es -C(R2)(OR3)-.

En ciertas modalidades de la invención, A es –CON(R2)-.

En modalidades específicas de la invención, n es 0 y A es -N(R2)CO- (como -NHCO-) en particular -N(R2)CO-. En otras modalidades, n es 0 y A es -C(R2)(OR3)- (tal como -C(R2)OH-).

En otras modalidades específicas de la invención, n es 1 y A es -N(R2)CO- (tal como -NHCO-) o -CON(R2)- (tal como -CONH-), en particular –CON(R2)-. En otras modalidades, n es 1 y A es -C(R2)(OR3)- (tal como -C(R2)OH-).

En ciertos compuestos de la invención R2 y R3 cada uno son independientemente H o C_{1-6} alquilo, tal como metilo. En modalidades específicas, R2 es H. En modalidades específicas, R3 es H.

En ciertas modalidades de la invención, A es -NHCO-, -N(Me)CO-, -OC(O)-, -CONH-, -CO-, -CH(OH)-, -CH(OMe)-, -C(=N-O-Me)-, -C(=N-O-H)-, $-CH_2-$ o $-C(=CH_2)-$.

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En ciertos compuestos de la invención, donde A es -C(R2)(haloC_{1-6} alquil)- o -C(OR3)(haloC_{1-6} alquilo), el grupo (haloC_{1-6} alquilo) puede ser un alquilo fluorinado, tal como CF_3.

En ciertas modalidades de la invención, X está ausente o es C_{1-4} alquileno (por ejemplo, metileno, etileno) o C_{2-4} alquenileno (por ejemplo vinileno), cada uno de los cuales puede ser opcionalmente sustituido con un grupo C_{1-4} alquilo (por ejemplo, metilo).

En modalidades específicas, X es un grupo C_{1-4} alquileno (preferentemente de cadena recta), opcionalmente teniendo uno o más sustituyentes (por ejemplo 1 a 3) metilo o etilo. En ciertos compuestos, X es metileno o etileno.

En ciertas modalidades de la invención, cuando A es -N(R2)CO- y X está ausente, R2 puede formar, junto con el átomo de nitrógeno adyacente y Z, un grupo heterociclilo que contiene N (por ejemplo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo), los cuales puede ser opcionalmente sustituidos por uno a tres átomos de halógeno (por ejemplo, F) o grupos carbamoilo.

En ciertos compuestos de la presente invención, Z es arilo, heteroarilo, C_{3-8} cicloalquilo o heterociclilo, cada uno de los cuales puede ser sustituido con uno o más (por ejemplo, 1 a 3) sustituyentes, seleccionados de C_{1-6} alquilo (tales como metilo, etilo o isopropilo), C_{1-6} cicloalquilo (tal como ciclobutilo), halógeno (tales como Cl, Br o F), haloC_{1-6} alquilo (tal como halometilo (por ejemplo, trifluorometilo)), ciano, amino, C_{1-6} alcoxi (tal como metoxi), carbonil (tal como C_{1-6} alquil-carbonilo (por ejemplo, acetilo), carboxilo, C_{1-6} alcoxi-carbonilo (por ejemplo, metoxicarbonilo)), amida (tales como carbamoilo, C_{1-6} alquil-carbamoilo (por ejemplo, metilcarbamoilo)), heterociclilo-amino (por ejemplo, ciclobutilamino, ciclopropilamino), arilo (como fenilo), y heteroarilo (como triazolilo, tiazolilo, pirazolilo, tiofenilo, pirrolidinilo, morfolinilo o piridinilo).

En modalidades en las cuales Z es, o comprende, heteroarilo, dicho heteroarilo puede ser seleccionado de los grupos tienilo, furilo, furazanilo, pirrolilo, triazolilo, tetrazolilo,

imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, isotiazolilo, isoxazolilo, tiadiazolilo, piranilo, pirazolilo, pirimidilo, piridazinilo, pirazinilo, piridilo, triazinilo, tetrazinilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, pteridinilo, cinnolinilo, ftalazinilo, naftiridinilo, indolilo, isoindolilo, azaindolilo, indolizinilo, indazolilo, purinilo, pirrolopiridinilo, fluropiridinilo, benzofuranilo, isobenzofuranilo, benzotienilo, benzimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzoxadiazolilo, benzotiadiazolilo y imidazopiridilo. En particular, dicho heteroarilo puede ser seleccionado de los grupos pirazolilo, piridilo, pirimidilo, piridazinilo, pirazinilo, indolilo, indazolilo, benzimidazolilo, benzotiazolilo, imidazopiridilo, imidazolilo, isoxazolilo, tienilo, oxazolilo, tiazolilo, furilo, imidazopiridilo y pirrolilo.

En modalidades en las cuales Z es, o comprende, arilo, dicho arilo puede ser en particular un grupo fenilo, naftilo, o tetrahidronaftalenilo, en particular un grupo fenilo.

En modalidades en las cuales Z es, o comprende heterociclilo, dicho heterociclilo puede ser seleccionado de pirrolidinilo, azetidinilo, pirazolidinilo, oxazolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, hydantoinilo, valerolactamilo, oxiranilo, oxetanilo, dioxolanilo, dioxanilo, oxatiolanilo, oxatianilo, ditianilo, dihidrofuranilo, tetrahidrofuranilo, dihidropiranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidropirimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo, diazepanilo, azepanilo, indolinilo, isoindolinilo, benzopiranilo, quinuclidinilo, 2,3,4,5-tetrahidro-1H-3-benzazepinilo y tetrahidroisoquinolinilo. En particular, dicho heterociclilo puede ser seleccionado de los grupos piperidinilo, azetidinilo, tetrahidrofuranilo, pirrolidinilo, dioxanilo, tetrahidrotiopiranilo, tetrahidrotiofenilo, morfolinilo y tetrahidropiranilo.

En modalidades en las cuales Z es, o comprende C_{3-8} cicloalquilo, dicho C_{3-8} cicloalquilo puede en particular ser seleccionado de los grupos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo, más en particular de los grupos ciclobutilo, ciclopentilo y ciclohexilo.

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En modalidades específicas, Z es arilo (preferentemente fenilo), heteroarilo (preferentemente pirazolilo, piridilo, indolilo, indazolilo, benzimidazolilo, benzotiazolilo, imidazopiridilo, imidazolilo, isoxazolilo, tienilo, oxazolilo, tiazolilo, furilo, piridazinilo, pirimidilo, pirazinilo o pirrolilo), C_{3-8} cicloalquilo (preferentemente ciclobutilo, ciclopentilo o ciclohexilo) o heterociclilo (preferentemente piperidinilo, tetrahidrofuranilo, morfolinilo, pirrolidinilo, tetrahidrotiofenilo, piperazinilo, tetrahidrotiopiranilo, dioxanilo o tetrahidropiranilo),

cada uno de los cuales puede ser opcionalmente sustituido por

(1) un grupo seleccionado de -Y-arilo, -Y-heteroarilo, Y-heterociclilo, y -Y-C_{3-8} cicloalquilo, en donde Y representa un enlace, O, NR14 o C_{1-6} alquileno (preferentemente metileno), y dicho arilo es fenilo, dicho heteroarilo es seleccionado de triazolilo, tiazolilo, tienilo y pirazolilo, dicho heterociclilo es seleccionado de morfolinilo, tetrahidrofuranilo, tetrahidropiranilo y pirrolidinilo, y dicho C_{3-8} cicloalquilo es seleccionado de ciclobutilo o ciclopropilo; o

(2) uno a tres sustituyentes seleccionados de

C_{1-6} alquilo (preferentemente metilo, etilo o isopropilo), C_{3-8} cicloalquilo (preferentemente ciclobutilo) halógeno (preferentemente F, Cl o Br), haloC_{1-6} alquilo (preferentemente trifluorometilo), ciano, hidroxi, amino, C_{1-6} alcoxi (preferentemente metoxi, etoxi o isopropoxi), C_{1-6} alquil-carbonilo (preferentemente acetilo), carboxilo, C_{1-6} alcoxi-carbonil (preferentemente metoxicarbonilo), carbamoilo, hidroxi-sustituido C_{1-6} alquil-carbonilo, C_{3-8} cicloalquil-carbonilo, C_{1-6} alquil-carbamoilo (preferentemente metilcarbamoilo), C_{1-6} alquilamino (preferentemente metilamino), y =O,

en donde los sustituyentes de Z seleccionados de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes seleccionados de =O, hidroxi, ciano, nitro, halógeno, haloC_{1-6} alquilo (como halometilo) y C_{1-6} alquilo.

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En ciertas modalidades Y es un enlace o C_{1-6} alquileno; en modalidades específicas, Y es un enlace.

En ciertos compuestos de la presente invención, Z es H cuando X está presente.

En ciertas modalidades del primer aspecto de la invención, A es -N(R2)CO- o -CON(R2)-, y n es 0, 1 o 2. En ciertas dichas modalidades, R2 es H. En modalidades específicas, A es -CON(R2)-.

En modalidades alternativas del primer aspecto de la invención, A es -OC(O)- o -C(O)O-, y n es 0, 1 o 2.

En otras modalidades del primer aspecto de la invención, A es -C(R2)(OR3)- o -CO-, y n es 0, 1 o 2. En ciertas dichas modalidades, R2 y/o R3 son H o C_{1-6} alquilo, como metilo.

Modalidades específicas del primer aspecto de la invención, incluyen compuestos en donde: R1 es C_{1-6} alquilo (preferentemente metilo, etilo, isopropilo o isobutilo), C_{3-8} cicloalquil-C_{1-6} alquileno- (preferentemente ciclopropilmetilo), o C_{3-8} cicloalquilo (preferentemente ciclobutilo o ciclopentilo), cada uno de los cuales puede opcionalmente ser sustituido por hidroxi, C_{1-6} alcoxi, o uno o dos halógenos (preferentemente F), o R1 es heterociclilo (preferentemente tetrahidrofuranilo), opcionalmente sustituido por hidroxi, C_{1-6} alcoxi, o C_{1-6} alquilo (como metilo);

n es 0, 1 o 2;

A es -N(R2)CO-, -OC(O)-, -CON(R2)-, -CO-, -C(R2)(OR3)-, C_{1-4} alquileno, -C(=N-O-R3)- o -C(=CHR3)-;

R2 y R3 son cada uno independientemente H o C_{1-6} alquilo (preferentemente metilo);

o cuando A es -N(R2)CO- y X está ausente, R2 puede formar, junto con el átomo de nitrógeno adyacente y Z, un grupo heterociclilo que contiene N (opcionalmente azetidinilo, pirrolidinilo, piperidinilo, piperazinilo o morfolinilo, y preferentemente azetidinilo, pirrolidinilo, piperidinilo, o morfolinilo), el cual puede ser opcionalmente sustituido por uno a tres átomos de halógeno (preferentemente F), grupos alquil carbonilo o carbamoilo;

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X está ausente o es C_{1-4} alquileno (preferentemente metileno o etileno) o C_{2-4} alquenileno (preferentemente vinileno), cada uno de los cuales puede ser opcionalmente sustituido con un grupo C_{1-4} alquilo (preferentemente metilo); y

Z es arilo (preferentemente fenilo), heteroarilo (preferentemente pirazolilo, piridilo (tal como 3-piridil), indolilo, indazolilo, benzimidazolilo, benzotiazolilo, imidazopiridilo, imidazolilo, isoxazolilo, tienilo, oxazolilo, tiazolilo, furilo, piridazinilo, pirimidilo, pirazinilo o pirrolilo), C_{3-8} cicloalquilo (preferentemente ciclobutilo, ciclopentilo o ciclohexilo) o heterociclilo (preferentemente piperidinilo, tetrahidrofuranilo, morfolinilo, pirrolidinilo, tetrahidrotiofenilo, piperazinilo, tetrahidrotiopiranilo, dioxanilo, o tetrahidropiranilo),

cada uno de los cuales puede ser opcionalmente sustituido por

(1) un grupo seleccionado de -Y-arilo, -Y-heteroarilo, Y-heterociclilo, y -Y-C_{3-8} cicloalquilo, en donde Y representa un enlace, O, NR14, o C_{1-6} alquileno (preferentemente metileno), y dicho arilo es seleccionado de fenilo, dicho heteroarilo es seleccionado de triazolilo, tiazolilo, tienilo y pirazolilo, dicho heterociclilo es seleccionado de morfolinilo, tetrahidrofuranilo, tetrahidropiranilo y pirrolidinilo, y dicho C_{3-8} cicloalquilo es seleccionado de ciclobutilo y ciclopropilo; o

(2) uno a tres sustituyentes seleccionados de

C_{1-6} alquilo (preferentemente metilo, etilo o isopropilo), halógeno (preferentemente F, Cl o Br), haloC_{1-6} alquilo (preferentemente trifluorometilo), ciano, hidroxi, amino, C_{1-6} alcoxi (preferentemente metoxi, etoxi o isopropoxi), C_{1-6} alquil-carbonilo (preferentemente acetilo), hidoxi-sustituido C_{1-6} alquil-carbonilo, C_{3-8} cicloalquil-carbonilo, carboxilo, C_{1-6} alcoxi-carbonilo (preferentemente metoxicarbonilo), carbamoilo, C_{1-6} alquil-carbamoilo (preferentemente metilocarbamoilo), C_{1-6} alquilamino (como metilamino), y =O; o

Z puede ser H cuando X está presente, o Z puede ser H cuando X está ausente y A es -C(R2)(OR3)- o -N(R2)CO-,

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en donde los sustituyentes de Z seleccionados de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes seleccionados de =O, hidroxi, ciano, nitro, halógeno, haloC_{1-6} alquilo como halometilo y C_{1-6} alquilo,

en donde, cuando A es C_{1-4} alquileno, dicho grupo Z cicloalquilo, arilo, heteroarilo o heterociclilo (como un grupo Z heterociclilo) es sustituido al menos con hidroxi, CF_3 o =O;

y en donde, cuando A is CON(R2), n es 1.

Modalidades específicas del primer aspecto de la invención, incluyen compuestos en donde: R1 es C_{1-6} alquilo (preferentemente metilo, etilo) o C_{3-8} cicloalquilo (preferentemente ciclobutilo o ciclopentilo);

n es 1;

A es -C(R2)(OR3)-;

R2 y R3 son cada uno independientemente H o C_{1-6} alquilo (preferentemente metilo);

X está ausente o es C_{1-4} alquileno (preferentemente metileno);

Z es heteroarilo (preferentemente piridilo), o heterociclilo (preferentemente piperidinilo, o tetrahidropiranilo),

cada uno de los cuales puede opcionalmente ser sustituido por uno a tres sustituyentes seleccionados de

C_{1-6} alquilo (preferentemente metilo, etilo o isopropilo), halógeno (preferentemente Cl o Br), haloC_{1-6} alquilo (preferentemente trifluorometilo), ciano, hidroxi, amino, C_{1-6} alcoxi (preferentemente metoxi), C_{1-6} alquilo-carbonil (preferentemente acetilo o propionil), hidroxi-sustituido C_{1-6} alquil-carbonilo, carboxilo, C_{1-6} alcoxi-carbonilo (preferentemente metoxicarbonil), C_{3-8} cicloalquil-carbonilo, carbamoilo, C_{1-6} alquil-carbamoilo (preferentemente metilcarbamoilo).

Otras modalidades del primer aspecto de la invención, incluyen compuestos en donde R1 es C_{1-6} alquilo (preferentemente metilo o etilo) o C_{3-8} cicloalquilo (preferentemente ciclobutilo o ciclopentilo);

n es 0,

A es C_{1-4} alquileno (preferentemente metileno);

R2 y R3 son cada uno independientemente H o C_{1-6} alquilo (preferentemente metilo);

X está ausente o es C_{1-4} alquileno (preferentemente metileno);

Z es heteroarilo (preferentemente piridilo o pirrolopiridinilo), o heterociclilo (preferentemetne piperidinilo, pirrolidinilo o tetrahidropiranilo),

cada uno de los cuales puede ser opcionalmente sustituido por uno a tres sustituyentes seleccionados de

C_{1-6} alquilo (preferentemente metilo, etilo o isopropilo), halógeno (preferentemente Cl o Br), haloC_{1-6} alquilo (preferentemente trifluorometilo), ciano, hidroxi, amino, C_{1-6} alcoxi (preferentemente metoxi), C_{1-6} alquil-carbonilo (preferentemente acetilo o propionilo), hidroxi-sustituido C_{1-6} alquil-carbonilo, carboxilo, C_{1-6} alcoxi-carbonilo (preferentemente metoxicarbonilo), C_{3-8} cicloalquil-carbonilo, carbamoilo, C_{1-6} alquil-carbamoilo (preferentemente metilcarbamoilo).

en donde dicho grupo Z heteroarilo o heterociclilo (como un grupo heterociclilo Z) es sustituido al menos con hidroxi, CF_3 o =O.

En compuestos específicos definidos de acuerdo a los dos párrafos anteriores, R1 es C_{3-8} cicloalquilo (preferentemente ciclobutilo). En ciertas modalidades, Z es heterociclilo (tales como piperidinilo, pirrolidinilo o tetrahidropiranilo), el cual puede ser sustituido con uno a tres (preferentemente 1 o 2) de los sustituyentes que contienen carbonilo, definidos en dichos párrafos.

Las modalidades alternativas específicas del primer aspecto de la invención, incluyen compuestos en donde: R1 es C_{1-6} alquilo (preferentemtente metilo o etilo), C_{3-8} cicloalquilo

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(preferentemente ciclobutilo o ciclopentilo), opcionalmente sustituido con halógeno (como F) o C_{1-6} alcoxi (como metoxi), o R1 es heterociclilo (preferentemente tetrahidrofuranilo), opcionalmente sustituido con C_{1-6} alquilo;

n es 1;

A es –CON(R2)- o -N(R2)CO-;

R2 es seleccionado de H y C_{1-6} alquilo (preferentemente metilo o isobutilo);

X está ausente o es C_{1-4} alquileno (preferentemente metileno, etileno, propileno, isopropileno, t-butileno o isobutileno), los cuales pueden ser opcionalmente sustituidos con uno o más grupos C_{1-4} alquilo (tal como metilo) o hidroxi;

Z es arilo (preferentemente fenilo), heteroarilo (preferentemente pirazolilo, piridilo (tal como 3-piridilo), pirrolilo, isoxazolilo, piridazinilo, pirimidilo, pirazinilo, tiazolilo, oxazolilo o furilo), C_{3-8} cicloalquilo (preferentemente ciclohexilo) o heterociclilo (preferentemente piperidinilo, tetrahidrofuranilo, morfolinilo, pirrolidinilo, tetrahidrotiofenilo, tetrahidropiridilo, piperazinilo, tetrahidrotiopiranilo, dioxanilo o tetrahidropiranilo),

cada uno de los cuales puede ser opcionalmente sustituido por

(1) un grupo seleccionado de -Y-arilo, -Y-heteroarilo, Y-heterociclilo, y -Y-C_{3-8} cicloalquilo, en donde Y representa un enlace, O, NR14 (como NH), o C_{1-6} alquileno (preferentemente metileno), y dicho arilo es seleccionado de fenilo, dicho heteroarilo es seleccionado de triazolilo, tiazolilo, tienilo y pirazolilo, dicho heterociclilo es seleccionado de morfolinilo, tetrahidrofuranilo, tetrahidropiranilo y pirrolidinilo, y dicho C_{3-8} cicloalquilo es seleccionado de ciclobutilo y ciclopropilo; o

(2) uno a tres sustituyentes seleccionados de

C_{1-6} alquilo (preferentemente metilo, etilo o isopropilo), halógeno (preferentemente F, Cl o Br), haloC_{1-6} alquilo (preferentemente trifluorometilo), ciano, amino, C_{1-6} alquilamino (tal como metilamino), N,N-C_{1-6} dialquilamino (tal como hidroxpropil(metil)amino) C_{1-6} alcoxi (preferentemente metoxi, etoxi o isopropoxi), C_{1-6} alquil-carbonilo (preferentemente

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acetilo), carboxilo, C_{1-6} alcoxi-carbonilo (preferentemente metoxicarbonilo), carbamoilo, C_{1-6} alquil-carbamoilo (preferentemente metilcarbamoilo), hidroxi C_{1-6} alquilo y =O; o

Z puede ser H cuando X está presente,

en donde los sustituyentes de Z seleccionados de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes seleccionados de =O, hidroxi, ciano, nitro, halógeno (como F), haloC_{1-6} alquilo (como halometilo) y C_{1-6} alquilo.

En compuestos específicos definidos de acuerdo al párrafo anterior, R1 es C_{3-8} cicloalquilo (preferentemente ciclobutilo). En ciertos compuestos, A es -CON(R2)-. En ciertas modalidades, Z es heteroarilo (como piridazinilo o piridilo), el cual puede ser sustituido con uno a tres (preferentemente 1 o 2) sustituyentes seleccionados de -Y-heterociclilo (como morfolinilo o pirrolidinilo), C_{1-6} alcoxi (como metoxi) y C_{1-6} alquilamino (como metilamino).

De acuerdo a un segundo aspecto de la invención, se proporciona una composición farmacéutica que comprende un compuesto, de acuerdo al primer aspecto de la invención, junto con uno o más excipientes aceptables para uso farmacéutico.

Las composiciones farmacéuticas de esta invención comprenden cualquiera de los compuestos del primer aspecto de la presente invención, o sales y ésteres aceptables para uso farmacéutico de los mismao, con cualquier portador, adyuvante o vehículo aceptable para uso farmacéutico. Los portadores, adyuvantes o vehículos aceptables para uso farmacéutico que se pueden usar en las composiciones farmacéuticas de esta invención, son aquellos empleados convencionalmente en el campo de la formulación farmacéutica e incluyen, pero no se limitan a, azúcares, alcoholes de azúcar, almidones, intercambiadores iónicos, alumina, estearato de aluminio, lecitina, proteínas de suero, tales como albúmina de suero humano, sustancias buffer tales como fosfatos, glicerina, ácido sórbico, sorbato de potasio, mezclas glicéridas parciales de ácidos grasos vegetales saturados, agua, sales o electrolitos, tales como sulfato de protamina, hidrógeno fosfato

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disódico, hidrógeno fosfato de potasio, cloruro de sodio, sales de cinc, sílice coloidal, trisilicato de magnesio, pirrolidona polivinílica, sustancias con base de celulosa, polietilen glicol, carboximetilcelulosa de sodio, poliacrilatos, ceras, polímeros en bloque de polioxipropileno-polietileno, polietile glicol y lanolina.

Las composiciones farmacéuticas de esta invención, se pueden administrar oralmente, parenteralmente, por inhalación de spray, rectalmente, nasalmente, bucalmente, vaginalmente, o via un reservorio implantado. Se prefiere la administración oral. Las composiciones farmacéuticas de esta invención, pueden contener cualquier portador, adyuvante o vehículo no tóxico convencional aceptable para uso farmacéutico. El término parenteral, según es usado en el presente documento, incluye inyección subcutánea, intracutánea, intravenosa, intramuscular, intra-articular, intrasinovial, intraesternal, intratecal, intralesional, e intracraneal, o técnicas de infusión.

Las composiciones farmacéuticas pueden estar en la forma de una preparación inyectable estéril, por ejemplo, una suspensión acuosa u oleaginosa inyectable estéril. Esta suspensión puede ser formulada de acuerdo a técnicas conocidas en el arte, usando agentes humectantes o de dispersión apropiados (tal como, por ejemplo, Tween 80) y agentes de suspensión. La preparación inyectable estéril puede también ser una solución o suspensión inyectable estéril en un diluyente o solvente no tóxico parenteralmente-aceptable, por ejemplo, como una solución en 1,3-butanediol. Entre los vehículos y solventes aceptables que se pueden emplear están manitol, agua, solución de Ringer y solución de cloruro de sodio isotónico. Adicionalmente, los aceites no-volátiles estériles son convencionalmente usados como solvente o medio de suspensión. Para este propósito, cualquier aceite no volátil suave puede ser usado, incluyendo monoglicéridos o diglicéridos sintéticos. Los ácidos grasos, como el ácido oleico y sus derivados glicéridos, son útiles en la preparación de inyectables, como lo son los aceites naturales aceptables para uso farmacéutico, tales como el aceite de oliva o el aceite de ricino, especialmente

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en sus versiones polioxietiladas. Estas soluciones o suspensiones oleosas pueden también contener un alcohol de cadena larga diluyente o dispersante, tales como los descritos en Ph. Helv, o un alcohol similar.

Las composiciones farmacéuticas de esta invención se pueden administrar oralmente en cualquier forma de dosificación aceptable oralmente, incluyendo, pero no limitado a, cápsulas, tabletas, polvos, gránulos y suspensiones y soluciones acuosas. Estas formas de dosificación son preparadas de acuerdo a técnicas bien conocidas en el arte de la formulación farmacéutica. En el caso de las tabletas para uso oral, los portadores que son comúnmente usados incluyen lactosa y almidón de maíz. Agentes lubricantes, como el estearato de magnesio, también son típicamente agregados. Para la administración oral en una forma de cápsula, los diluyentes útiles incluyen lactosa y almidón de maíz seco. Cuando las suspensiones acuosas son administradas oralmente, el ingrediente activo es combinado con agentes emulsionantes y de suspensión. Si se desea, se pueden agregar algunos agentes endulzantes y/o saborizantes y/o colorantes.

Las composiciones farmacéuticas de esta invención, también pueden ser administradas en la forma de supositorios para administración rectal. Estas composiciones se pueden preparar mezclando un compuesto de esta invención con un excipiente no irritante apropiado, el cual es sólido a temperatura ambiente pero líquido a temperatura rectal y, por lo tanto, se derretirá en el recto para liberar los componentes activos. Dichos materiales incluyen, pero no están limitados, a la mantequilla de cacao, la cera de abeja y polietilen glicoles.

Las composiciones farmacéuticas de esta invención se pueden administrar por aerosol nasal o inhalación. Dichas composiciones son preparadas de acuerdo a técnicas bien conocidas en el arte de la formulación farmacéutica y se pueden preparar como soluciones en solución salina, empleando alcohol bencílico u otros preservantes

apropiados, promotores de absorción para aumentar la biodisponibilidad, los fluorocarbonos y/u otros agentes de dispersión o solubilizantes conocidos en el arte.

Los compuestos de la presente invención se pueden administrar en una dosis de alrededor de 1 a aproximadamente 20,000 µg/kg por dosis, dependiendo de la condición a ser tratada o prevenida, y de las características del sujeto a quien se le está administrando el compuesto. En muchas instancias, la dosis puede ser alrededor de 1 a aproximadamente de 1500 µg/kg por dosis. El regimen de dosis para un compuesto dado, podría ser fácilmente determinado por el especialista que tiene acceso a esta divulgación.

En una modalidad en particular, la composición farmacéutica de la invención comprende adicionalmente uno o más ingredientes farmacéuticos activos adicionales. Estos ingredientes activos adicionales pueden ser agentes conocidos para los expertos, como útiles en el tratamiento o prevención de las enfermedades mencionadas en la presente divulgación.

En un tercer aspecto, la presente invención proporciona un compuesto de acuerdo al primer aspecto de la invención, o una composición de acuerdo al segundo aspecto, para uso en terapia.

En un cuarto aspecto, la invención proporciona un compuesto de acuerdo al primer aspecto de la invención, o a una composición de acuerdo al segundo aspecto, para uso en el tratamiento o prevención de una condición cuyo desarrollo o síntomas están ligados a la actividad del receptor H3 de histamina, en donde las condiciones del primer aspecto no aplican.

En ciertas modalidades del cuarto aspecto, la primera, segunda, tercera y/o cuarta condiciones del primer aspecto sí aplican.

El experto conoce una cantidad de condiciones cuyo desarrollo o síntomas están ligados a la actividad del receptor H3 de histamina.

En un quinto aspecto, la invención también proporciona un método de tratamiento o prevención de una condición, cuyo desarrollo o síntomas están ligados a la actividad del receptor H3 de histamina , el método consistiendo en la administración, a un sujeto en necesidad de dicho tratamiento o prevención, de una cantidad terapéuticamente efectiva de un compuesto de acuerdo al primer aspecto de la invención o de una composición de acuerdo al segundo aspecto, en donde las condiciones del primer aspecto no aplican.

En ciertas modalidades del quinto aspecto, la primera, segunda, tercera y/o cuarta condiciones del primer aspecto, sí aplican.

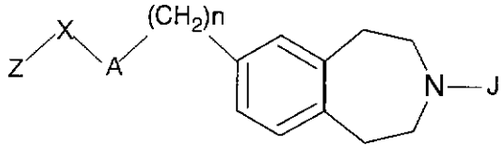
Un compuesto de acuerdo al cuarto aspecto, o un método de acuerdo al quinto aspecto, en donde la condición es un trastorno del Sistema Nervioso Central.

En ciertas modalidades, la condición a tratar puede ser seleccionada de los trastornos del sueño (como narcolepsia), desórdenes cognitivos (como demencia), desórdenes atencionales (como trastorno de déficit atencional e hiperactividad), desórdenes neurodegenerativos (como EA), esquizofrenia, epilepsia, dolor (como dolor neuropático) y obesidad.

En modalidades preferidas, la condición puede ser seleccionada de la esquizofrenia, la enfermedad de Alzheimer (EA) y la demencia. En una modalidad alternativa, la condición puede ser seleccionada de la narcolepsia, el dolor y la obesidad.

En modalidades específicas, la condición se puede seleccionar de narcolepsia, dolor neuropático y obesidad.

En un sexto aspecto, la presente invención proporciona un compuesto intermediario que tiene la fórmula:



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en donde n, A, X y Z tienen el mismo significado que en la Fórmula 1 anterior, o Z-X-A- juntos representan C_{1-6} alquilsulfoniloxi, nitro, halógeno (tal como Br), carbaldehído O-C_{1-6} alquil oxima, amino, amino unido a un grupo amino protector o arilsulfonilo, y en donde J es un grupo amino protector o H, siempre que Z esté ligado a X o A via un átomo de carbono cuando Z contiene un grupo piperazinilo, y siempre que:

cuando A es -OC(O)-, J es H, n es 0 y X es -CH_2CH_2-, Z no sea H;

cuando A es -OC(O)-, J es tert-butoxicarbonilo, n es 0 y X es -CH_2-, Z no sea H;

cuando A is -NHCO-, J es tert-butoxicarbonilo, n es 0 y X es -isopropilo, Z no sea H; y

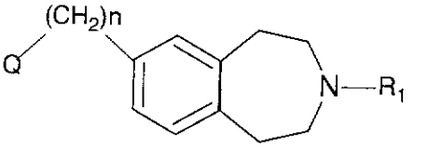
cuando A es -NHCO-, J es tert-butoxicarbonilo o H, n es 0 y X es -CH_2- o -CH_2CH_2-, Z no es pirrolidin-2-ilo sustituido con oxo, fenilpropilo y sustituyentes ácidos acéticos.

En modalidades específicas del sexto aspecto, A, X y Z tienen el mismo significado que en la Fórmula I anterior. En ciertas modalidades del sexto aspecto, Z está ligado a X o A via un átomo de carbono (es decir, sin importar si Z contiene un grupo piperazinilo o no).

En ciertas modalidades del sexto aspecto, cuando A es -NHCO, J es H, n es 0 y X está ausente, Z no es 1-[[5-cloro-2(2-metilpropoxi)fenil]metil]-5-metil-1H-pirazol-3-ilo.

Un grupo amino protector preferido es *tert*-butoxicarbonilo (Boc), aunque muchos otros grupos protectores serán conocidos para el experto. Los métodos de adición y remoción de dichos grupos protectores son aquellos que serían usados convencionalmente en relación al tipo de molécula en particular o al grupo siendo protegido, por ejemplo, los métodos descritos en trabajos estándar de referencia en metodología sintética, tales como Kocienski (2004) *Protecting Groups.* 4th Edn. Georg Tieme Verlag.

En un séptimo aspecto, la presente invención también proporciona un compuesto intermediario, que tiene la fórmula:



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en donde n y R1 tienen el mismo significado que en la Fórmula I anterior, y en donde Q es seleccionado de ciano, amino, amino unido a un grupo amino protector (tal como t-butiloxicarbonilo), arilsulfonilo (tal como fenilsulfonilo) y halógeno (tal como Br).

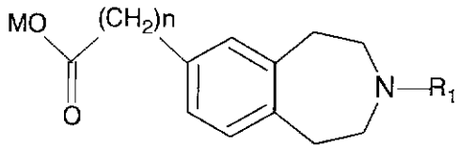
En un octavo aspecto relacionado, la invención también proporciona el uso de un compuesto intermediario, de acuerdo al sexto o séptimo aspecto, en la síntesis de un compuesto de acuerdo al primer aspecto, en donde las condiciones especificadas en el sexto aspecto no aplican. En ciertas modalidades del octavo aspecto, una o más de las condiciones especificadas en el sexto aspecto sí aplican.

El experto apreciará que después de la remoción del grupo protector (cuando está presente) en el intermediario, el nitrógeno del anillo de azepina se vuelve disponible para un ataque nucleofílico en un reactivo que contiene R1 apropiado (por ejemplo, en una reacción de alquilación o reacción de aminación reductiva).

En un noveno aspecto, la presente invención proporciona el uso de un compuesto, de acuerdo al primer aspecto de la invención, en la preparación de un medicamento para el tratamiento o prevención de una condición, cuyo desarrollo o síntomas están ligados a la actividad del receptor H3 de histamina, en donde las condiciones del primer aspecto no aplican.

Las condiciones ejemplares de relevancia del noveno aspecto, son mencionadas anteriormente.

En un décimo aspecto, la presente invención también proporciona un método de síntesis de un compuesto, de acuerdo al primer aspecto, en donde A es -N(R2)CO-, el método comprende la reacción de un intermediario, que tiene la fórmula:

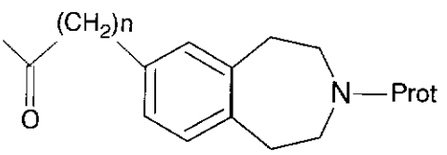


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con un amina (Z-X)(R2)NH en la presencia de un catalizador, en donde n, Z, X, R1 y R2 tienen el mismo significado según el proporcionado en relación al primer aspecto, y en donde M representa H o un catión metálico monovalente.

En ciertas modalidades del décimo aspecto, M es un catión metálico monovalente, tal como Li. El catalizador puede ser cloruro de tionilo, de manera que la reacción proceda via la creación de un cloruro de acilo intermediario. El cloruro de acilo puede, si es necesario, ser aislado antes de la introducción de (Z-X)(R2)NH.

En un undécimo aspecto, la presente invención proporciona un método de síntesis de un compuesto, de acuerdo al primer aspecto, en donde A es -CO- o -C(R2)(OR3)- y X está presente, el método comprende la reacción de un intermediario protegido:



con un aldehído Z-CHO en la presencia de un catalizador, seguido por la desprotección de la amina protegida y la sustitución de ésta con R1 y, opcionalmente, por hidrogenación catalítica, en donde n, Z, X, R1, R2 y R3 tienen el mismo significado que se dio en relación al primer aspecto, y en donde Prot representa un grupo protector de amina.

El catalizador puede ser, por ejemplo, 1,8-Diazabiciclo[5.4.0]undec-7-ene (DBU). En compuestos en los cuales X es alquenileno, la etapa de hidrogenación catalítica puede ser omitida. Dicha etapa (por ejemplo usando H_2 gaseoso en la presencia de $Pt(IV)O_2$) satura el doble enlace que resulta de la reacción entre Z-CHO y el intermediario protegido. Grupos de protección de amina apropiados son descritos anteriormente.

De aquí en adelante, la invención será descrita en más detalle, por medio de ejemplo solamente.

1. Metodologías de Síntesis

Los métodos usados para la síntesis de los compuestos de la invención, son ilustrados por los esquemas generales más abajo y los ejemplos preparativos que siguen. Todos los compuestos e intermediarios fueron caracterizados al menos por cromatografía líquida - espectrometría de masas (LCMS). Las materias primas y los reactivos usados al preparar estos compuestos, pueden encontrarse en proveedores comerciales. Estos esquemas generales son simplemente ilustrativos de los métodos por los cuales los compuestos de esta invención pueden ser sintetizados, y se pueden hacer varias modificaciones a estos esquemas y serán sugeridas al experto que se ha referido a esta divulgación.

El espectro de resonancia magnética nuclear (NMR) fue registrado a 400MHz; los cambios químicos (δ) son informados en partes por millón.

El espectro de masa fue registrado usando un sistema LCMS (detector de espectro de masa ZQ).

Los compuestos fueron purificados usando cromatografía de fase normal en sílice o alumina, o por métodos cromatográficos de fase reversa.

Temperatura ambiente en los siguientes esquemas significa que la temperatura oscila de 20°C a 25°C.

Los compuestos deseados de la Fórmula 1 se pueden preparar según lo explicado en los **Esquemas 1-16**, de la siguiente manera:

Lista de Abreviaturas:

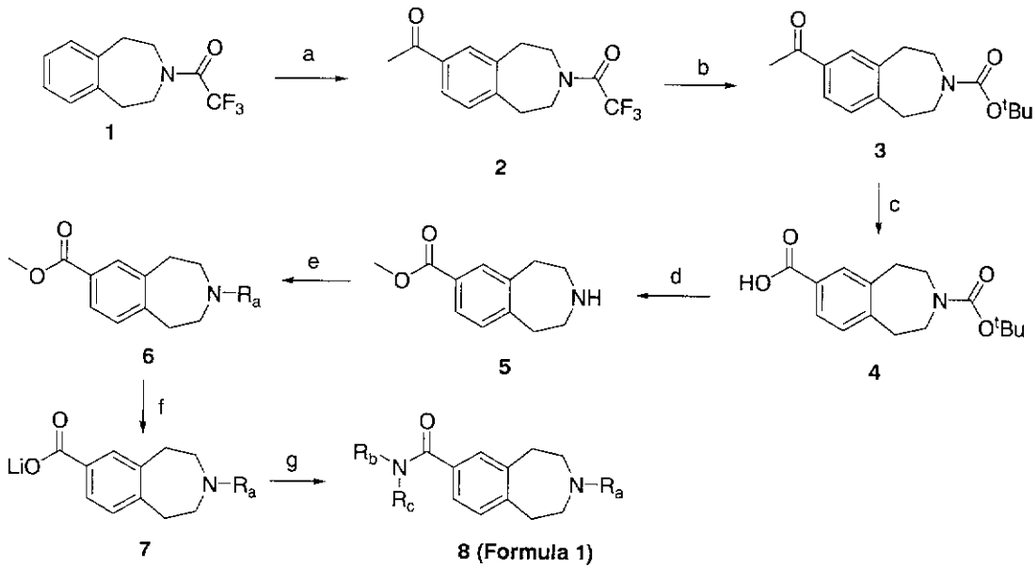
Ac	Acetilo
AcOH	Acido Acético
$(Boc)_2O$	Anhídrido de Boc
DCM	Diclorometano
DMSO	Dimetil Sulfóxido
DMF	Dimetil Formamida

EtOAc	Acetato de Etilo
EtOH	Etanol
HCl	Acido Hidroclórico
H_2SO_4	Acido Sulfúrico
IPE	Diisopropileter
KOH	Hidróxido de Potasio
LCMS	Cromatografía de Líquidos acoplado a Espectrometría de Masas
$MgSO_4$	Sulfato de Magnesio
MS	Espectro de Masa
MeOD	Metanol Deuterizado
MeOH	Metanol
Min	Minuto
NaOH	Hidróxido de Sodio
NMR	Resonancia Nuclear Magnética
RT	Temperatura Ambiente
THF	Tetrahidrofurano
TLC	Cromatografía de Capa Fina

En los siguientes esquemas, R_a representa R1, R_b y R_c independientemente representan R2 o R3, o R_b y R_c representan X-Z, y R_d representa X-Z, en donde R1, R2, R3, X y Z son según lo definido anteriormente.

1.1 Esquema 1

Este esquema puede ser utilizado para sintetizar los **compuestos de los ejemplos 1-115 y los compuestos de los ejemplos 158-174.**



Reactivos y condiciones: a) MeCoCl, $AlCl_3$, CH_2Cl_2; b)i. K_2CO_3, H_2O, MeOH; ii. K_2CO_3, Boc_2O, dioxano; c) NaOH aq, Br_2; d) $SOCl_2$, MeOH; e) R_aI, K_2CO_3, DMA; o R_aCO o R_aHCO, AcOH, $Na(OAc)_3BH$, DCM; f) LiOH, THF, H_2O g)i. $SOCl_2$, MeOH; ii. R_bR_cNH

1.1.1 El *intermediario benzazepina* **(1)** se puede preparar por medio de los métodos explicados en WO 2005/058328 y WO 2005/094834. La benzazepina alcanoil **(2)** se puede preparar de la correspondiente (1) acilación de Friedel-Crafts, según lo explicado en US 2005/20616. La remoción del grupo trifluoroacetilo de **(2)** bajo condiciones básicas seguidos por la protección del nitrógeno de la benzazepina como un t-butil carbamato, usando condiciones estándar bien conocidas en el arte (por ejemplo, Bioorg.Med.Chem 13 (2005) 1901-1911) dieron el intermediario **(3)**. La modificación del grupo acilo usando condiciones de la literatura estándares (por ejemplo US2003/207863) dio el ácido carboxílico intermediario **(4)**. El ácido carboxílico de **(4)** se puede convertir en un éster de metilo, utilizando condiciones bien conocidas. Estas condiciones también pueden remover el grupo protector t-butil oxi carbonilo. El grupo protector t-butil oxi carbonilo también se puede remover usando otras condiciones estándares bien conocidas en el arte, tales como el tratamiento con ácido trifluoroacético. La alquilación del nitrógeno de la benzazepina se puede hacer usando condiciones estándar bien conocidas de aminación reductiva o por el uso de halogenuros de alquilo. Otras modificaciones que utilizan

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condiciones estándares bien conocidas en el arte para la saponificación del éster, la conversión del ácido resultante en cloruro de ácido con la subsiguiente formación de la amida, proporcionan compuestos de la fórmula 1.

1.1.2 Intermediario 2

A una solución de 1-(4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona (15.5g, 63.7mmol) **(1)** y cloruro de acetilo (10eq, 50g, 637mmol) en diclorometano (300ml) se agregó cloruro de aluminio (34g, 255mmol) por porciones. La reacción se dejó agitar a temperatura ambiente por 1 hora. La reacción fue templada vertiéndola sobre una mezcla de hielo y solución saturada de bicarbonato de sodio. Luego, se agregó bicarbonato de sodio sólido adicional hasta que la solución acuosa se transformó en básica. La mezcla de reacción despúes fue filtrada a través de diatomita y diluída con diclorometano. Los orgánicos combinados luego fueron secados sobre sulfato de sodio y concentrados *in vacuo* para dar 1-(7-acetil-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona **(2)** como un sólido rosado oscuro en 60mmol.

MS ES^+: 286

1H NMR (400 MHz, DMSO-d6): = 7.72 - 7.82 (m, 2H), 7.29 - 7.39 (m, 1H), 3.72 (br. s., 4H), 3.02 - 3.16 (m, 4H), 2.56 (s, 3H)

1.1.3 Intermediario 3

A una suspensión de 1-(7-acetil-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona **(2)** (10g, 35mmol) en metanol (496ml) se le agregó agua (164ml) y solución saturada de carbonato de potasio (164 ml) y la reacción se dejó agitar a temperatura ambiente por 16 horas. La mezcla de reacción fue concentrada *in vacuo* y el residuo particionado entre acetato de etilo y agua. La capa acuosa fue lavada con acetato de etilo y los orgánicos combinados lavados con salmuera y secados sobre sulfato de magnesio. El residuo formó una mezcla azeotrópica con tolueno y el material fue usado directamente.

000234

MS ES$^+$: 190

1H NMR (400 MHz, DMSO-d6): □ 7.64 - 7.70 (m, 2H), 7.20 - 7.26 (m, 1H), 2.86 - 2.93 (m, 4H), 2.73 - 2.80 (m, 4H), 2.53 (s, 3H)).

A una solución de 1-(2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)etanona (10.44g, 35mmol) en dioxano (93ml) y agua (35ml) se agregó anhídrido de Boc (7.64g, 35mmol) y carbonato de potasio (4.84g, 35mmol), y la reacción se dejó agitar a temperatura ambiente por 48 horas. La mezcla de reacción fue concentrada *in vacuo* y particionada entre acetato de etilo y una solución acuosa saturada de bicarbonato de sodio. Los orgánicos combinados fueron lavados con salmuera y secados sobre sulfato de magnesio. El aceite crudo fue cristalizado durante la noche para dar *tert*-butil 7-acetil-4,5-dihidro-1H-benzo[d]azepin-3(2H)-carboxilato **(3)** como un sólido crema en 16.8mmol.

MS ES$^+$: 189, ES: 216

1H NMR (400 MHz, DMSO-d6) □ 7.66 - 7.74 (m, 2H), 7.21 - 7.30 (m, 1H), 3.37 - 3.48 (m, 4H), 2.83 - 2.93 (m, 4H), 2.50 (s, 3H), 1.36 (s, 9H)

1.1.4 Intermediario 4

A una solución de *tert*-butil 7-acetil-4,5-dihidro-1H-benzo[d]azepin-3(2H)-carboxilato **(3)** (2g, 6.9mmol) en dioxano (23ml) se le agregó una solución acuosa de hidróxido de sodio (2.2g, 55.2mmol en 32ml de agua) por goteo. La mezcla de reacción fue luego enfriada hasta 0° C y se le agregó bromo (1.06ml, 20.7mmol) por goteo. La reacción se dejó agitar a 0° C durante 1 hora. La reacción fue cuidadosamente templada con acetona y la reacción redujo *in vacuo*. La capa acuosa remanente fue lavada con acetato de etilo y luego acidificada con ácido de clorhídrico 5N. La capa acuosa fue luego extraída con acetato de etilo y los orgánicos combinados lavados con salmuera y secados sobre sulfato de magnesio para dar 3(*tert*-butoxicarbonil)-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-ácido carboxílico **(4)**, como un sólido amarillo pálido en rendimiento cuantitativo.

MS ES$^+$: 192

000235

1H NMR (400 MHz, DMSO-d6) □ 7.60 - 7.80 (m, 2H), 7.16 - 7.32 (m, 1H), 3.41 - 3.52 (m, 4H), 2.84 - 2.97 (m, 4H), 1.34 - 1.47 (m, 9H)

1.1.5 Intermediario 5

Se agregó cloruro de tionilo (60mL, 825mmol) por goteo a una solución agitada de metanol (1L) a -20°C y la reacción fue entibiada hasta temperatura ambiente. A esta solución se agregó ácido 3-(*tert*-butoxicarbonil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxílico 25g, 85.8mmol) **(4)** por goteo para dar una solución naranja. La mezcla de reacción fue concentrada *in vacuo* y se formó una mezcla azeotrópica con tolueno para dar metilo 2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato **(5)** como un sólido café pálido en rendimiento cuantitativo.

MS ES^+ : 206 1H NMR (400 MHz, DMSO-d6): □ 9.46 (br. s., 2H), 7.71 - 7.87 (m, 2H), 7.32 - 7.42 (m, 1H), 3.85 (s, 3H), 3.19 (br. s., 8H)

1.1.6 Síntesis del Intermediario 6

Método A

Alquilación:

A una solución de metil 2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato **(5)** (7.58g, 31.4mmol) in dimetilacetamida (75mL) se agregó carbonato de potasio (10.8g, 78.5mmol) y yodoetano (2.63mL, 32.9mmol), y la reacción fue agitada a temperatura ambiente por 18 horas. La mezcla de reacción fue diluída con acetato de etilo y lavada con carbonato de potasio acuoso saturado y salmuera, secada sobre sulfato de magnesio y reducida *in vacuo*. La purificación por cromatografia de sílice, usando mezclas de metanol/diclorometano con amonio agregado, dió metil 3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato **(6)** en 12.9mmol.

MS ES^+ : 234 ^{1}H NMR (400 MHz, DMSO-d_6): □ 7.66 - 7.75 (m, 2H), 7.21 - 7.32 (m, 1H), 3.83 (s, 3H), 2.87 - 2.97 (m, 4H), 2.43 - 2.60 (m, 6H), 0.97 - 1.05 (m, 3H)

000230

Método B

Aminación reductiva:

A una solución de metil 2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato (**5**) (20g, 82.7mmol) en diclorometano (200mL) se agregó ciclobutanona (9.27mL, 124.1mmol), ácido acético (0.5mL), triacetoxiborohidruro de sodio (26.3g, 124.1mmol) y trietilamina (11.5mL, 82.7mmol). La reacción fue agitada por 18 horas y la mezcla de reacción fue concentrada *in vacuo*. Se agrego hidróxido de sodio acuoso y la fase acuosa fue extraída en diclorometano (2x100mL). Los orgánicos combinados fueron secados sobre sulfato de magnesio y concentrados *in vacuo* para dar metil 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato (**6**) como un sólido café en rendimiento cuantitativo.

MS ES^+: 260

^1H NMR (400 MHz, DMSO-d_6): □ 7.67 - 7.74 (m, 2H), 7.23 - 7.29 (m, 1H), 3.83 (s, 3H), 2.86 - 2.95 (m, 4H), 2.71 - 2.82 (m, 1H), 2.35 (br. s., 4H), 1.95 - 2.05 (m, 2H), 1.72 - 1.84 (m, 2H), 1.51 - 1.66 (m, 2H)

1.1.7 Síntesis del Intermediario 7

A una solución de metil 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato (**6**) (22.03g, 84.9mmol) en tetrahidrofurano (300mL) y agua (100mL) se agregó hidróxido de litio (2.44g, 101.9mmol) y la reacción sometida a reflujo por 18 horas. La mezcla de reacción fue concentrada *in vacuo* y se formó una mezcla azeotrópica con tolueno (x3) para dar una sal de litio de ácido 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxílico (**7**) como un sólido café pálido en rendimiento cuantitativo.

MS ES^+: 246

^1H NMR (400 MHz, DMSO-d_6): □ 7.60 - 7.70 (m, 2H), 6.95 - 7.05 (m, 1H), 2.81 (br. s., 4H), 2.69 - 2.77 (m, 1H), 2.33 (br. s., 4H), 1.95 - 2.05 (m, 2H), 1.71 - 1.84 (m, 2H), 1.51 - 1.65 (m, 2H)

000237

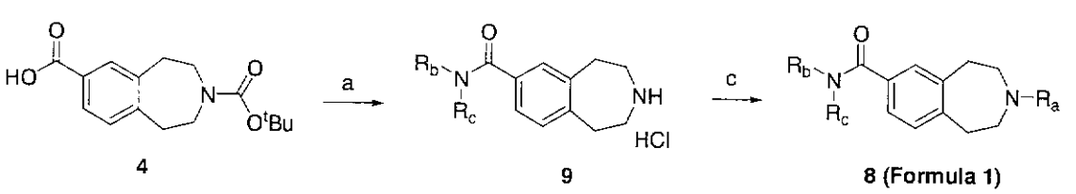
1.1.8 Síntesis del Compuesto 8 (Fórmula 1)/**Ejemplo 1**

La sal de lítio de ácido 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxílico (**7**)(0.502g, 2mmol) fue agitada en cloruro de tionilo (7.30mL, 100mmol) durante 60 minutos y luego concentrada *in vacuo,* y se formó una mezcla azeotrópicacon tolueno para dar el cloruro del ácido como un sólido café. Este material fue suspendido en diclorometano (10mL) y a esto se agregó C-(2-metilo-2H-pirazol-3-il)-metilamina (0.22g, 2mmol) y trietilamina (0.28mL, 8mmol) y la reacción fue agitada por 18 horas. La mezcla de reacción fue concentrada *in vacuo* y cargada en un cartucho SCX-2 (20g) eluyendo primero con metanol (10mL x3) y luego con amoníaco/metanol 2M. Las fracciones correspondientes al producto fueron combinadas y concentradas *in vacuo,* y luego purificadas por cromatografia de sílice usando mezclas de metanol/diclorometano con amoníaco agregado para dar 3-ciclobutil-N-((1-metil-1H-pirazol-5-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida (**8**) en 0.9mmol.

^{1}H NMR (400 MHz, DMSO-d_6): 8.80 - 8.91 (m, 1H), 7.57 - 7.66 (m, 2H), 7.26 - 7.33 (m, 1H), 7.16 - 7.23 (m, 1H), 6.11 - 6.18 (m, 1H), 4.45 - 4.53 (m, 2H), 3.81 (s, 3H), 2.81 - 2.94 (m, 4H), 2.69 - 2.80 (m, 1H), 2.34 (br. s., 4H), 1.95 - 2.06 (m, 2H), 1.71 - 1.84 (m, 2H), 1.49 - 1.65 (m, 2H)

Los compuestos de la Fórmula 1 también pueden ser preparadas según lo ilustrado en el Esquema 2, usando condiciones estándares bien conocidas en el arte.

1.2 Esquema 2



4 9 **8 (Formula 1)**

Reactivos y condiciones: a) R_bR_cNH, HATU, Et_3N, MeCN; b) HCl 2M en dioxano; c) R_aCO o R_aHCO, $NaB(OAc)_3H$, DCM

1.2.1 Síntesis de Intermediario 9

000238

A una solución de ácido 3(*tert*-butoxicarbonil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxílico(4.86g, 16.67mmol) (**4**) en acetonitrilo (20mL) se agregó trietilamina (5.5mL, 40.01mmol), benzilamina (2mL, 18.34mmol) y 2-(1H-7-Azabenzotriazol-1-il)--1,1,3,3-tetrametiluronio hexafluorofosfato (HATU) (7.61g, 20mmol) y la reacción fue agitada durante 16 horas. La mezcla de reacción fue concentrada *in vacuo*, lavada con salmuera y extraída a acetato de etilo (3 x 50mL) y los orgánicos combinados secados sobre sulfato de magnesio. Los orgánicos fueron concentrados *in vacuo* y el material crudo purificado por cromatografía de sílice usando mezclas de metanol/diclorometano con amoníaco agregado para dar *tert*-butil 7-(benzilcarbamoil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato como un sólido amarillo en 15.7mmol.

MS ES^+: 381, 324

^1H NMR (400 MHz, DMSO-d_6): □ 8.98 - 9.05 (m, 1H), 7.70 - 7.78 (m, 2H), 7.35 - 7.42 (m, 4H), 7.27 - 7.34 (m, 2H), 4.50 - 4.56 (m, 2H), 3.50 - 3.57 (m, 4H), 2.92 - 3.00 (m, 4H), 1.48 (s, 9H)

Se agitó *Tert*-butil 7-(benzilcarbamoil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (5.95g, 15.64mmol) en HC1 metanólico saturado en reflujo por 2 horas. La mezcla de reacción fue concentrada *in vacuo* para dar hidrocloruro de N-benzil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida (**9**) como un sólido pálido en rendimiento cuantitativo.

MS ES^+: 281

^1H NMR (400 MHz, DMSO-d_6): □ 9.27 (br. s., 1H), 8.93 - 9.06 (m, 1H), 7.69 - 7.78 (m, 2H), 7.17 - 7.39 (m, 6H), 4.43 - 4.50 (m, 2H), 3.61 - 3.88 (m, 8H)

1.2.2 Síntesis del Compuesto 8 (Fórmula 1)/**Ejemplo 115**

A una solución de hidrocloruro de N-benzil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida (**9**) (0.28g, 1mmol) en diclorometano (5mL) se agregó 3-metilbutanal (0.18mL, 2mmol) y ácido acético (1 gota). La reacción fue agitada a temperatura ambiente durante 15 minutos previo a la adición de triacetoxiborohidruro de sodio (0.42g, 2mmol).

000233

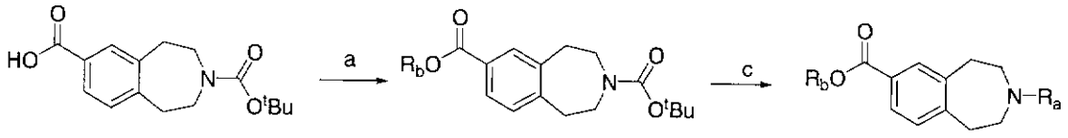
Después de 1 hora, el material crudo fue cargado en un cartucho SCX-2 eluyendo con metanol y luego con amoníaco/metanol 2M. Las fracciones correspondientes al producto fueron combinadas y concentradas *in vacuo* y luego purificadas por HPLC preparativo para dar N-benzil-3-isobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida (**8**) en 0.72mmol.

MS ES^+: 337

^1H NMR (400 MHz, $CDCl_3$): ⁻ 7.49 - 7.57 (m, 2H), 7.28 - 7.40 (m, 5H), 7.11 - 7.16 (m, 1H), 4.63 - 4.68 (m, 2H), 2.91 - 2.98 (m, 4H), 2.55 - 2.64 (m, 4H), 2.16 - 2.22 (m, 2H), 1.74 - 1.86 (m, 1H), 0.89 - 0.96 (m, 6H)

1.3 Esquema 3

Otros ejemplos de compuestos de fórmula 1 se pueden sintetizar según lo ilustrado en el Esquema 3, usando métodos estándares. Este esquema, o el Esquema 4 (ver más adelante) es apropiado para sintetizar los compuestos de los ejemplos 116-119.



4 **10** **11(Formula 1)**

Reactivos y condiciones: a) R_bOH, EDC, DMAP, CH_2Cl_2; b) HCl 2M en Et_2O; c) R_aCO o R_aHCO, AcOH, $Na(OAc)_3BH$, THF

1.3.1 Síntesis de Intermediario10

A una solución de 1-benzilpiperidin-4-il)metanol (0.211g, 1mmol) en diclorometano (15mL) se agregó ácido 3(*tert*-butoxicarbonil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxílico (**4**) (0.3g, 1mmol), N-(3-dimetilaminopropil)-N-etilcarbodiimida (EDC) (575mg, 3mmol), 4-dimetilaminopiridina (DMAP) (catalítico) y trietilamina (0.42mL, 3mmol) y la reacción fue agitada durante 18 horas. La mezcla de reacción fue concentrada *in vacuo* y particionada entre acetato de etilo y 5% de ácido cítrico/salmuera acuoso. Los orgánicos fueron lavados con bicarbonato de sodio acuoso saturado y salmuera, secados sobre sulfato de

magnesio y concentrados *in vacuo*. El material fue purificado por cromatografia de sílice, usando mezclas de acetato de etilo/gasolina para dar 7-(1-benzilpiperidin-4-il)metil 3-tert-butil 4,5-dihidro-1H-benzo[d]azepina-3,7(2H)-dicarboxilato (**10**) en 0.45mmol.

MS ES^+ : 479

^1H NMR (400 MHz, DMSO-d_6): □ 7.70 - 7.76 (m, 2H), 7.21 - 7.34 (m, 6H), 4.10 - 4.15 (m, 2H), 3.42 - 3.49 (m, 6H), 2.88 - 2.95 (m, 4H), 2.79 - 2.86 (m, 2H), 1.89 - 1.97 (m, 2H), 1.66 - 1.78 (m, 3H), 1.39 (s, 9H), 1.22 - 1.35 (m, 2H)

1.3.2 Síntesis del Compuesto 11 (Fórmula 1)/**Ejemplo 116**

A una solución de dado 7-(1-benzilpiperidin-4-il)metil 3-tert-butil 4,5-dihidro-1H-benzo[d]azepina-3,7(2H)-dicarboxilato (**10**) (0.214g, 0.45mmol) en dietiléter (2mL) se agregó HCl 2M en dietiléter (2mL) para dar un sólido blanco. Se agregó metanol para dar una solución sin color que precipitó lentamente durante 1 hora. La mezcla de reacción fue concentrada *in vacuo* para dar hidrocloruro de (1-benzilpiperidin-4-il)metil 2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato en 0.39mmol. Éste fue usado sin más purificación en la siguiente etapa.

MS ES^+ : 379

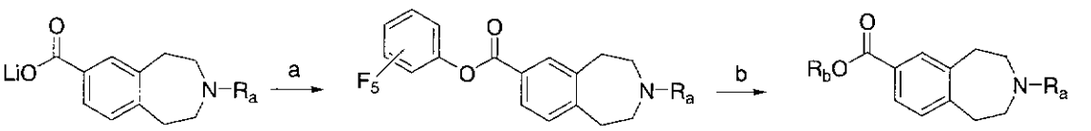
A una suspensión parcial de hidrocloruro de (1-benzilpiperidin-4-il)metil 2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato (0.162g, 0.39mmol) en tetrahidrofurano (8mL) se agregó acetaldehído (0.12mL, 2.14mmol), ácido acético (0.05mL, 0.86mmol), cernidores moleculares de 4Å y triacetoxiborohidruro de sodio (0.146g, 0.69mmol) y la mezcla de reacción fue agitada a temperatura ambiente durante 1 hora. La reacción fue filtrada y concentrada *in vacuo* y el residuo particionado entre acetato de etilo y bicarbonato de sodio acuoso saturado y los orgánicos lavados con salmuera, secados sobre sulfato de magnesio y reducidos *in vacuo*. La purificación por cromatografía de sílice usando mezclas de metanol/diclorometano dio (1-benzilpiperidin-4-il)metil 3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato (**11**) en 0.32mmol.

MS ES$^+$: 407

^{1}H NMR (400 MHz, DMSO-d_6): □ 7.60 - 7.67 (m, 2H), 7.13 - 7.29 (m, 6H), 4.01 - 4.08 (m, 2H), 3.38 (s, 2H), 2.81 - 2.89 (m, 4H), 2.72 - 2.79 (m, 2H), 2.36 - 2.50 (m, 6H), 1.81 - 1.91 (m, 2H), 1.59 - 1.70 (m, 3H), 1.15 - 1.29 (m, 2H), 0.90 - 0.97 (m, 3H)

1.4 Esquema 4

Los compuestos de la invención también se pueden sintetizar usando el **Esquema 4** via un intermediario pentafluorofenoxi como **12**. El Intermediario **12** puede ser sintetizado usando métodos similares a aquellos bosquejados en la literatura (J Med. Chem., 35, 15, 1992, 2843; J Org. Chem., 70, 2, 2005, 489).



7 **12** **11(Formula 1)**

Reactivos y condiciones: a) C_6F_5OH, EDC, Et_3N, CH_2Cl_2 ; b) R_bOH, MeCN, reflujo

1.4.1 Síntesis del Intermediario12

Una suspensión del derivado de litio de ácido 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7- carboxílico (**7**) (1.08g, 4.40mmol) en diclorometano (30mL) fue tratada com pentafluorofenol (0.81g, 4.4mmol), trietilamina (2.2mL, 15.4mmol) y N-(3-dimetilaminopropil)-N-etilcarbodiimida (EDC) (1.01g, 5.28mmol). La reacción fue agitada por 18 horas a temperatura ambiente, después de lo cual la reacción fue concentrada *in vacuo*, lavada con agua y extraída en diclorometano y secada sobre sulfato de magnesio. Los solventes fueron removidos *in vacuo* y el residuo fue purificado por cromatografia de sílice usando mezclas de metanol/acetato de etilo para dar perfluorofenil 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato (**12**) en 1.94mmol.

C00242

^{1}H NMR (400 MHz, MeOD): □ 7.94 - 7.99 (m, 2H), 7.35 - 7.39 (m, 1H), 3.03 - 3.09 (m, 4H), 2.85 - 2.93 (m, 1H), 2.48 - 2.61 (m, 4H), 2.08 - 2.17 (m, 2H), 1.91 - 2.01 (m, 2H), 1.65 - 1.77 (m, 2H)

1.4.2 Síntesis del Compuesto 11 (Fórmula 1)/**Ejemplo 119**

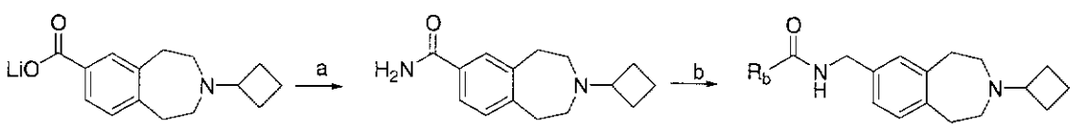
A una solución de acetonitrilo (10mL) de perfluorofenil 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato (**12**) (0.087g, 0.20mmol) se agregó (4-metoxifenil)metanol (0.028g, 0.20mmol) y la reacción sometida a reflujo por 48 horas. La mezcla de reacción fue concentrada *in vacuo* y purificada por cromatografía de sílice, usando mezclas de metanol/acetato de etilo para dar 4-metoxibenzil 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato (**11**) en 6.0mmol.

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.81 - 7.87 (m, 1H), 7.80 (s, 1H), 7.35 - 7.41 (m, 2H), 7.13 - 7.19 (m, 1H), 6.88 - 6.94 (m, 2H), 5.28 (s, 2H), 3.82 (s, 3H), 3.08 (br. s., 4H), 2.90 - 3.01 (m, 1H), 2.67 (br. s., 4H), 2.07 - 2.24 (m, 4H), 1.56 - 1.81 (m, 2H)

MS ES^+: 366

1.5 Esquema 5

Otro ejemplo de los compuestos de la Fórmula 1, se puede sintetizar según lo expuesto en el **Esquema 5**, usando condiciones estándares bien conocidas en el arte.



7 13 **14 (Formula 1)**

Reactivos y condiciones: a)i. $SOCl_2$; ii. NH_4OH, thf; b)i. $LiAlH_4$, THF; ii. K_2CO_3, R_bCOCl, dioxano

1.5.1 Intermediario 13

Un matraz de fondo redondo de 100ml fue cargado con cloruro de 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carbonilo (2 g, 7.58 mmol) (preparado a partir del intermediario **7**) en THF, para dar una suspensión naranja. Se agregó hidróxido de amonio concentrado y la mezcla de reacción fue agitada durante una hora. La mezcla de

reacción fue extraída con diclorometano y secada y evaporada para producir 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida (6.14 mmol).

MS ES^+: 245

^1H NMR (400 MHz, MeOD): □ 7.61 (m, 2H), 7.15 - 7.21 (m, 1H), 2.96 (br. s., 4H), 2.77 - 2.86 (m, 1H), 2.47 (br. s., 4H), 2.03 - 2.14 (m, 2H), 1.86 - 1.98 (m, 2H), 1.60 - 1.76 (m, 2H).

1.5.2 Síntesis del Compuesto 14 (Fórmula 1)/**Ejemplo 120**

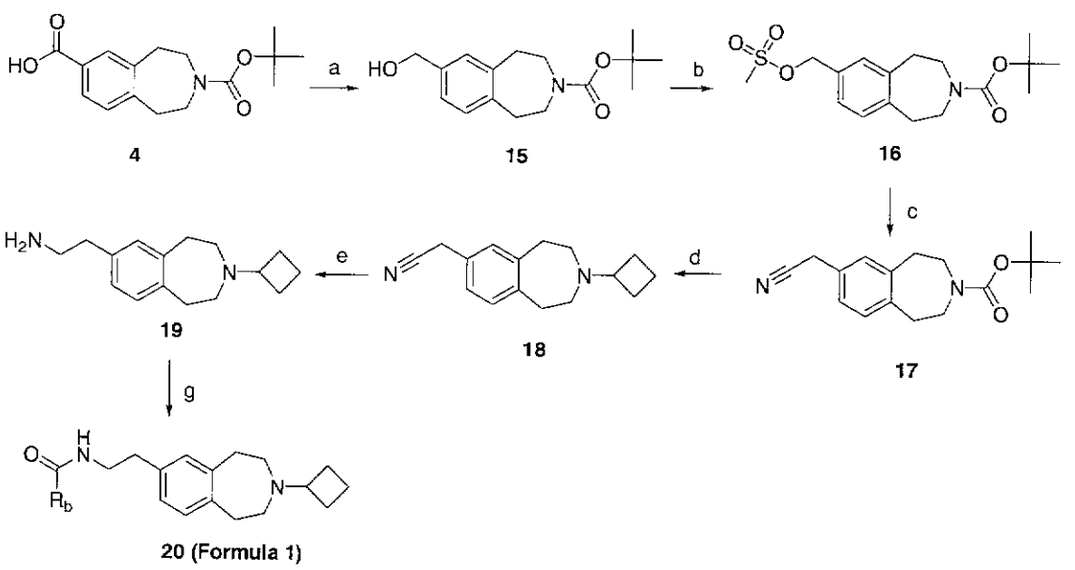
Un matraz de fondo redondo de 100ml fue cargado con 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida (2 g, 8.19 mmol) en tetrahidrofurano (20mL), para dar una suspensión color marrón claro. Se agregó hidruro de litio aluminio (16.37 ml, 16.37 mmol) y la reacción fue agitada a reflujo durante 2 horas. La reacción fue enfriada y cuidadosamente templada con sulfato de sodio saturado. La reacción fue secada con sulfato de magnesio, filtrada a través de diatomita y evaporada. El residuo fue llevado a dioxano y se agregó carbonato de potasio saturado, seguido por cloruro de nicotinoilo 1.159 g, 8.19 mmol). La reacción fue agitada por 2 horas antes de extraerla dentro de diclorometano (x3) y de secarla y evaporarla. El residuo fue purificado por Biotage SNAP 50g eluyendo con amonio metanol diclorometano para producir N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)nicotinamida (0.626 mmol,).

MS ES^+: 336

^1H NMR (400 MHz, MeOD): □ 8.96 - 9.02 (m, 1H), 8.65 - 8.71 (m, 1H), 8.21 - 8.30 (m, 1H), 7.50 - 7.58 (m, 1H), 7.02 - 7.14 (m, 3H), 4.53 (s, 2H), 2.87 - 2.96 (m, 4H), 2.76 - 2.86 (m, 1H), 2.36 - 2.53 (m, 4H), 2.05 - 2.14 (m, 2H), 1.86 - 1.99 (m, 2H), 1.61 - 1.78 (m, 2H)

1.6 Esquema 6

Otro ejemplo de compuestos de Fórmula 1 se puede preparar, según lo expuesto en el **Esquema 6**, usando condiciones estándares bien conocidas en el arte.



4 15 16 19 18 17

20 (Formula 1)

Reactivos y condiciones: a) BH_3.THF, THF; b) $MeSO_2Cl$, TEA, EtOAc; c) NaCN, EtOH, H_2O; d) i. HCl 4M, dioxano; ii. ciclobutanona, AcOH, $Na(OAc)_3BH$, DCM; e) $LiAlH_4$, THF; g) R_BCOCl, Píridina+

1.6.1 Intermediario 15

Un matraz de fondo redondo de 500 ml fue cargado con ácido 3-(tert-butoxicarbonil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxílico(5.83 g, 20 mmol) en tetrahidrofurano (100 ml), para dar una solución sin color. Se agregó un complejo de tetrahidrofurano-borano (30.4 ml, 30.4 mmol) por goteo a 0° C. La solución fue agitada a 0° C durante una hora y luego agitada a temperatura ambiente por 16 horas. La reacción fue templada por la adición de 100 mL de una solución saturada de bicarbonato y el THF fue removido por evaporación. El residuo fue llevado a acetato de etilo y lavado con agua (x2). La capa orgánica fue evaporada y el residuo fue purificado por una columna de Biotage SNAP 50g, usando gasolina - acetato de etilo 1:1 para producir un aceite sin color tert-butil 7-(hidroximetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (15.14 mmol).

ES^+ 278 (M+H)

^1H NMR (400 MHz, MeOD): □ 7.11 (s, 3H), 4.54 (s, 2H), 3.47 - 3.58 (m, 4H), 2.85 - 2.92 (m, 4H), 1.47 (s, 9H)

1.6.2 Intermediario 16

Un matraz de fondo redondo de 100 mL fue cargado con tert-butil 7-(hidroximetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (4.2 g, 15.14 mmol) y trietilamina (2 ml, 15.14 mmol) en acetato de etilo (50 ml) para dar una solución sin color. Se agregó cloruro de metanosulfonilo y la reacción fue agitada durante 16 horas. La mezcla de reacción fue diluída con acetato de etilo y lavada con bicarbonato saturado, secada, filtrada y evaporada. El residuo fue purificado por una columna Biotage SNAP 50g de acetato de etilo / gasolina 1:1 para producir tert-butil 7-((metilsulfoniloxi)metil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (11.25 mmol,).

MS ES^+: 378

1.6.3 Intermediario 17

Un matraz de fondo redondo de 100 mL fue cargado con cianuro de sodio (0.551 g, 11.25 mmol) y tert-butil 7-((metilsulfoniloxi)metil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (4 g, 11.25 mmol) en Agua (2.500 ml) y Etanol (10 ml) para dar una solución sin color. La reacción fue calentada a reflujo durante 2 horas. Después de un tratamiento del acuoso y de la purificación por Biotage (20% EtOAc/ gasolina) se obtuvo tert-butil 7-(cianometil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (2.79 mmol,).

MS ES^+: 213

^1H NMR (400 MHz, MeOD): δ 7.06 - 7.16 (m, 3H), 3.78 (s, 2H), 3.50 (br. s., 4H), 2.79 - 2.93 (m, 4H), 1.45 (s, 9H)

1.6.4 Intermediario 18

tert-Butil 7-(cianometil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (**Intermediario 17**) (2.5 mmol) fue agitado en HCl 4M en dioxano durante 2 horas y luego el solvente fue removido por evaporación.

MS ES^+: 187

A este residuo se le agregó triacetoxiborohidruro de sodio (0.795 g, 3.75 mmol), ácido acético (0.215 ml, 3.75 mmol) y ciclobutanona (0.263 g, 3.75 mmol) en diclorometano

(10ml) para dar una solución sin color. La reacción fue agitada durante 1 hora. La mezcla de reacción fue diluída con hidróxido de sodio acuoso al 5% y extraída con diclorometano (x3) secada y evaporada para producir un aceite, triturado con éter para producir un sólido blanco 2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-il)acetonitrilo (2.351 mmol), el cual fue utilizado en la siguiente etapa sin más purificación.

1.6.5 Intermediario 19

Un matraz de fondo redondo de 25 ml fue cargado con hidruro de litio aluminio (0.134 g, 3.53 mmol) en tetrahidrofurano (10 ml), para dar una solución sin color. Se agregó hidruro de litio aluminio (0.134 g, 3.53 mmol) en tetrahidrofurano (3.5mL). La reacción fue sometida a reflujo durante 12 horas y luego enfriada y templada con sulfato de sodio saturado. La mezcla de reacción fue secada, filtrada y evaporada y usada sin más purificación en la siguiente etapa .2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-il)etanamina (1.179 mmol).

1.6.6 Compuesto 20 (Fórmula 1)/**Ejemplo 121**

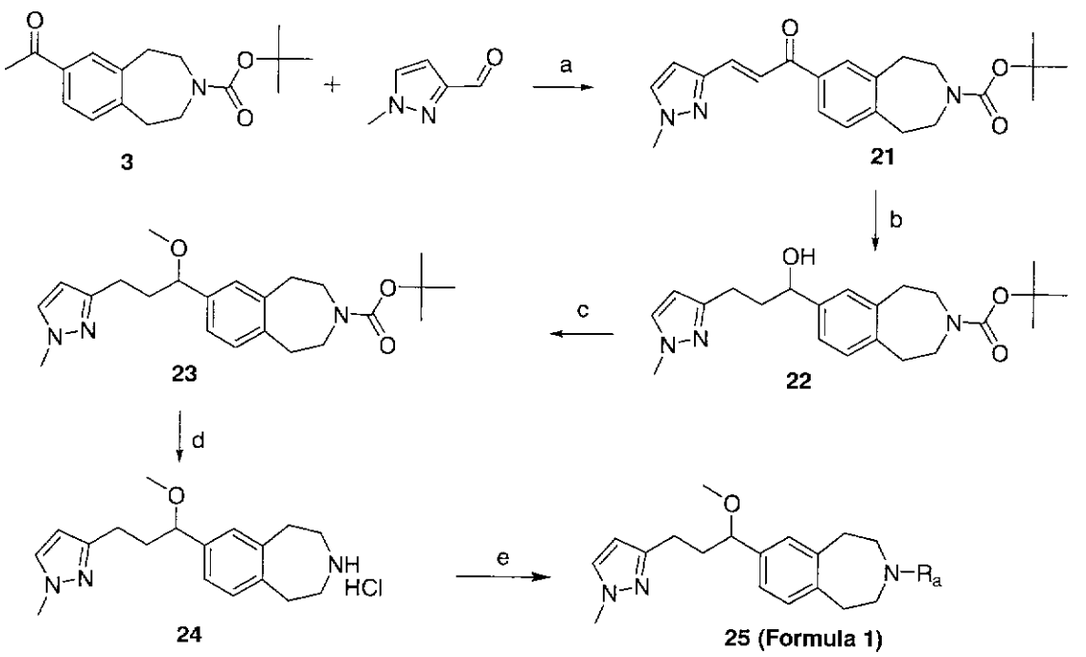
Un matraz de fondo redondo de 25 ml fue cargado con 2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-il)etanamina (0.288 g, 1.179 mmol) y cloruro de nicotinoilo (0.250 g, 1.769 mmol) en piridina (10ml) para dar una solución sin color. La reacción fue agitada por una hora y luego se formó una mezcla azeotrópica con tolueno. El residuo fue llevado a acetato de etilo y lavado con una solución de hidróxido de sodio 1M. La capa orgánica fue secada y el residuo fue purificado usando metanol al 10% en diclorometano con 0.2% de hidróxido de amonio para producir un producto crudo, el cual fue purificado usando un HPLC preparativo para dar N-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)etil)nicotinamida (0.086 mmol).

MS ES^+ : 350

^{1}H NMR (400 MHz, MeOD): 8.87 - 8.91 (m, 1H), 8.64 - 8.69 (m, 1H), 8.15 - 8.20 (m, 1H), 7.50 - 7.56 (m, 1H), 6.97 - 7.05 (m, 3H), 3.55 - 3.62 (m, 2H), 2.77 - 2.96 (m, 7H), 2.44 (br. s., 4H), 2.05 - 2.14 (m, 2H), 1.86 - 1.99 (m, 2H), 1.61 - 1.77 (m, 2H)

1.7 Esquema 7

Otros compuestos de Fórmula 1 se pueden sintetizar según lo expuesto en el **Esquema 7**, usando condiciones estándares bien conocidas en el arte. Este esquema, así como los **Esquemas 8 y 9** (ver más adelante), son apropiados para preparar los **compuestos de los Ejemplos 122-137**.



Reactivos y condiciones: a) DBU, MeCN; b) $Pt(IV)O_2$, H_2, EtOAc; c) NaH, MeI, NMP; d) HCl 4M; e) TEA, AcOH, $NA(OAc)_3BH$, DCM, R_aCO

1.7.1 Intermediario 21

Un matraz de fondo redondo de 25 ml fue cargado con cloruro de litio (0.366 g, 8.64 mmol), 1-metil-1H-pirazol-3-carbaldehído (0.951 g, 8.64 mmol), y tert-butil 7-acetil-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (2.5 g, 8.64 mmol) en acetonitrilo (10 ml) para dar una solución sin color. Se agregó DBU (1.302 ml, 8.64 mmol) y cernidores moleculares 4A. La reacción fue agitada durante una hora. El solvente fue evaporado y el

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residuo fue llevado a acetato de etilo y lavado con ácido cítrico al 5% (x2), bicarbonato de sodio saturado, y secado y evaporado. El residuo fue purificado por una columna de Biotage 50g SNAP, usando 50% EtOAc/ gasolina para producir (E)-tert-butil 7-(3-(1-metil-1H-pirazol-3-il)acriloil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (6.82 mmol) puro.

MS ES^+: 326

^1H NMR (400 MHz, MeOD): □ 7.80 - 7.85 (m, 2H), 7.64 - 7.66 (m, 2H), 7.60 - 7.63 (m, 1H), 7.27 - 7.32 (m, 1H), 6.75 - 6.78 (m, 1H), 3.92 (s, 3H), 3.56 (br. s., 4H), 2.95 - 3.02 (m, 4H), 1.44 (s, 9H)

1.7.2 Intermediario 22

Un matraz de fondo redondo de 100 ml fue cargado con (E)-tert-butil 7-(3-(1-metil-1H-pirazol-3-il)acriloil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (2.6 g, 6.82 mmol) y óxido de platino (IV) (0.077 g, 0.341 mmol) en acetato de etilo (50ml) para dar una suspensión negra. La reacción fue hidrogenada a presión atmosférica monitoreada por LCMS. La reacción fue filtrada a través de diatomita y evaporada para producir un aceite, purificado por Biotage 50g usando acetato de etilo para eluír el producto tert-butil 7-(1-hidroxi-3-(1-metil-1H-pirazol-3-il)propil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (6.23 mmol).

MS ES^+: 408

^1H NMR (400 MHz, MeOD): □ 7.41 - 7.45 (m, 1H), 7.08 - 7.25 (m, 3H), 5.97 - 6.10 (m, 1H), 4.52 - 4.67 (m, 1H), 3.80 (s, 3H), 3.44 - 3.65 (m, 4H), 2.82 - 2.99 (m, 4H), 2.51 - 2.74 (m, 2H), 1.87 - 2.13 (m, 2H), 1.47 (s, 9H)

1.7.3 Intermediario 23

Un matraz de fondo redondo de 50 ml fue cargado con tert-butil 7-(1-hidroxi-3-(1-metil-1H-pirazol-3-il)propil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (1 g, 2.59 mmol) en N-metilopirrolidona (NMP), para dar una solución sin color. Se agregó hidruro de sodio

(0.125 g, 3.11 mmol) y la reacción fue agitada durante una hora y luego se agregó yodometano a la mezcla y la reacción fue agitada por 16 horas. La reacción fue diluída con agua y extraída con acetato de etilo. La capa orgánica fue lavada con agua (x3) secada y evaporada. El residuo fue purificado con Biotage SNAP 50g, usando gasolina - acetato de etilo (1:1) para producir tert-butil7-(1-metoxi-3-(1-metil-1H-pirazol-3-il)propil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (1.502 mmol).

MS ES^+: 422

^1H NMR (400 MHz, MeOD): □ 7.41 - 7.45 (m, 1H), 7.10 - 7.15 (m, 1H), 7.03 - 7.07 (m, 2H), 6.01 - 6.06 (m, 1H), 4.07 - 4.13 (m, 1H), 3.80 (s, 3H), 3.54 (br. s., 4H), 3.17 (s, 3H), 2.86 - 2.92 (m, 4H), 2.51 - 2.70 (m, 2H), 2.00 - 2.12 (m, 1H), 1.82 - 1.95 (m, 1H), 1.46 (s, 9H)

1.7.4 Intermediario 24

Un matraz de fondo redondo de 25 ml fue cargado con tert-butil 7-(1-metoxi-3-(1-metil-1H-pirazol-3-il)propil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (.65 g, 1.627 mmol) en HCl 4M, para dar una solución sin color. La reacción fue agitada durante dos horas y luego evaporada para producir cloruro de 7-(1-metoxi-3-(1-metil-1H-pirazol-3-il)propil)-2,3,4,5-tetrahidro-1H-benzo[d]azepinium (1.548 mmol). Este material fue utilizado sin más purificación.

MS ES^+: 268

*1.7.5 Síntesis del Compuesto 25 (Fórmula 1)/***Ejemplo 136**

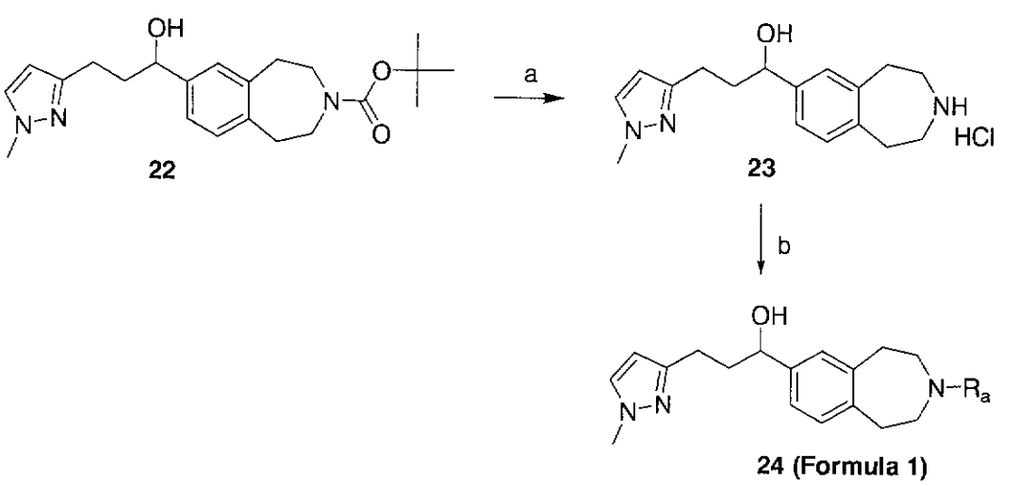
Un matraz de fondo redondo de 50 ml fue cargado con cloruro de 7-(1-metoxi-3-(1-metil-1H-pirazol-3-il)propil)-2,3,4,5-tetrahidro-1H-benzo[d]azepinium (0.520 g, 1.548 mmol), ciclobutanona (0.217 g, 3.10 mmol), y trietilamina (0.216 ml, 1.548 mmol) en diclorometano (25mL) para dar una solución sin color. Se agregó triacetoxiborohidruro de sodio (0.656 g, 3.10 mmol) y ácido acético (0.886 ml, 15.48 mmol), y la reacción fue agitada durante 16 horas antes de diluírla con diclorometano y lavarla con una solución de hidróxido de sodio al 5%. La fase orgánica fue secada y evaporada y el residuo fue

purificado por Biotage SNAP 50g eluyendo con 2% de amoníaco metanol / diclorometano (1-20%) para producir cloruro de 3-ciclobutil-7-(1-metoxi-3-(1-metil-1H-pirazol-3-il)propil)-2,3,4,5-tetrahidro-1H-benzo[d]azepinium después del tratamiento con HC1 etéreo.

MS ES^+: 322

^{1}H NMR (400 MHz, MeOD): 7.85 - 7.90 (m, 1H), 7.09 - 7.20 (m, 3H), 6.35 - 6.41 (m, 1H), 4.09 - 4.15 (m, 1H), 3.96 (s, 3H), 3.56 - 3.70 (m, 4H), 3.27 - 3.39 (m, 2H), 3.12 (s, 3H), 2.97 - 3.08 (m, 2H), 2.67 - 2.84 (m, 4H), 2.26 - 2.45 (m, 4H), 1.67 - 2.10 (m, 3H)

1.8 Esquema 8



22 **23** **24 (Formula 1)**

Reactivos y condiciones: a) HCl 4M, dioxano, b) R_aCHO, AcOH, $Na(OAc)_3BH$, DCM

1.8.1 Intermediario 23

Un matraz de fondo redondo de 25 ml fue cargado con tert-butil 7-(1-hidroxi-3-(1-metil-1H-pirazol-3-il)propil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (1.7 g, 4.41 mmol) en HCl 4M, para dar una solución sin color. La reacción fue agitada durante dos horas y luego evaporada para producir cloruro de 7-(1-hidroxi-3-(1-metil-1H-pirazol-3-il)propil)-2,3,4,5-tetrahidro-1H-benzo[d]azepinium (4.35 mmol).

MS ES^+: 268 M-18

1.7.5 Síntesis del Compuesto 24 (Fórmula 1)/**Ejemplo 135**

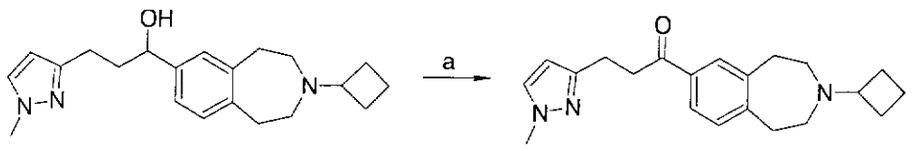
Un matraz de fondo redondo de 100 ml fue cargado con ácido acético (2.490 ml, 43.5 mmol), triacetoxiborohidruro de sodio (1.844 g, 8.70 mmol), cloruro de 7-(1-hidroxi-3-(1-metil-1H-pirazol-3-il)propil)-2,3,4,5-tetrahidro-1H-benzo[d]azepinium (1.4 g, 4.35 mmol) y trietilamina (0.606 ml, 4.35 mmol) en DCM (50ml) para dar una solución sin color. Se agregó ciclobutanone (0.610 g, 8.70 mmol). La reacción fue agitada durante 16 horas y luego la mezcla de reacción fue lavada con una solución de NaOH al 5% y secada y evaporada. El residuo fue purificado por Biotage SNAP 100g, usando Metanol al 10% / DCM con 2% de amonio para producir 1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(1-metil-1H-pirazol-3-il)propan-1-ol (2.504 mmol).

MS ES^+: 323

^1H NMR (400 MHz, MeOD): □ 7.40 - 7.46 (m, 1H), 7.03 - 7.13 (m, 3H), 6.02 - 6.10 (m, 1H), 4.53 - 4.62 (m, 1H), 3.80 (s, 3H), 2.77 - 2.97 (m, 5H), 2.34 - 2.70 (m, 6H), 1.87 - 2.15 (m, 6H), 1.59 - 1.78 (m, 2H)

1.9 Esquema 9

Esquema 9



24 **24 (Fórmula 1)/Compuesto del Ejemplo 134**

Reactivos y condiciones: a) MnO_2, THF

1.9.1 Síntesis del Compuesto 25 (Fórmula 1)/**Ejemplo 134**

Un matraz de fondo redondo de 100 ml fue cargado con 1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(1-metil-1H-pirazol-3-il)propan-1-ol (0.5 g, 1.473 mmol) y dióxido de manganeso (1.280 g, 14.73 mmol) en tetrahidrofurano (50ml) para dar una suspensión negra. La reacción fue calentada bajo reflujo durante 2 horas, y luego filtrada y evaporada y purificada por SNAP 100g eluyendo con metanol al 10% en diclorometano con

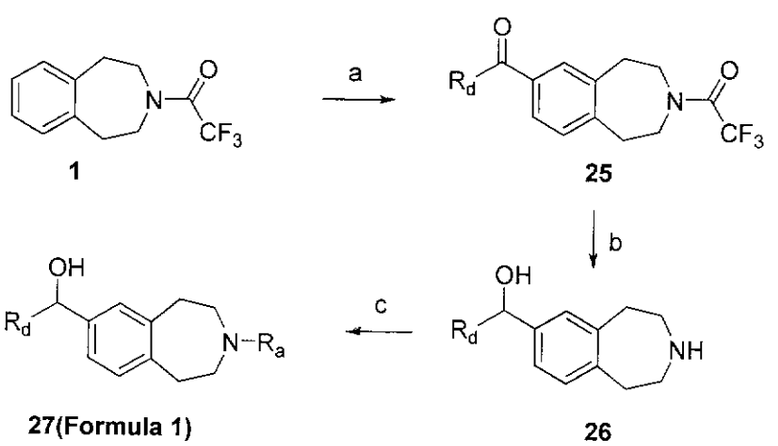
amoníaco para producir 1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(1-metil-1H-pirazol-3-il)propan-1-ona (0.504 mmol).

MS ES^+: 338

^1H NMR (400 MHz, $CDCl_3$): 7.71 - 7.78 (m, 2H), 7.23 - 7.26 (m, 1H), 7.15 - 7.20 (m, 1H), 6.05 - 6.11 (m, 1H), 3.88 (s, 3H), 3.30 - 3.39 (m, 2H), 3.03 - 3.12 (m, 2H), 2.97 (br. s., 4H), 2.72 - 2.85 (m, 1H), 2.45 (br. s., 4H), 2.03 - 2.15 (m, 2H), 1.84 - 1.99 (m, 2H), 1.55 - 1.79 (m, 2H).

1.10 Esquema 10

Este esquema es apropiado para preparar los **compuestos de los ejemplos 138-141**



a)i. RdCOOH, $SOCl_2$; ii. $AlCl_3$, CH_2Cl_2; b)$NaBH_4$, MeOH;
c) R_aCO or R_aHCO, $NaB(OAc)_3H$, DCM, AcOH

*1.10.1 Intermediario **25***

Un matraz de fondo redondo fue cargado con cloruro de tionilo (7.3 ml, 100 mmol) y ácido 1-acetilpiperidina-4-carboxílico (1.7 g, 10.00 mmol) para dar una solución sin color. Después de aproximadamente 15 minutos se formaron cristales. La reacción fue diluída con gasolina y la reacción fue filtrada y lavada con gasolina. Los cristales fueron secados y evaporados y se agregó 1-(4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona (2.4 g, 10 mmol) y la mezcla fue disuelta en diclorometano (20 mL). Se agregó cautelosamente por goteo tricloruro de aluminio (4 g, 30 mmol) y la mezcla fue

000253

agitada durante dos horas antes de verterla en hielo y extraerla con acetato de etilo. El extracto orgánico fue lavado con salmuera y secado y evaporado. El residuo fue purificado por cromatografía de columna en sílice, usando metanol al 10% en diclorometano para producir 1-(7-(1-acetilpiperidina-4-carbonil)-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona (2.6 g, 6.6 mmol, 65.6 % de rendimiento) como un aceite.

^{1}H NMR (400 MHz, MeOD-d4) □ 7.77 - 7.95 (m, 2H), 7.32 - 7.45 (m, 1H), 4.47 - 4.58 (m, 1H), 3.95 - 4.09 (m, 1H), 3.65 - 3.91 (m, 5H), 3.35-3.40 (m, 1H), 3.06 - 3.22 (m, 4H), 2.83 - 3.02 (m, 1H), 2.09 - 2.20 (m, 3H), 1.84 - 2.02 (m, 2H), 1.48 - 1.79 (m, 2H)

MS ES$^+$: 397

*1.10.2 Intermediario **26***

Un matraz fue cargado con 1-(7-(1-acetilpiperidina-4-carbonil)-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona (2.6 g, 6.6 mmol) y borohidruro de sodio (0.76 g, 20 mmol) en metanol (20 mL) para dar una solución sin color. La reacción fue agitada durante 16 horas. El solvente fue removido y el producto fue usado crudo en la siguiente etapa.

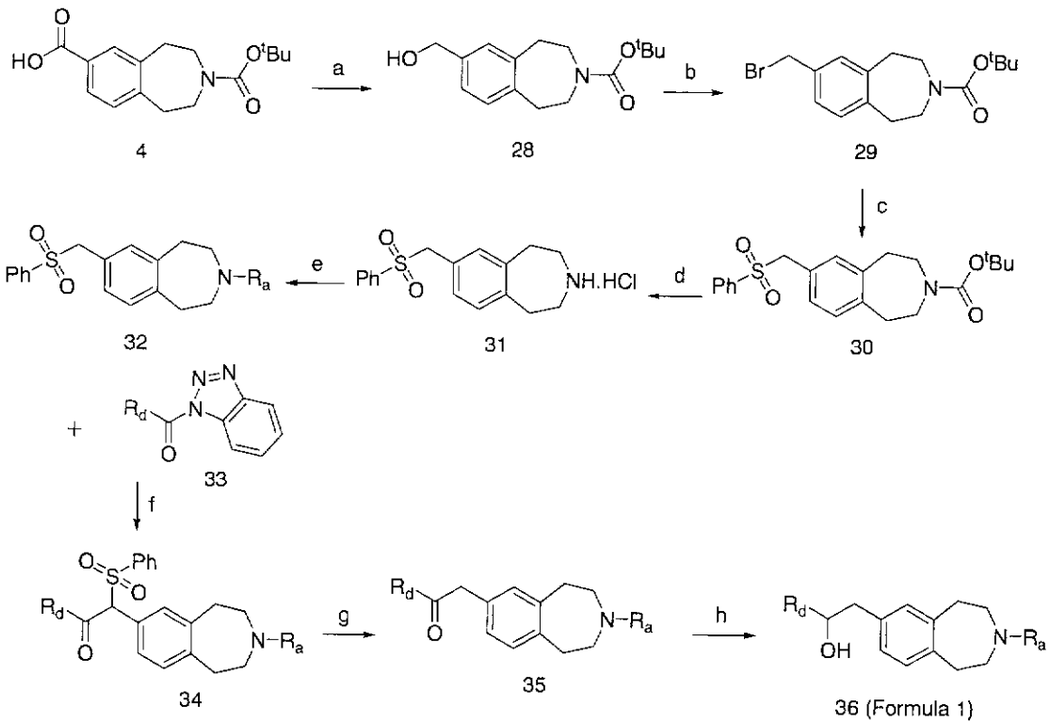
*1.10.3 Compuesto **27** (Fórmula 1)/ **Ejemplo 138***

Un matraz fue cargado con 1-(4-(hidroxi(2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)piperidin-1-il)etanona) (2.0g, 6.6mmol), ciclobutanona (0.25g, 13.2mmol) y trietilamina (0.69g, 6.6 mmol) en diclorometano (20 mL) para dar una solución sin color. Se agregó triacetoxiborohidruro de sodio (2.1 g, 9.9 mmol) y la reacción fue agitada durante dos horas antes de diluírla con hidróxido de sodio 2M y extraerla con diclorometano. La capa orgánica fue secada y evaporada y purificada por cromatografía de sílice, eluyendo con metanol al 10% en diclorometano para producir 1-(4-((3-ciclobutil-

2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)(hidroxi)metil)piperidin-1-il)etanona (0.9 g, 2.6 mmol, 40% de rendimiento) como un sólido blanco después de la trituración con éter.

1.11 Esquema 11

Este esquema es apropiado para preparar los **compuestos de los ejemplos 142-157, 227-228, 240-241, 244, 305-307 y 325.**



a) BH_3.THF; b)CBr_4, PPh_3,CH_2Cl_2; c)PhSOONa,DMF;d)HCl, DCM/MeOH
e)RaCO or RaHCO, $NaB(OAc)_3H$, DCM;f)n-BuLi, THF g)i.EtOH, sat NH_4Cl, AcOH, Zn;ii. 2M NaOH;
h) $NaBH_4$, MeOH

1.11.1 Intermediario 4

Hecho utilizando un método previamente descrito (ver 1.1.4).

1.11.2 Intermediario 28

Se agregó ácido 3-(tert-butoxicarbonil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina--carboxílico (10 g, 34.32 mmol) por goteo a borano 1M en tetrahidrofurano (51.5 ml, 51.49 mmol) y la mezcla resultante fue agitada durante 16 horas a temperatura ambiente bajo nitrógeno.

000255

Se agregó lentamente bicarbonato de sodio hasta que cesó el burbujeo. La reacción fue luego extraída con EtOAc y la fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada *in vacuo* para producir tert-butil 7-(hidroximetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato como un aceite sin color (9.34 g, 33.67 mmol, 98 %).

^{1}H NMR (400 MHz, MeOD) □ ppm 1.49 (s, 9 H) 2.84 - 2.96 (m, 4 H) 3.48 - 3.62 (m, 4 H) 4.50 - 4.59 (m, 2 H) 7.12 (s, 3 H)

MS ES$^-$ 276

1.11.3 Intermediario 29

Tert-butil 7-(hidroximetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (19.85 g, 71.57 mmol) y trifenilfosfina (18.77 g, 71.57 mmol) en diclorometano (60 mL) fueron enfriadas ahasta 0° C y se agregó una solución de tetrabromuro de carbono (23.73 g, 71.57 mmol) en diclorometano (60 mL) por medio de un embudo de goteo por 1 hora. Después de completar la adición, la mezcla fue entibiada a RT y agitada durante la noche (LCMS indicó la mayor parte del producto después de este tiempo). La mezcla de reacción fue vertida en gasolina (500 mL) y filtrada a través de Diatomita. El sólido residual remanente en el matraz fue triturado con gasolina (3 x 200 mL) y filtrada como anteriormente mencionado. El filtrado fue concentrado y se agregaron diclorometano y sílice en gel. Después de la concentración a sequedad, el producto fue purificado por cromatografía flash seca en gel de sílice, eluyéndolo con un gradiente por etapas de 0-30% de EtOAc / gasolina (producto eluído a 10-20% EtOAc) para dar 4 como un aceite, el cual cristalizó a tert-butil 7-(bromometil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato como un sólido blanco al rasparlo / formar pepitas / fijarse (16.24 g, 47.73 mmol, 67%).

^{1}H NMR (400 MHz, MeOD) □ ppm 1.48 (s, 9 H) 2.85 - 2.98 (m, 4 H) 3.48 - 3.64 (m, 4 H) 4.48 - 4.59 (m, 2 H) 7.08 - 7.25 (m, 3 H)

MS ES$^+$ 340 342

1.11.4 Intermediario 30

000256

Tert-butil 7-(bromometil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (10.00 g, 29.4 mmol) fue suspendida en DMF (30 mL) y se agregó bencenosulfinato de sodio (7.24 g, 44.1 mmol). La reacción fue agitada durante 16 horas a temperatura ambiente.

La mezcla de reacción fue diluida con EtOAc (50 mL) y lavada con salmuera (5 x 50 mL). La fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada *in vacuo* para producir 12.097 g de polvo blanco. Ésta fue lavada con dietiléter y filtrada para producir tert-butil 7-(fenilsulfonilmetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (8.75 g, 21.79 mmol, 74 %).

^{1}H NMR (400 MHz, MeOD) □ ppm 1.49 (s, 9 H) 2.72 - 2.84 (m, 2 H) 2.85 - 2.94 (m, 2 H) 3.41 - 3.61 (m, 4 H) 4.44 (s, 2 H) 6.75 - 7.00 (m, 2 H) 7.05 (s, 1 H) 7.56 (d, J=7.33 Hz, 2 H) 7.68 (d, J=7.58 Hz, 3 H)

MS ES$^+$ 402

1.11.5 Intermediario 31

Tert-butil 7-(fenilsulfonilmetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (8.75 g, 21.79 mmol) fue disuelto en 10 mL de DCM / MeOH (9:1) y se agregó HCl 4M en 1,4-Dioxano (25 ml, 25 mmol) y la mezcla fue agitada durante 1 hora a temperatura ambiente. La mezcla fue concentrada *in vacuo* a sequedad para producir 7-(fenilsulfonilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (6.781 g, 22.50 mmol, 100%) como un sólido blanco.

^{1}H NMR (400 MHz, MeOD) □ ppm 3.02 - 3.11 (m, 2 H) 3.12 - 3.19 (m, 2 H) 3.23 - 3.30 (m, 4 H) 4.49 (s, 2 H) 6.97 - 7.08 (m, 2 H) 7.13 - 7.20 (m, 1 H) 7.53 - 7.63 (m, 2 H) 7.66 - 7.78 (m, 3 H)

MS ES$^+$ 302

1.11.6 Intermediario 32

7-(fenilsulfonilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (6.78 g, 22.49 mmol) fue suspendida en CH_2Cl_2 (20 mL) y se agregó trietilamina (3.43 mL, 24.74 mmol) y

000257

ciclobutanona (2.52 mL, 33.70 mmol). La mezcla fue agitada bajo nitrógeno y se agregó triacetoxiborohidruro de sodio (7.15 g, 33.70 mmol) y ácido acético (1.93 mL, 33.70 mmol). La mezcla fue agitada a temperatura ambiente durante 16 horas. La mezcla fue templada con NaOH (2M, aq, 50 mL) y las fases fueron separadas. La fase acuosa fue extraída con DCM (3 x 10 mL) y las capas orgánicas combinadas, fueron secadas sobre sulfato de magnesio, filtradas y concentradas *in vacuo* para producir un aceite sin color. El aceite fue triturado con dietiléter para producir 3-ciclobutil-7-(fenilsulfonilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (5.361 g, 15.08 mmol, 67 %) como un sólido blanco.

^{1}H NMR (400 MHz, MeOD) □ ppm 1.59 - 1.83 (m, 2 H) 1.87 - 2.02 (m, 2 H) 2.05 - 2.19 (m, 2 H) 2.23 - 2.61 (m, 4 H) 2.74 - 2.97 (m, 5 H) 4.44 (s, 2 H) 6.78 - 6.85 (m, 1 H) 6.87 - 6.94 (m, 1 H) 6.98 - 7.07 (m, 1 H) 7.49 - 7.59 (m, 2 H) 7.66 (s, 3 H)

MS ES$^+$ 356

1.11.7 Intermediario 33

Un vial para microondas de 20 mL fue cargado con 1-(metilsulfonil)-1H-benzo[d][1,2,3]triazolo (0.986 g, 5.00 mmol) y ácido 2-(1-propionilpiperidin-4-il)acético (0.996 g, 5 mmol) en THF (10 ml) para dar una solución sin color. Se agregó trietilamina (0.976 mL, 7.00 mmol) y la reacción fue puesta al microondas a 130° C durante 20 minutos. TLC 1:1 EtOAc / gasolina mostró una reacción completa. El solvente fue evaporado y el residuo fue purificado por cromatografía de sílice usando acetato de etilo /gasolina 0-100% para producir 1-(4-(2-(1H-benzo[d][1,2,3]triazol-1-il)-2-oxoetil)piperidin-1-il)propan-1-ona (1.1 g, 3.66 mmol, 73.2 % de rendimiento).

^{1}H NMR (400 MHz, $CDCl_3$) □ 8.28 - 8.35 (m, 1H), 8.12 - 8.19 (m, 1H), 7.66 - 7.73 (m, 1H), 7.50 - 7.58 (m, 1H), 3.55 - 5.00 (bm, 2H), 3.37 - 3.44 (m, 2H), 2.50 - 3.33 (bm, 2H), 2.32 - 2.44 (m, 3H), 1.89 - 2.00 (m, 2H), 1.31 - 1.45 (m, 2H), 1.13 - 1.22 (m, 3H)

1.11.8 Intermediario 34

3-Ciclobutil-7-(fenilsulfonilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.422 g, 4 mmol) fue disuelta en THF (30mL) a 0°C y se agregó n-butilitio (5.00 mL de 1.6M, 8.00 mmol) por goteo. La reacción fue entibiada hasta temperatura ambiente por una hora y luego enfriada hasta -78°C. Se agregó por goteo 1-(4-(2-(1H-Benzo[d][1,2,3]triazol-1-il)-2-oxoetil)piperidin-1-il)propan-1-ona (1.201 g, 4.00 mmol) en THF (5mL). La reacción fue dejada para entibiarse hasta temperatura ambiente durante el curso de 16 horas. La reacción fue templada con cloruro de amonio saturado, diluída con DCM y basificada con una solución de carbonato de sodio. La capa acuosa fue extraída (x3) con diclorometano, secada y evaporada. El residuo fue purificado por cartucho de sílice KPNH para producir 1-(4-(3-(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-oxo-3-(fenilsulfonil)propil)piperidin-1-il)propan-1-ona (1.6 g, 2.98 mmol, 74.5 % de rendimiento). ^{1}H NMR (400 MHz, MeOD) □ 7.59 - 7.72 (m, 3H), 7.47 - 7.55 (m, 2H), 6.96 - 7.13 (m, 3H), 4.41 (br. s., 1H), 3.86 (br. s., 1H), 2.98 - 3.11 (m, 1H), 2.76 - 2.98 (m, 5H), 2.32 - 2.70 (m, 8H), 1.84 - 2.18 (m, 5H), 1.51 - 1.81 (m, 4H), 0.82 - 1.44 (m, 7H)

1.11.9 Intermediario 35

Se disolvió 1-(4-(3-(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-oxo-3-(fenilsulfonil)propil)piperidin-1-il)propan-1-ona (1.6 g, 2.98 mmol en etanol (50mL) y se agregó cloruro de amonio saturado y ácido acético (3.41 mL, 59.6 mmol) seguido por cinc (1.950 g, 29.8 mmol) y la reacción fue sometida a reflujo por 1.5 horas. LCMS mostró que la reacción se completó, y la mezcla de reacción fue enfriada, basificada con NaOH 2M y extraída con diclorometano (x3), secada y evaporada. El residuo fue purificado por un cartucho KPNH (55g) eluyéndolo con gasolina acetato de etilo 0-100% para producir 1-(4-(3-(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-oxopropil)piperidin-1-il)propan-1-ona (1.1 g, 2.77 mmol, 93 % de rendimiento).

^{1}H NMR (400 MHz, MeOD) δ 7.02 - 7.12 (m, 1H), 6.97 (br. s., 2H), 4.39 - 4.52 (m, 1H), 3.82 - 3.94 (m, 1H), 3.67 (s, 2H), 3.00 - 3.13 (m, 1H), 2.77 - 3.00 (m, 5H), 2.31 - 2.69 (m, 9H), 1.87 - 2.19 (m, 5H), 1.59 - 1.81 (m, 4H), 0.90 - 1.15 (m, 5H)

MS ES$^+$ 397

*1.11.10 Compuesto 36 (Fórmula 1) / **Ejemplo 147***

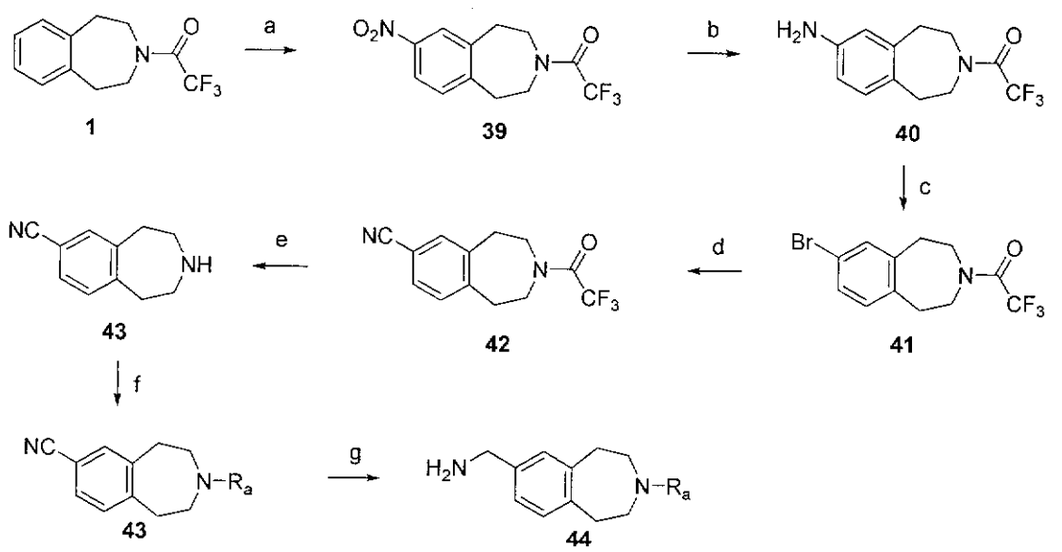
1-(4-(3-(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-oxopropil)piperidin-1-il)propan-1-ona (1.1 g, 2.77 mmol) fue disuelta en metanol (30mL) y se agregó borohidruro de sodio (0.315 g, 8.32 mmol) a la solución agitada. La reacción fue agitada durante una hora antes de templarla con HCl 2M (10mL) y evaporarla. El residuo fue llevado a diclorometano y basificado con NaOH 2M y extraído con más diclorometano. El extracto fue evaporado y el residuo fue purificado por sílice KPNH, usando acetato de etilo / gasolina para producir un sólido, el cual fue recristalizado de heptano acetato de etilo para producir 1-(4-(3-(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)propan-1-ona (.739 g, 1.854 mmol, 66.8 % de rendimiento) como un primer cultivo.

^{1}H NMR (400 MHz, MeOD) δ 6.90 - 7.07 (m, 3H), 4.42 - 4.56 (m, 1H), 3.82 - 3.98 (m, 2H), 2.98 - 3.12 (m, 1H), 2.79 - 2.98 (m, 5H), 2.31 - 2.77 (m, 9H), 2.05 - 2.19 (m, 2H), 1.89 - 2.05 (m, 2H), 1.58 - 1.89 (m, 5H), 1.27 - 1.49 (m, 2H), 0.86 - 1.23 (m, 5H)

MS ES$^+$ 399

1.12 Esquema 12

Este esquema se puede utilizar para sintetizar los **compuestos de ejemplos 175- 220, 248, 230, 234, 236-239, 242-243, 245-247, 249, 252, 254-257, 259-264, 265-276, 279-282, 284-285, 287-293, 295-302, 309-324** y como un método alternativo para sintetizar el *Intermediario 13.*



a) H_2SO_4, KNO_3, 0°C; b) $NH_4(HCOO)_2$, $Pd(OH)_2$; c) HBr, $NaNO_2$; d) $Pd(Ph_3)_4$; $Zn(CN)_2$, H_2O, DMF
e) aq. NaOH, MeCN, EtOH; f) R_aCO or RaHCO, $NaB(OAc)_3H$, DCM; g) $LiAlH_4$, THF

1.12.1 *Intermediario 39*

Se disolvió 1-(4,5-Dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona (100g, 411 mmol) en ácido sulfúrico (400 ml) y la solución fue enfriada en un baño de hielo. Se agregó nitrato de potasio (45.7 g, 452 mmol) por goteo durante 20 minutos (no se observó exotermia, la solución se tornó amarillo pálido). La solución fue agitada por 10 minutos más, tiempo después del cual la reacción fue completada por TLC (acetato de etilo en gasolina al 30%, tinción de permanganato de potasio). La mezcla de reacción fue vertida lentamente en vasos precipitados de 2 x 2 litros, llenos de hielo con agitación. Se formó un precipitado blanco espeso y una vez que se hubo agregado aproximadamente la mitad de la solución producto, se agregó alrededor de 400 ml de DCM a los vasos precipitados para disolver esto. Se agregaron 200 ml de DCM adicionales a los vasos precipitados y las capas de frío-hielo fueron separadas y la capa acuosa fue extraída con DCM (1 x 200 ml). Las capas orgánicas combinadas fueron lavadas con salmuera (500 ml) y secadas (MgSO4) y el solvente fue removido bajo presión reducida. Se agregó acetato de etilo

(200 ml) al aceite resultante, y el producto se dejó cristalizar durante la noche y luego se filtró para dar 2,2,2-trifluoro-1-(7-nitro-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)etanona como un sólido blanco, 50g, 42%.

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.95 - 8.16 (m, 2H), 7.24 - 7.47 (m, 1H), 3.62 - 4.01 (m, 4H), 2.95 - 3.32 (m, 4H)

1.12.2 Intermediario 40

Se disolvió 2,2,2-Trifluoro-1-(7-nitro-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)etanona (50g, 174 mmol) en etanol (1 litro) y se agregó formiato de amonio (110g, 10 eq.), seguido por $Pd(OH)_2$ (20% en carbono, húmedo, 2 g). La mezcla fue agitada vigorosamente bajo nitrógeno y la reacción se inició al entibiarla en un baño de agua caliente durante 5 minutos. La mezcla de reacción comenzó a burbujear vigorosamente. Después de 30 minutos, la reacción se completó por tlc (30% EtOAc, gasolina) y la mezcla fue filtrada a través de diatomita con lavado de etanol. El etanol fue luego removido bajo presión reducida y un tratamiento con acetato de etilo / agua se llevó a cabo, y las capas orgánicas combinadas fueron secadas ($MgSO_4$) y el solvente se removió para dar un sólido color blanco marfil, el cual fue triturado con éter para dar 1-(7-Amino-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona como un sólido blanco 40g, 89%.

1H NMR (400 MHz, $CDCl_3$) □ 6.82 - 7.09 (m, 1H), 6.44 - 6.61 (m, 2H), 3.59 - 3.84 (m, 4H), 2.66 - 2.99 (m, 4H).

1.12.3 Intermediario 41

Se suspendió 1-(7-Amino-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona (70.3 g, 272 mmol) en ácido bromhídrico (210 ml), y la mezcla fue enfriada en un baño de hielo y salmuera y se agregó una solución de nitrito de sodio en agua (20 ml) por goteo, durante 20 minutos para dar una suspensión espesa de color amarillo brillante. Mientras, se disolvió 1-(7-amino-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona (70.3 g, 272 mmol) en ácido bromhídrico (210 ml) y la solución fue calentada hasta 85° C en un

matraz de 2 bocas de 2 litros con condensador. Luego, se agregó la suspensión de sal de diazonio vertiéndola por goteo durante 20 minutos a través de un embudo, se observó efervescencia en cada adición. La sal de diazonio residual fue lavada con aproximadamente 20 ml de ácido bromhídrico y la solución se agitó por 1 hora más a 85° C. Después de este tiempo, el TLC (30% acetato de etilo / gasolina, tinción de permanganato de potasio, no uv) de un alícuota templada en agua y extraído con DCM, mostró conversión completa de la materia prima al producto deseado (mancha superior, y algo del fenol que se mostró brillante con tinción de permanganato de potasio. El espectro 1H NMR mostró aproximadamente 70% de producto + alguna impureza, probablemente el fenol. La mezcla fue enfriada hasta temperatura ambiente y diluída con agua (alrededor de 600 ml) y la mezcla fue extraída con DCM (2 x 500 ml), y las capas orgánicas combinadas lavadas con $NaHCO_3$ (400 ml) saturado, secadas (MgSO4) y el solvente se removió bajo presión reducida para dar un aceite café. Este material fue purificado por cromatografía de columna flash seca, eluyéndolo con acetato de etilo en gasolina al 10-30% para dar 1-(7-Bromo-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona como un sólido cristalino blanco, (40g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) ¯ 6.85 - 7.07 (m, 1H), 6.40 - 6.61 (m, 2H), 3.62 - 3.87 (m, 4H), 2.69 - 3.05 (m, 4H).

1.12.4 Intermediario 42

Se disolvió 1-(7-Bromo-4,5-dihidro-1H-benzo[d]azepin-3(2H)-il)-2,2,2-trifluoroetanona (20 g, 62.1 mmol) en DMF (150 ml) y agua (0.50 ml), y se agregaron tetrakis(trifenilfosfina) paladio (0) (0.789 g, 0.683 mmol) y cianuro de cinc (5.04 g, 43.5 mmol) y la solución se calentó bajo reflujo bajo nitrógeno durante 3 horas. Después de este tiempo, todavía había algo de materia prima por tlc (30% EtOAc /gasolina, tinción de permanganato de potasio, no uv), por lo tanto se agregaron otros 500 mg de tetrakis(trifenilfosfina) paladio (0) y la solución fue calentada por una hora más, tiempo después del cual la reacción fue

completada. La mayoría del DMF fue removido bajo presión reducida y se agregaron salmuera saturada y acetato de etilo y las capas fueron separadas. La capa orgánica fue lavada con salmuera (3 x 100 ml), secada (MgSO4) y el solvente fue removido para dar un aceite café-gris oscuro. Este producto crudo fue purificado por cromatografía de columna flash seca, eluyéndolo con acetato de etilo en gasolina al 30% para dar el producto como un aceite sin color, el cual cristalizó en reposo para dar 3-(2,2,2-Trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carbonitrilo como un sólido blanco, 12.8g, 77%.

^{1}H NMR (400 MHz, $CDCl_3$) 7.50 (s, 2H), 7.28 (s, 1H), 3.57 - 3.93 (m, 4H), 2.82 - 3.30 (m, 4H).

1.12.5 Intermediario 43

Se disolvió 3-(2,2,2-Trifluoroacetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carbonitrilo (2g, 7.46 mmol) en etanol (50 ml) y acetonitrilo (10.0 ml) y se agregó hidróxido de sodio acuoso 2 M (7.5 ml, 14.91 mmol), y la solución fue agitada durante 30 minutos, tiempo después del cual la reacción se completó por TLC (EtOAc/gasolina al 30%). El solvente fue removido bajo presión reducida y agua (50 ml) y se agregaron DCM (100 ml) y las capas fueron separadas y la capa orgánica fue lavada con salmuera (50 ml) y secada ($MgSO_4$) para dar 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carbonitrilo como un aceite sin color, 1.1 g, 86%.

^{1}H NMR (400 MHz, $CDCl_3$) 7.32 - 7.48 (m, 2H), 7.13 - 7.24 (m, 1H), 2.80 - 3.10 (m, 8H).

1.12.6 Intermediario 44

Se disolvió 3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carbonitrilo (8.1 g, 35.8 mmol) en THF (50 ml) y la solución fue agregada por goteo durante 20 minutos a una solución agitada de $LiAlH_4$ en THF 1.0 M (35.8 ml, 35.8 mmol), la cual fue entibiada hasta aproximadamente de 30° C en un baño de agua. Después de 1 hora, la reacción fue completada por tlc de una alícuota templada con agua y diluída con acetato de etilo

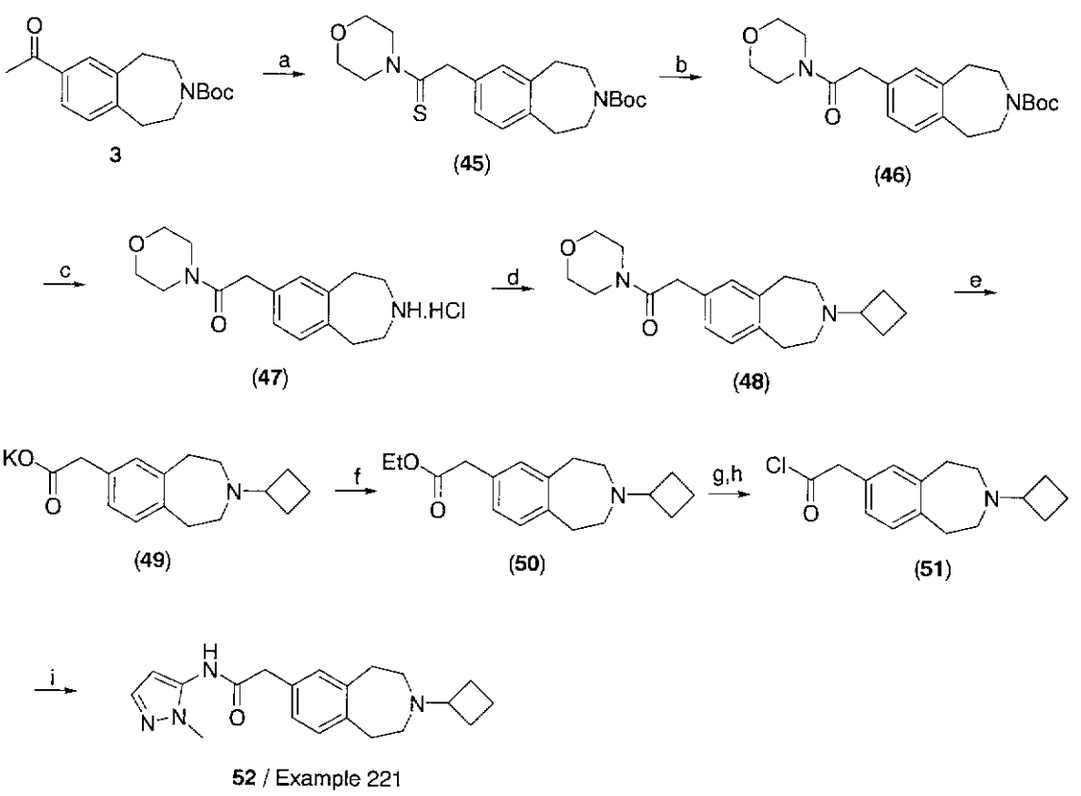
(MeOH/DCM al 10% + NH_3, ninhidrina). De ahí la solución fue enfriada en un baño de hielo y templada por la adición por goteo de Na_2SO_4 saturado y luego fue diluída con acetato de etilo (200 ml) y secada ($MgSO_4$) y la solución fue filtrada a través de diatomita y el solvente removido para dar (3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metanamina como un sólido color blanco marfil ceroso, 6.96g, 84%.

MS ES+ 231

^{1}H NMR (400 MHz, $CDCl_3$) □ 6.95 (s, 3H), 3.71 (s, 2H), 2.75 - 2.91 (m, 4H), 2.59 - 2.75 (m, 1H), 2.16 - 2.51 (m, 4H), 1.89 - 2.06 (m, 2H), 1.68 - 1.88 (m, 2H), 1.42 - 1.67 (m, 2H).

1.13 Esquema 13

Este esquema es apropiado para preparar los compuestos de los ejemplos 221-226, 274, 294.



a) S_8, morfolina, $Ti(OEt)_4$, 60 °C, 45 minutos, luego 90 °C, 30 minutos; b) KOH, H_2O, Etanol; c) HCl 4M en Dioxano; d) Ciclobutanona, $NaBH(OAc)_3$, Et_3N, AcOH, DCM; e) KOH, H_2O, Etanol, reflujo; f) H_2SO_4, Etanol, reflujo; g) LiOH, THF, H_2O; h) $SOCl_2$, reflujo; i) Amina, Piridina.

2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-N-(1-metil-1H-pirazol-5-il)acetamida (**Ejemplo 221)**

1.13.1 Intermediario 45

A una lechada (*slurry*) de *tert*-butil 7-acetil-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (20.00 g, 69.12 mmol) en morfolina (9.1 mL, 9.03 g, 87.12 mmol) a RT, se le agregó polvo de azufre (3.32 g, 103.67 mmol). La mezcla café fue agitada durante 5 minutos y luego se agregó etóxido de titanio (IV) (29.0 mL, 31.53 g, 138.24 mmol). La reacción fue calentada hasta 60° C por 45 minutos y luego hasta 90° C por 30 minutos. LCMS indicó la reacción completa, y se agregaron EtOAc (100 mL) y salmuera (50 mL), la mezcla fue agitada a RT durante 30 minutos y luego fue filtrada a través de diatomita y el sólido lavado con EtOAc. El filtrado fue lavado con salmuera (2 x 50 mL), secado ($MgSO_4$), filtrado y concentrado. Purificado en columna de gel de sílice Biotage, eluído con un gradiente de EtOAc / gasolina 10–50% para dar *tert*-butil 7-(2-morfolino-2-tioxoetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato como una goma café (18.60 g, 47.63 mmol, 69%).

^{1}H NMR (400 MHz, MeOD) δ 7.05 - 7.21 (m, 3H), 4.26 - 4.38 (m, 4H), 3.64 - 3.81 (m, 4H), 3.45 - 3.64 (m, 4H), 3.38 - 3.46 (m, 2H), 2.78 - 3.01 (m, 4H), 1.40 - 1.58 (m, 9H)

MS ES$^+$ 391

1.13.2 Intermediario 46

A una solución de tert-butil 7-(2-morfolino-2-tioxoetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (**45**) (18.60 g, 47.63 mmol) en etanol (200 mL) se agregó KOH (1M, aq., 95.3 mL, 95.30 mmol). La mezcla fue agitada durante la noche a RT y luego se agregó más KOH (1M, aq., 47.6 mL, 47.60 mmol) y la reacción fue agitada por 20 horas más a RT. La reacción fue vertida en agua (50 mL) y se agregó DCM (150 mL). Las fases fueron separadas, y la fase acuosa extraída con DCM (3 x 100 mL). Las fases orgánicas combinadas fueron lavadas con salmuera (2 x 100 mL), secadas ($MgSO_4$), filtradas y

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concentradas. Purificadas en gel de sílice, eluídas con un gradiente paso a paso de EtOAc / gasolina 20-40-60-80-100% para dar tert-butil 7-(2-morfolino-2-oxoetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato como un sólido amarillo claro (13.04 g, 34.82 mmol, 73%).

^{1}H NMR (400 MHz, DMSO □ 7.03 - 7.12 (m, 1H), 6.92 - 7.03 (m, 2H), 3.64 (s, 2H), 3.38 - 3.57 (m, 12H), 2.81 (d, *J* = 3.54 Hz, 4H), 1.33 - 1.52 (m, 9H)

MS ES$^+$ 375

1.13.3 Intermediario 47

Una solución de *tert*-butil 7-(2-morfolino-2-oxoetil)-4,5-dihidro-1H-benzo[d]azepina-3(2H)-carboxilato (13.00 g, 34.72 mmol) en dioxano (100 mL) fue tratada con HC1 en dioxano (4M, 40 mL). La reacción fue tratada con más HC1 en dioxano (4M, 25 mL) y se dejó durante el fin de semana. La remoción del solvente bajo presión reducida dio el producto como la sal de HCl hidrocloruro de 1-morfolino-2-(2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)etanona (**47**) en rendimiento cuantitativo, la cual fue usada inmediatamente en la próxima reacción.

^{1}H NMR (400 MHz, DMSO-d_6) 9.03 - 9.25 (m, 2 H), 7.09 - 7.17 (m, 1 H), 6.98 - 7.09 (m, 2 H), 3.63 - 3.69 (m, 2 H), 3.38 - 3.55 (m, 8 H), 2.98 - 3.22 (m, 8 H)

MS ES$^+$ 275

1.13.4 Intermediario 48

A una solución de hidrocloruro de 1-morfolino-2-(2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il) etanona (asume 34.72 mmol) en DCM (100 mL) se le agregó trietilamina (5.32 mL, 3.86 g, 38.19 mmol) y ciclobutanona (3.9 mL, 3.65 g, 52.08 mmol). La mezcla fue agitada por 5 minutos y luego se agregó triacetoxiborohidruro de sodio (11.04 g, 52.08 mmol), seguido por AcOH (1 mL). La mezcla fue agitada a RT durante 3 horas, LCMS indicó la completación y la mezcla de reacción fue vertida en NaOH (2M, aq., 100 mL). Las fases fueron separadas y la fase acuosa fue extraída con DCM (3 x 50 mL). Las fases orgánicas

combinadas fueron lavadas con salmuera (2 x 50 mL), secadas ($MgSO_4$), filtradas y concentradas. Purificadas por columna de gel de sílice Biotage, eluídas con 1 – 10% de 2% NH_3 / metanol en DCM. Las fracciones puras concentradas y el producto cristalizado por adición de éter para producir 2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-morfolinoetanona (9.21 g, 28.04 mmol, 81%).

^{1}H NMR (400 MHz, DMSO) ⌐ 6.99 - 7.07 (m, 1H), 6.90 - 6.99 (m, 2H), 3.63 (s, 2H), 3.41 - 3.56 (m, 8H), 2.65 - 2.85 (m, 5H), 2.32 (br. s., 4H), 1.92 - 2.08 (m, 2H), 1.69 - 1.85 (m, 2H), 1.49 - 1.67 (m, 2H)

MS ES^+ 329.

1.13.5 Intermediario 49

Una mezcla de 2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-morfolinoetanona (5.16 g, 15.72 mmol) y KOH (4M, aq., 19.7 mL, 78.60 mmol) en etanol (100 mL) fue calentada a reflujo durante 6 horas, se enfrió hasta RT y se dejó agitar durante el fin de semana y luego fue calentada a reflujo por 7 horas más. La mezcla de reacción fue concentrada y utilizada directamente en la reacción de esterificación.

A una solución de 2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il) acetato de potasio (**49**) (asume 17.24 mmol) en etanol (200 mL) se agregó H_2SO_4 (conc., 30 mL). La mezcla fue calentada a reflujo y etanol/agua son eliminados por destilación. Se agregó además etanol según lo necesario, así como también más H_2SO_4 (10 mL). Cuando se completó por LCMS, la mezcla de reacción fue vertida en hielo y se agregó DCM (100 mL). Se agregó Na_2CO_3 sólido para neutralizar el ácido y subir el pH hasta ~10. El sólido fue removido por filtración, lavado con DCM (200 mL) y las fases de filtrado fueron separadas. La fase acuosa fue extraída con DCM (3 x 100 mL) y las fases orgánicas combinadas fueron secadas ($MgSO_4$), filtradas y concentradas. La purificación por columna de gel de sílice Biotage, eluída con 0 – 10% de 2% NH_3 / MeOH en DCM dio etil

2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)acetato como un aceite amarillo (4.28 g, 14.89 mmol, 86% (2 etapas)).

^{1}H NMR (400 MHz, MeOD) δ 6.95 - 7.14 (m, 3H), 4.07 - 4.24 (m, 2H), 3.57 (s, 2H), 2.80 - 3.01 (m, 5H), 2.50 (br. s., 4H), 2.06 - 2.22 (m, 2H), 1.89 - 2.03 (m, 2H), 1.61 - 1.82 (m, 2H), 1.17 - 1.33 (m, 3H)

MS ES$^+$ 288.

*1.13.6 Compuesto 52 / (**Ejemplo 221**)*

Se hidrolizó 2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il) acetato de etilo (1.4 g, 4.87 mmol) con hidróxido de litio (0.117 g, 4.87 mmol) en THF agua 5:1 sometida a reflujo durante 16 horas. La mezcla de reacción fue evaporada y se formó una mezcla azeotrópica con tolueno (x3) para producir ácido crudo. Este luego fue convertido alcloruro del ácido por medio del calentamiento a reflujo con exceso de cloruro de tionilo. Los solventes fueron removidos y el residuo formó una mezcla azeotrópica con tolueno (x3) para producir 2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il) cloruro de acetilo (**51**), el cual fue usado impurificado en la próxima etapa.

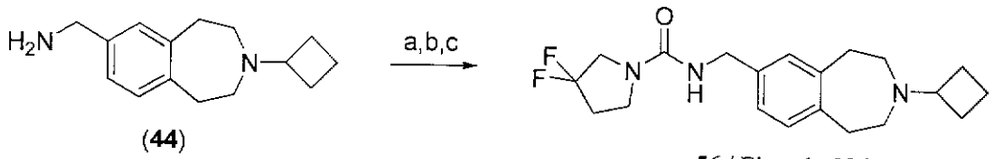
Se disolvió 2-(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il) cloruro de acetilo (**51**) (0.895g, 3.2mmol) en piridina (3 mL) y se agregó 1-metil-1Hpirazol-5-ilamina y se agitaron juntos durante 65 horas. El solvente fue removido por evaporación y el residuo fue particionado entre acetato de etilo y NaOH 2M. El extracto orgánico fue secado y evaporado, y el residuo fue purificado por cromatografía de sílice, usando un 0-10% de Metanol DCM con amoníaco para producir 2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-N-(1-metil-1H-pirazol-5-il)acetamida (0.45g, 41%).

^{1}H NMR (400 MHz, MeOD) δ 7.33 - 7.44 (m, 1H), 7.07 - 7.19 (m, 3H), 6.18 - 6.26 (m, 1H), 3.60 - 3.74 (m, 5H), 2.82 - 3.01 (m, 5H), 2.52 (br. s., 4H), 2.07 - 2.21 (m, 2H), 1.87 - 2.04 (m, 2H), 1.59 - 1.83 (m, 2H)

MS ES$^+$ 339

1.14 Esquema 14

Este esquema es apropiado para preparar los compuestos de los ejemplos 255, 265, 277, 279, 283 y 286.



(**44**)

56 / Ejemplo 286

a) DBU, DCM; b) Bis(triclorometil) carbonato; c) hidrocloruro de difluoropirrolidina

1.14.1 *Compuesto 56 / (**Ejemplo 286**)*

Bis(triclorometil) carbonato (587 mg, 1.978 mmol) fue disuelto en 20 ml de diclorometano, y la solución fue enfriada en un baño de hielo. Se suspendió dihidrocloruro de (3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metanamina (500 mg, 1.649 mmol) en 20 ml de DCM y se agregó DBU (1g, 6.6mmol) para dar una solución sin color, la cual fue agregada por goteo a la solución de bis(triclorometil) carbonato. Después de 10 minutos, se agregó hidrocloruro de 3,3-difluoropirrolidina (473 mg, 3.30 mmol) y la solución fue entibiada hastaa temperatura ambiente y agitada durante una hora y luego calentada a reflujo por 30 minutos. La mezcla de reacción fue lavada con una solución saturada de carbonato de sodio y el extracto orgánico fue secado y evaporado. El residuo fue purificado por cromatografía de sílice eluyendo con 0-12% de metanol / diclorometano con amoníaco para dar un aceite sin color, el cual fue convertido a la sal del hidrocloruro al disolverlo en etanol y agregarle ácido clorhídrico 2M en éter. El producto fue cristalizado usando *tert*-butilmetileter y etanol para dar hidrocloruro de N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3,3-difluoropirrolidina-1-carboxamida como un sólido blanco.

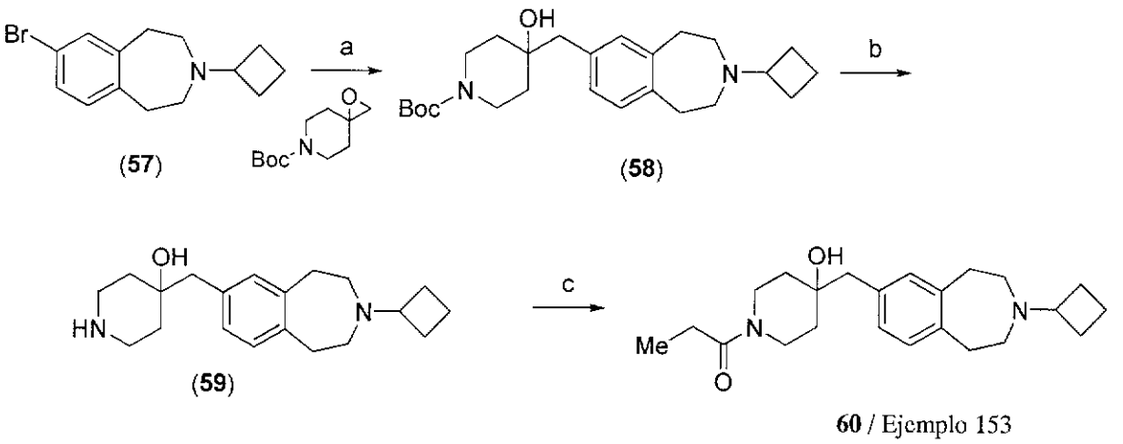
^{1}H NMR (400 MHz, METANOL-d_4) δ 7.07 (s, 3H), 4.21 (s, 2H), 3.42 - 3.67 (m, 7H), 3.06 - 3.17 (m, 2H), 2.90 - 3.04 (m, 2H), 2.61 - 2.76 (m, 2H), 2.12 - 2.39 (m, 6H), 1.60 - 1.91 (m, 2H)

ES+ 364

5

1.15 Esquema 15

Este esquema es apropiado para preparar los compuestos de los ejemplos 153, 155, 231 y 235



60 / Ejemplo 153

a) n-BuLi, THF, -78 °C, 1.5 horas, 2. BF_3-OEt_2, -78 °C, 15 minutos, 3. epóxido, -78 °C hasta rt-, b) TMSOTf, CH_2Cl_2, 0 °C, 1 hora; c) EtCOCl, Et_3N, THF, 0 °C, 15 minutos.

10

1.15.1 Intermediario 57

Se agregó ácido acético (2 mL) a una solución de 7-bromo-2,3,4,5-tetrahidro-1H-benzo[d]azepina (3.73 g, 16.50 mmol) y ciclobutanona (6.16 mL, 82 mmol) en diclorometano (38 mL) a 0 °C. La mezcla fue agitada a 0 °C durante 1 hora. Se agregó triacetoxiborohidruro de sodio (10.49 g, 49.5 mmol) a 0 °C y la mezcla de reacción se dejó entibiar lentamente hasta 20° C y y fue agitada durante 16 horas. Se agregó NaOH 2N (aq.) (200 mL) a la mezcla de reacción y la mezcla fue agitada durante 20 minutos. El producto fue extraído con diclorometano (3 x 150 mL), y el solvente fue removido bajo

15

presión reducida. El residuo fue purificado por un cartucho de intercambio catiónico fuerte (50g), cargandolo con diclorometano y lavádolo con metanol y eluyendo con amoníaco 2M en metanol. El solvente eluído fue removido bajo presión reducida para dar 7-bromo-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina (4.47 g, > 90%) como un sólido blanco.

MS ES^+ 280, 282

^{1}H NMR (400 MHz, DMSO-d_6) □ 7.29 - 7.35 (m, 1H), 7.23 - 7.29 (m, 1H), 7.03 - 7.09 (m, 1H), 2.69 - 2.85 (m, 5H), 2.32 (br. s., 4H), 1.93 - 2.05 (m, 2H), 1.68 - 1.82 (m, 2H), 1.47 - 1.65 (m, 2H)

1.15.2 Intermediario 58

Se agregó una solución de *n*-butilitio en n-hexano (1.6 M, 3.35 mL) a una solución de 7-bromo-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina (1.5g) en tetrahidrofurano (20 mL) a -78 °C. La mezcla resultante fue agitada a -78 °C durante 1.5 horas. Se agregó triofluoruro de boro eterato (0.68 mL) a -78 °C. La mezcla resultante fue agitada a -78 °C durante 15 minutos. Se agregó una solución de *tert*-butil 1-oxa-6-azaspiro[2.5]octano-6-carboxilato (1.14 g) en tetrahidrofurano (10 mL) a -78 °C. La mezcla fue agitada a -78 °C duranate 2 horas y luego entibiada hasta temperatura ambiente por 16 horas. Se agregó una solución acuosa saturada de cloruro de amonio (5.0 mL) a 0 °C. La mezcla de reacción fue particionada entre acetato de etilo y NaOH (aq.) 2N. La capa orgánica fue lavada con salmuera y secada (Na_2SO_4), y el solvente fue removido bajo presión reducida. El residuo fue purificado en sílice básica eluyendo con 15-50% de acetato de etilo en gasolina para dar *tert*-butil 4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-4-hidroxipiperidina-1-carboxilato (1.11 g, 50%) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO-d_6) ⌐ ppm 1.39 - 1.49 (m, 13 H) 1.58 - 1.76 (m, 2 H) 1.81 - 1.94 (m, 2 H) 2.04 - 2.16 (m, 2 H) 2.34 - 2.52 (m, 4 H) 2.67 - 2.73 (m, 2 H) 2.75 - 2.95 (m, 5 H) 3.01 - 3.28 (m, 2 H) 3.65 - 3.82 (m, 2 H) 4.41 (s, 1 H) 6.96 - 7.13 (m, 3 H)

1.15.3 Intermediario 59

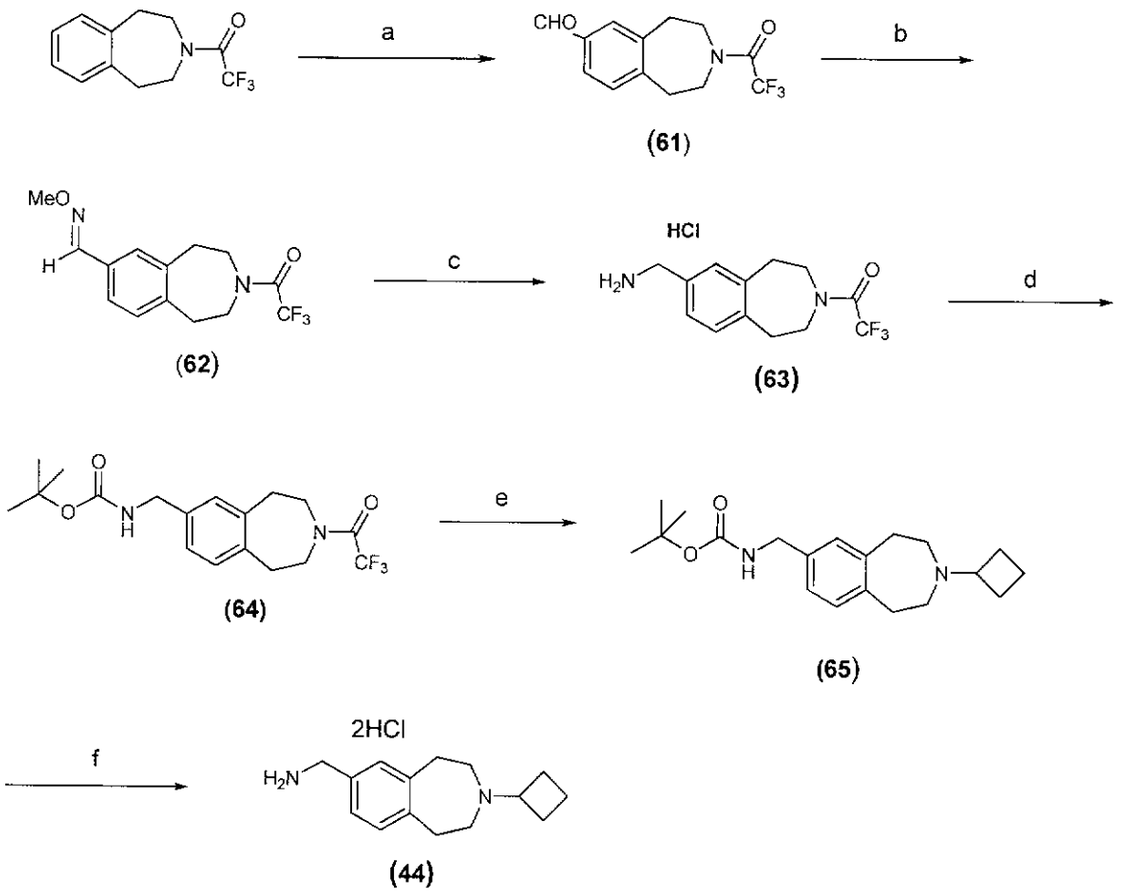
Se agregó trimetilosililtrifluorometano sulfonato (0.286 mL) a una solución de *tert*-butil 4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-4-hidroxipiperidina-1-carboxilato (328 mg) en diclorometano (10 mL) a 0 °C. La mezcla fue agitada a 0° C durante 1 hora. La mezcla de reacción fue particionada entre diclorometano y NaOH (aq.) 2N. La capa orgánica fue lavada con salmuera y secada (Na_2SO_4), y el solvente fue removido bajo presión reducida para dar 4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)piperidin-4-ol (231 mg, 93%) como una espuma amarillo pálido. ^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.11 - 1.38 (m, 4 H) 1.41 - 1.61 (m, 2 H) 1.64 - 1.79 (m, 2 H) 1.88 - 2.00 (m, 2 H) 2.20 - 2.35 (m, 4 H) 2.47 - 2.78 (m, 12 H) 3.93 (s, 1 H) 6.79 - 6.96 (m, 3 H)

*1.15.4 Compuesto 60 / **Ejemplo 153***

Se agregó cloruro de propionilo (70 □L) a una solución de 4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)piperidin-4-ol (230 mg) y trietilamina (150 □L) en THF (7.5 mL) a 0 °C. La mezcla fue agitada a 0° C durante 15 minutos. La mezcla de reacción fue particionada entre acetato de etilo y NaOH (aq.) 2N. La capa orgánica fue lavada con salmuera y secada (Na_2SO_4), y el solvente fue removido bajo presión reducida. El residuo fue purificado con sílice básico, eluyendo con 25-100% de acetate de etilo en gasolina) y por recristalización desde acetato de etilo para dar 1-(4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-4-hidroxipiperidina-1-il)propan-1-ona(207 mg, 76%) como cristales blancos.

1.16 Esquema 16

Este esquema es apropiado para preparar el intermediario 44.



a) Cl_2CHOMe, $AlCl_3$ / $PhNO_2$, b) $MeONH_2HCl$, Na_2CO_3 c) H_2, Pd/C HCl d) $(Boc)_2O$,Et_3N
e) 1) NaOH 2) ciclobutanona, AcOH, $NaBH(OAc)_3$ f) HCl 2M en EtOH

1.16.1 Intermediario 61

A una mezcla de compuesto 3-(trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-3-benzazepina (24.3 g, 0.10 mol) y $PhNO_2$ (24 mL), se agregó $AlCl_3$ (26.7 g, 0.20 mol) a 5ºC (temperatura interna) en una porción, y se agitó durante 15 min. A la mezcla resultante, se agregó una solución de Cl_2CHOCH_3 (34.5 g, 0.30 mol) en $PhNO_2$ (24 mL) por goteo a 5° C por durante 50 minutos y la mezcla fue agitada a r.t. por 8 horas. La mezcla de reacción fue diluída con AcOEt (100 mL) y vertida sobre hielo (150 g) cuidadosamente. La mezcla fue

extraída con AcOEt (100 mL x 2) y fue lavada con agua (50 mL x 2). Las capas orgánicas combinadas fueron lavadas con salmuera (200 mL), secadas sobre $MgSO_4$ y concentradas. El residuo fue purificado por cromatografía de columna en SiO_2 (350 g) (AcOEt/hexano =1/20 a 3/7) para dar un sólido crudo (25.0 g). El sólido obtenido fue disuelto en IPE (30 mL) y se agregó hexano (90 mL) por goteo a la solución agitándola a 50° C. La mezcla fue enfriada hasta r.t. y fue agitada durante 30 min. El precipitado depositado fue filtrado y fue lavado (AcOEt/hexano =1/5, 50 mL) para dar 3-(Trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-3-benzazepina-7-carbaldehído como un polvo amarillo pálido (20.3 g, 74.8%).

^{1}H-NMR (300MHz, $CDCl_3$) □: 3.05–3.10 (4H, m), 3.72–3.82 (4H, m), 7.31–7.72 (2H, m), 9.981 (1H, s). MS (POS/ESI), m/z 272.00 $(M+1)^+$.

1.16.2 Intermediario 62

A una solución de Na_2CO_3 (6.36 g, 0.060 mol) en agua (140 mL) se agregó $MeONH_2$ HCl (10.0 g, 0.120 mol) por goteo a 5° C (temperatura interna) y fue agitada durante 30 min. A la mezcla, se agregó una solución de 3-(Trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-3-benzazepina-7-carbaldehído 1 (27.1 g, 0.100 mol) en THF (140 mL) por goteo a 5° C y la mezcla fue agitada a temperatura ambiente durante 2 horas. La mezcla de reacción fue diluída con AcOEt (280 mL) y el material no disuelto fue filtrado. La capa acuosa separada fue extraída con AcOEt (140 mL) y las capas orgánicas fueron combinadas y lavadas con salmuera (140 mL), y luego secadas sobre $MgSO_4$. El solvente fue evaporado bajo presión reducida para dar un aceite amarillo (31 g), el cual fue disuelto en IPE (62 mL) y luego se agregó hexano (124 m) por goteo con agitación. El precipitado que apareció fue recolectado por filtración y lavado con IPE-hexano (1:2, 50 mL), y luego fue secado bajo presión reducida para dar 3-(Trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-3-benzazepina-7-carbaldehído O-metiloxima como un polvo amarillo pálido (23.0 g, 76.6%).

^{1}H-NMR (400MHz, $CDCl_3$) □: 2.97–3.02 (4H, m), 3.68–3.71 (2H, m), 3.76–3.78 (2H, m), 3.97 (3H, s), 7.13–7.18 (1H, m), 7.33–7.36 (1H, m), 7.41–7.44 (1H, m), 8.03 (1H, s). MS (POS/ESI), m/z 300.98 M^+.

1.16.3 Intermediario 63

A una solución de 3-(Trifluoroacetil)-2,3,4,5-tetrahidro-1*H*-3-benzazepina-7-carbaldehído O-metiloxima 2 (21.0 g, 0.070 mol) en MeOH (420 mL) y HCl 12N acuoso (5.3 mL, 175 mmol), se agregó 10% Pd/C (húmedo 50%, 2.1 g) y la mezcla fue hidrogenada bajo presión atmosférica a temperatura ambiente durante 1 hora. El catalizador fue removido por filtración y el filtrado fue concentrado bajo presión reducida. El sólido resultante fue tratado con IPE (200 mL) y fue recolectado por filtración, y luego fue secado bajo presión reducida para dar hidrocloruro de 1-[3-(Trifluoroacetil)-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il]metanamina (20.1 g, 92.8%) como un sólido blanco.

^{1}H-NMR (400MHz, DMSO-d_6) □: 2.96–3.02 (4H, m), 3.66–3.71 (4H, m), 3.96 (2H, s), 7.21–7.30 (3H, m), 8.33 (3H, brs).

1.16.4 Intermediario 64

A una solución de hidrocloruro de 1-[3-(Trifluoroacetil)-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il]metanamina (18.5 g, 60 mmol) en THF (90 mL) y agua (82 mL), se agregó (Boc)2O (13.1 g, 60 mmol) en una porción a 5° C (temperatura interna), y luego se agregó la solución acuosa NaOH 8N (7.5 mL, 60 mL) por goteo a la misma temperatura. La mezcla fue agitada a temperatura ambiente durante 1 hora. La mezcla de reacción fue extraída con AcOEt (90 mL x 2) y las capas orgánicas combinadas fueron lavadas con salmuera (90 mL), y luego secadas sobre $MgSO_4$. El solvente fue evaporado bajo presión reducida para dar un jarabe café claro, el cual fue tratado con hexano (70 mL) para dar un precipitado blanco. El precipitado obtenido fue recolectado por filtración y lavado con hexano (20 mL), y luego fue secado bajo presión reducida para dar *tert*-Butil {[3-

000276

(trifluoroacetil)-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il]metil}carbamato (21.0 g, 94%) como un polvo blanco.

^{1}H-NMR (400MHz, $CDCl_3$) □: 1.46 (9H, s), 2.94–2.99 (4H, m), 3.67–3.69 (2H, m), 3.74 3.78 (2H, m), 4.27–4.29 (2H, m), 4.83 (1H, brs), 7.06–7.14 (3H, m).

1.16.5 Intermediario 65

A una solución de *tert*-Butil {[3-(trifluoroacetil)-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il]metil}carbamato (16.8 g, 45.0 mmol) en MeOH (170 mL), se agregó una solución acuosa deNaOH 8N (6.2 mL, 49.5 mmol) a 5ºC (temperatura interna) y la mezcla fue agitada a temperatura ambiente durante 1 hora. A la mezcla resultante, se le agregó AcOH (3.9 mL, 67.5 mmol), ciclobutanona (4.7 g, 67.5 mmol), y $NaBH(OAc)_3$ (14.3 g, 67.5 mmol) a 5ºC y la mezcla fue agitada a temperatura ambiente durante 3 horas. A la mezcla, se le agregó nuevamente ciclobutanona (4.7 g, 67.5 mmol) y $NaBH(OAc)_3$ (14.3 g, 67.5 mmol) y la mezcla fue agitada a temperatura ambiente durante 1 hora. La mezcla de reacción fue concentrada bajo presión reducida y el residuo fue tratado con agua (150 mL). La mezcla acuosa fue basificada (pH = 9) con una solución acuosa de NaOH bajo enfriamiento y fue extraída con AcOEt (150 mL x 2). Las capas orgánicas combinadas fueron lavadas con salmuera (150 mL) y secadas sobre $MgSO_4$. La solución fue sometida a una almohadilla corta de gel-sílice (40 g) y el solvente fue evaporado bajo presión reducida. El sólido obtenido fue tratado con hexano-IPE (1:1, 100 mL) y fue recolectado por filtración. El sólido fue lavado con hexano (10 mL) y fue secado bajo presión reducida para dar *tert*-Butil [(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]carbamato .(12.4 g, 83.3 %) como un sólido blanco.

^{1}H-NMR (400MHz, $CDCl_3$) □: 1.55–1.75 (2H, m), 1.85–1.97 (2H, m), 2.03–2.12 (2H, m), 2.35–2.50 (4H, m), 2.72–2.81 (1H, m), 2.87–2.94 (4H, m), 4.25–4.27 (2H, m), 4.78 (1H, brs), 7.01–7.07 (3H, m). MS (POS/ESI), m/z 331.22 $(M+1)^+$.

000277

La desprotección del nitrógeno de la benzazepina del intermediario 64 (etapa (e)(1) del Esquema 17) conduce a *tert*-butil (2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metilcarbamato. ^{1}H-NMR (400MHz, CDCl3) δ 1.55–1.75 (2H, m), 1.85–1.97 (2H, m), 2.03–2.12 (2H, m), 2.35–2.50 (4H, m), 2.72–2.81 (1H, m), 2.87–2.94 (4H, m), 4.25–4.27 (2H, m), 4.78 (1H, brs), 7.01–7.07 (3H, m).

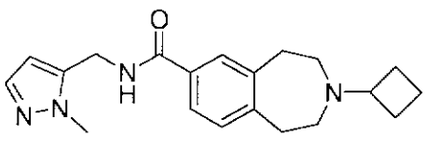
1.16.6 Intermediario 44

Una mezcla de *tert*-Butil [(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]carbamato (11.6 g, 35.0 mmol) y solución de HCl 2M etanólica (87.5 mL, 175 mmol) fue entibiada a 50 °C por 30 minutos. La mezcla de reacción fue enfriada en un baño de agua con hielo y tratada con IPE (100 mL). El precipitado depositado fue recolectado por filtración y fue lavado con IPE (20 mL), y luego fue secado bajo presión reducida para dar dihidrocloruro de 1-(3-Ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metanamina (9.5 g, 90.0%) como un polvo blanco.

^{1}H-NMR (400MHz, DMSO-d_6) : 1.58–1.74 (2H, m), 2.15–2.17 (2H, m), 2.49–2.54 (2H, m), 2.68–2.71 (2H, m), 2.94–3.00 (2H, m), 3.50–3.52 (4H, m), 3.64–3.66 (1H, m), 7.23–7.26 (1H, m), 7.33–7.34 (2H, m), 8.56 (3H, brs), 11.94 (1H, brs). MS (POS/ESI), m/z 231.15 $(M+1)^+$.

2. Compuestos de Ejemplo

2.1 Ejemplo1



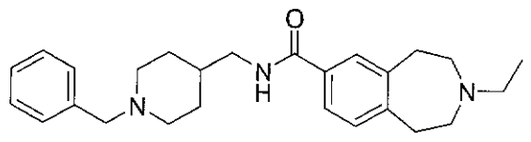
3-Ciclobutil-N-((1-metil-1H-pirazol-5-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) 8.79 - 8.96 (m, 1H), 7.56 - 7.68 (m, 2H), 7.27 - 7.34 (m, 1H), 7.15 - 7.25 (m, 1H), 6.11 - 6.20 (m, 1H), 4.43 - 4.55 (m, 2H), 3.35 (s, 3H), 2.81 - 2.96

(m, 4H), 2.69 - 2.80 (m, 1H), 2.34 (br. s., 4H), 1.91 - 2.08 (m, 2H), 1.70 - 1.85 (m, 2H), 1.47 - 1.67 (m, 2H)

Espectro de Masa: ES^+ 339

2.2 Ejemplo 2

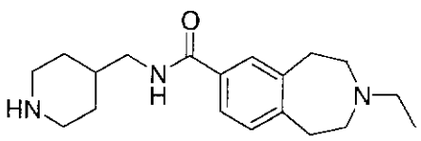


N-((1-Benzilpiperidin-4-il)metil)-3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.38 - 7.53 (m, 2H), 7.17 - 7.35 (m, 6H), 7.03 - 7.17 (m, 1H), 6.13 (t, *J* = 5.43 Hz, 1H), 3.46 (s, 2H), 3.31 (t, *J* = 6.32 Hz, 2H), 2.79 - 3.03 (m, 5H), 2.47 - 2.73 (m, 5H), 1.85 - 2.01 (m, 2H), 1.51 - 1.76 (m, 3H), 1.16 - 1.42 (m, 3H), 1.01 - 1.11 (m, 3H)

Espectro de Masa: ES^+ 406

2.3 Ejemplo 3

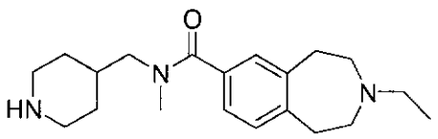


Hidrocloruro de 3-Etil-N-(piperidin-4-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.69 - 7.78 (m, 2H), 7.33 - 7.41 (m, 1H), 3.76 - 3.86 (m, 2H), 3.27 - 3.49 (m, 9H), 3.14 - 3.26 (m, 2H), 2.94 - 3.13 (m, 4H), 1.93 - 2.09 (m, 3H), 1.38 - 1.59 (m, 5H)

Espectro de Masa: ES^+ 316

2.4 Ejemplo 4

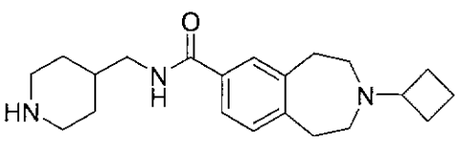


3-Etil-N-metil-N-(piperidin-4-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.08 - 7.28 (m, 3H), 3.43 - 3.53 (m, 1H), 3.23 - 3.31 (m, 1H), 3.11 - 3.22 (m, 1H), 3.08 (br. s., 1H), 3.01 (br. s., 4H), 2.49 - 2.76 (m, 8H), 1.95 - 2.09 (m, 1H), 1.74 - 1.91 (m, 3H), 1.53 - 1.62 (m, 1H), 1.25 - 1.42 (m, 2H), 1.10 - 1.19 (m, 3H), 0.82 - 0.97 (m, 1H)

Espectro de Masa: ES$^+$ 330

2.5 Ejemplo 5

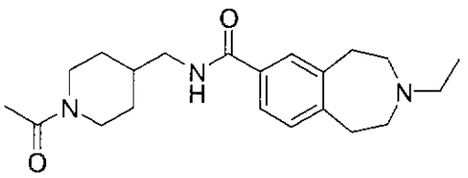


3-Ciclobutil-N-(piperidin-4-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, D_2O) □ 7.43 - 7.60 (m, 2H), 7.19 - 7.34 (m, 1H), 3.37 - 3.46 (m, 1H), 3.24 - 3.37 (m, 4H), 3.06 - 3.21 (m, 1H), 2.88 - 3.06 (m, 7H), 2.73 (br. s., 4H), 2.08 - 2.22 (m, 1H), 1.87 - 2.07 (m, 5H), 1.56 - 1.80 (m, 2H), 1.35 - 1.53 (m, 2H)

Espectro de Masa: ES$^+$ 342

2.6 Ejemplo 6

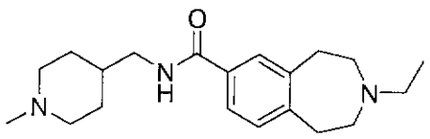


N-((1-Acetilpiperidin-4-il)metil)-3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.41 - 7.67 (m, 2H), 7.00 - 7.34 (m, 1H), 4.34 - 4.66 (m, 1H), 3.82 - 4.04 (m, 1H), 2.92 - 3.18 (m, 7H), 2.48 - 2.84 (m, 8H), 2.09 (s, 3H), 1.67 - 2.00 (m, 3H), 1.01 - 1.37 (m, 5H)

Espectro de Masa: ES$^+$ 358

2.7 Ejemplo 7

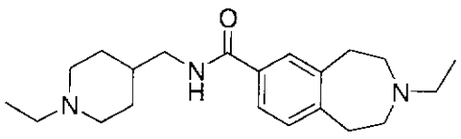


3-Etil-N-((1-metilpiperidin-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

1H NMR (400 MHz, MeOD) □ 7.52 - 7.62 (m, 2H), 7.14 - 7.28 (m, 1H), 3.24 - 3.28 (m, 1H), 2.94 - 3.10 (m, 4H), 2.79 - 2.94 (m, 2H), 2.46 - 2.79 (m, 6H), 2.17 - 2.37 (m, 3H), 1.92 - 2.14 (m, 2H), 1.51 - 1.89 (m, 4H), 1.23 - 1.44 (m, 2H), 1.01 - 1.22 (m, 3H)

Espectro de Masa: ES$^+$ 330

2.8 Ejemplo 8

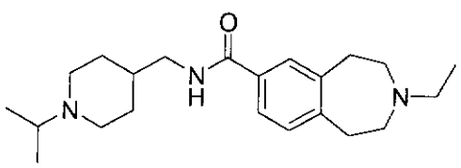


3-Etil-N-((1-etilpiperidin-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □7.52 - 7.62 (m, 2H), 7.15 - 7.24 (m, 1H), 3.25 - 3.29 (m, 2H), 2.90 - 3.10 (m, 6H), 2.53 - 2.82 (m, 6H), 2.38-2.45, 2H), 1.87 - 2.08 (m, 2H), 1.59 - 1.85 (m, 3H), 1.23 - 1.45 (m, 2H), 0.99 - 1.23 (m, 6H)

Espectro de Masa: ES$^+$ 344

2.9 Ejemplo 9



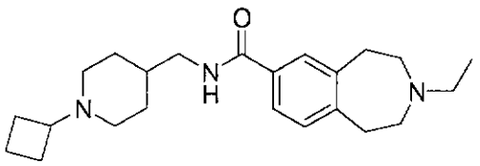
000231

3-Etil-N-((1-isopropilpiperidin-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.51 - 7.63 (m, 2H), 7.16 - 7.25 (m, 1H), 3.26 (d, *J* = 6.57 Hz, 2H), 2.84 - 3.12 (m, 6H), 2.48 - 2.80 (m, 7H), 2.07 - 2.30 (m, 2H), 1.56 - 1.87 (m, 3H), 1.22 - 1.45 (m, 2H), 0.97 - 1.21 (m, 9H)

Espectro de Masa: ES$^+$ 358

2.10 Ejemplo 10

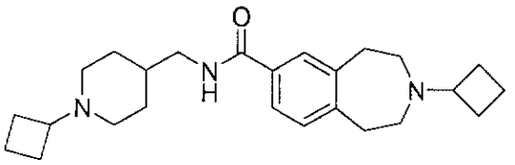


N-((1-Ciclobutilpiperidin-4-il)metil)-3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.51 - 7.63 (m, 2H), 7.16 - 7.24 (m, 1H), 3.24 - 3.29 (m, 2H), 2.88 - 3.10 (m, 6H), 2.51 - 2.88 (m, 7H), 1.99 - 2.16 (m, 2H), 1.59 - 2.00 (m, 9H), 1.22 - 1.45 (m, 2H), 1.05 - 1.21 (m, 3H)

Espectrode Masa: ES$^+$ 370

2.11 Ejemplo 11



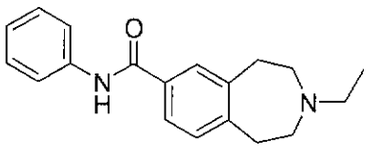
3-Ciclobutil-N-((1-ciclobutilpiperidin-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.45 - 7.68 (m, 2H), 7.14 - 7.28 (m, 1H), 3.25 - 3.29 (m, 2H), 2.98 (br. s., 6H), 2.78 - 2.93 (m, 2H), 2.51 (br. s., 4H), 2.03 - 2.19 (m, 4H), 1.86 - 2.03 (m, 6H), 1.61 - 1.86 (m, 7H), 1.25 - 1.46 (m, 2H)

Espectro de Masa: ES$^+$ 396

000282

2.12 Ejemplo 12

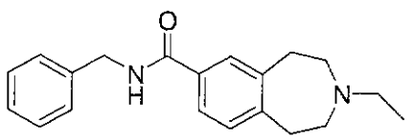


3-Etil-N-fenil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.12 (s, 1H), 7.76 (d, *J* = 7.83 Hz, 2H), 7.65 - 7.73 (m, 2H), 7.29 - 7.41 (m, 2H), 7.21 - 7.29 (m, 1H), 7.00 - 7.17 (m, 1H), 2.83 - 3.02 (m, 4H), 2.41 - 2.67 (m, 8H), 0.95 - 1.08 (m, 3H)

Espectro de Masa: ES^+ 295

2.13 Ejemplo 13

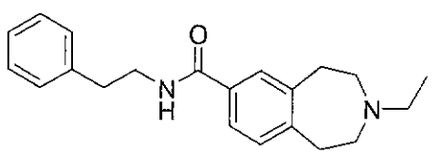


N-Benzil-3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) ppm 7.53 - 7.69 (m, 2H), 7.15 - 7.44 (m, 6H), 4.49 - 4.65 (m, 2H), 2.90 - 3.08 (m, 4H), 2.47 - 2.79 (m, 6H), 1.04 - 1.20 (m, 3H)

Espectro de Masa: ES^+ 309

2.14 Ejemplo 14

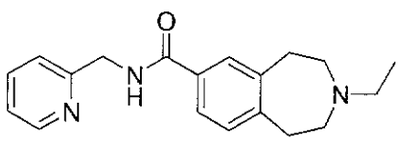


3-Etil-N-fenetil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) ppm 7.45 - 7.64 (m, 2H), 7.03 - 7.36 (m, 6H), 3.48 - 3.65 (m, 2H), 2.83 - 3.07 (m, 6H), 2.45 - 2.75 (m, 6H), 0.98 - 1.29 (m, 3H)

Espectro de Masa: ES^+ 323

2.15 Ejemplo 15

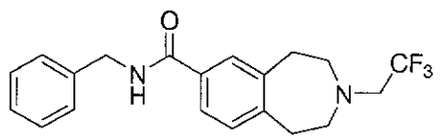


3-Etil-N-(piridin-2-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 8.49 (d, 1H), 7.76 - 7.85 (m, 1H), 7.63 - 7.69 (m, 2H), 7.39-7.42, 1H), 7.27 - 7.35 (m, 1H), 7.19 - 7.27 (m, 1H), 4.68 (s, 2H), 2.92 - 3.13 (m, 4H), 2.45 - 2.81 (m, 6H), 1.05 - 1.22 (m, 3H)

Espectro de Masa: ES$^+$ 310

2.16 Ejemplo 16

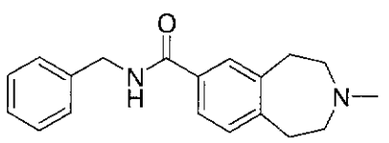


N-Benzil-3-(2,2,2-trifluoroetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

1H NMR (400 MHz, $CDCl_3$) □ 7.49 - 7.65 (m, 2H), 7.24 - 7.46 (m, 5H), 7.10 - 7.20 (m, 1H), 6.48 (br. s., 1H), 4.35 - 4.92 (m, 2H), 3.11 - 3.27 (m, 2H), 2.82 - 3.03 (m, 8H)

Espectro de Masa: ES$^+$ 363

2.17 Ejemplo 17

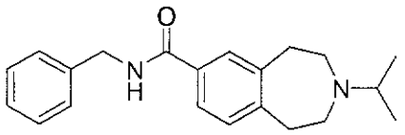


N-Benzil-3-metil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, $CDCl_3$) □7.49 - 7.66 (m, 2H), 7.24 - 7.45 (m, 5H), 7.01 - 7.21 (m, 1H), 6.51 (br. s., 1H), 4.64 (d, *J* = 5.56 Hz, 2H), 2.97 (br. s., 4H), 2.47 - 2.70 (m, 4H), 2.36 (s, 3H)

Espectro de Masa: ES$^+$ 295

2.18 Ejemplo 18

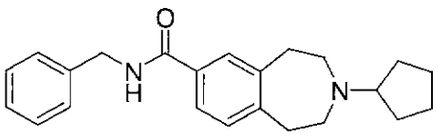


N-Benzil-3-isopropil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.48 - 7.60 (m, 2H), 7.28 - 7.41 (m, 5H), 7.12 - 7.18 (m, 1H), 6.37 (br. s., 1H), 4.57 - 4.73 (m, 2H), 2.85 - 3.06 (m, 5H), 2.53 - 2.74 (m, 4H), 0.90 - 1.11 (m, 6H)

Espectro de Masa: ES^+ 323

2.19 Ejemplo 19

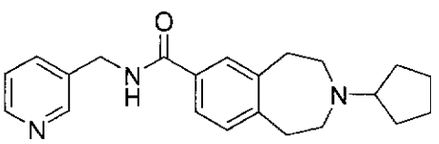


N-Benzil-3-ciclopentil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.47 - 7.60 (m, 2H), 7.28 - 7.44 (m, 5H), 7.10 - 7.18 (m, 1H), 6.33 (br. s., 1H), 4.49 - 4.80 (m, 2H), 2.91 - 3.04 (m, 4H), 2.79 - 2.91 (m, 1H), 2.62 - 2.77 (m, 4H), 1.80 - 1.93 (m, 2H), 1.61 - 1.76 (m, 2H), 1.39 - 1.62 (m, 4H)

Espectro de Masa: ES^+ 349

2.20 Ejemplo 20



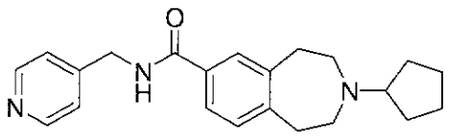
3-Ciclopentil-N-(piridin-3-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD)□ 8.52 - 8.58 (m, 1H), 8.41 - 8.49 (m, 1H), 7.82 - 7.89 (m, 1H), 7.67 - 7.76 (m, 2H), 7.38 - 7.46 (m, 1H), 7.29 - 7.36 (m, 1H), 4.60 (s, 2H), 3.57 (br. s., 1H), 3.15 - 3.27 (m, 8H), 2.08 - 2.22 (m, 2H), 1.61 - 1.90 (m, 6H)

Espectro de Masa: ES^+ 350

000285

2.21 Ejemplo 21

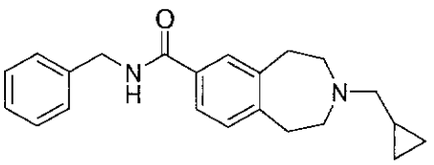


3-Ciclopentil-N-(piridin-4-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) 8.80 - 8.96 (m, 1H), 8.44 - 8.56 (m, 2H), 7.57 - 7.70 (m, 2H), 7.24 - 7.35 (m, 2H), 7.15 - 7.24 (m, 1H), 4.39 - 4.55 (m, 2H), 2.90 (br. s., 4H), 2.64 (br. s., 4H), 1.69 - 1.88 (m, 2H), 1.28 - 1.69 (m, 6H)

Espectro de Masa: ES^+ 315

2.22 Ejemplo 22

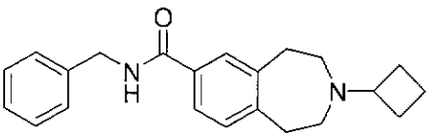


N-Benzil-3-(ciclopropilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, $CDCl_3$) 8.41 (s, 1H), 7.44 - 7.57 (m, 2H), 7.19 - 7.32 (m, 3H), 7.18 (s, 1H), 7.04 - 7.13 (m, 1H), 6.37 - 6.53 (m, 1H), 4.47 - 4.63 (m, 2H), 2.98 - 3.30 (m, 8H), 2.63 - 2.85 (m, 2H), 0.85 - 1.10 (m, 1H), 0.55 - 0.66 (m, 2H), 0.12 - 0.30 (m, 2H)

Espectro de Masa: ES^+ 335

2.23 Ejemplo 23



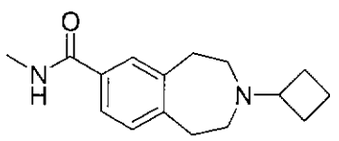
N-Benzil-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.60 - 7.65 (m, 2H), 7.29 - 7.38 (m, 4H), 7.17 - 7.28 (m, 2H), 4.46 - 4.67 (m, 2H), 2.90 - 3.10 (m, 4H), 2.75 - 2.91 (m, 1H), 2.49 (br. s., 4H), 2.02 - 2.21 (m, 2H), 1.85 - 2.03 (m, 2H), 1.58 - 1.82 (m, 2H)

000286

Espectro de Masa: ES^+ 335

2.24 Ejemplo 24

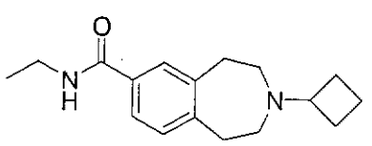


3-Ciclobutil-N-metil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.54 - 7.59 (m, 2H), 7.17 - 7.22 (m, 1H), 2.94 - 3.04 (m, 4H), 2.91 (s, 3H), 2.80 - 2.88 (m, 1H), 2.49 (br. s., 4H), 2.06 - 2.16 (m, 2H), 1.88 - 2.01 (m, 2H), 1.62 - 1.79 (m, 2H)

Espectro de Masa: ES^+ 259

2.25 Ejemplo 25

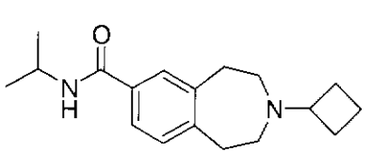


3-Ciclobutil-N-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.58 (m, 2H), 7.09 - 7.27 (m, 1H), 3.36 - 3.49 (m, 2H), 2.93 - 3.08 (m, 4H), 2.74 - 2.92 (m, 1H), 2.50 (br. s., 4H), 2.02 - 2.22 (m, 2H), 1.83 - 2.05 (m, 2H), 1.60 - 1.82 (m, 2H), 1.12 - 1.36 (m, 3H)

Espectro de Masa: ES^+ 273

2.26 Ejemplo 26



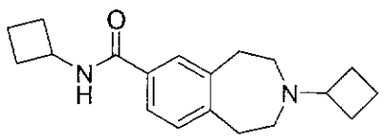
3-Ciclobutil-N-isopropil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.57 (d, 2H), 7.07 - 7.29 (m, 1H), 4.07 - 4.29 (m, 1H), 2.99 (br. s., 4H), 2.78 - 2.91 (m, 1H), 2.49 (br. s., 4H), 2.03 - 2.21 (m, 2H), 1.86 - 2.03 (m, 2H), 1.56 - 1.82 (m, 2H), 1.15 - 1.36 (m, 6H)

000287

Espectro de Masa: ES^+ 287

2.27 Ejemplo 27

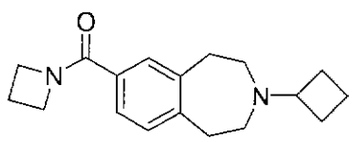


N,3-Diciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) δ 7.46 - 7.68 (m, 2H), 7.09 - 7.29 (m, 1H), 4.40 - 4.60 (m, 1H), 2.91 - 3.06 (m, 4H), 2.77 - 2.91 (m, 1H), 2.39 - 2.61 (m, 4H), 2.28 - 2.38 (m, 2H), 2.03 - 2.19 (m, 4H), 1.86 - 2.02 (m, 2H), 1.60 - 1.84 (m, 4H)

Espectro de Masa: ES^+ 299

2.28 Ejemplo 28

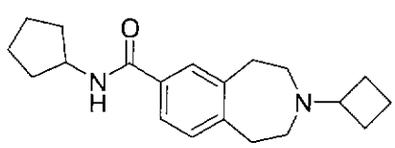


Azetidin-1-il(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metanona

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 - 7.41 (m, 2H), 7.12 - 7.22 (m, 1H), 4.18 - 4.37 (m, 2H), 3.93 - 4.13 (m, 2H), 2.81 - 2.94 (m, 4H), 2.68 - 2.82 (m, 1H), 2.34 (br. s., 4H), 2.18 - 2.29 (m, 2H), 2.01 (q, J = 7.8 Hz, 2H), 1.70 - 1.86 (m, 2H), 1.49 - 1.67 (m, 2H)

Espectro de Masa: ES^+ 285

2.29 Ejemplo 29



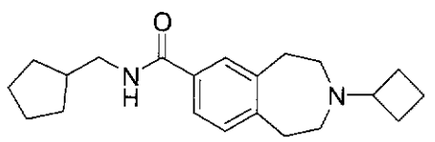
3-Ciclobutil-N-ciclopentil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) δ 7.44 - 7.65 (m, 2H), 7.11 - 7.26 (m, 1H), 4.20 - 4.41 (m, 1H), 2.90 - 3.05 (m, 4H), 2.76 - 2.91 (m, 1H), 2.35 - 2.61 (m, 4H), 1.48 - 2.20 (m, 14H)

000288

Espectro de Masa: ES^+ 313

2.30 Ejemplo 30

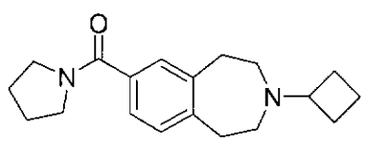


3-Ciclobutil-N-(ciclopentilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) 8.21 - 8.48 (m, 1H), 7.47 - 7.71 (m, 2H), 7.07 - 7.30 (m, 1H), 3.11 - 3.22 (m, 2H), 2.68 - 2.98 (m, 4H), 2.22 - 2.45 (m, 4H), 2.07 - 2.21 (m, 1H), 1.95 - 2.07 (m, 2H), 1.72 - 1.89 (m, 2H), 1.42 - 1.71 (m, 9H), 1.17 - 1.31 (m, 2H)

Espectro de Masa: ES^+ 327

2.31 Ejemplo 31

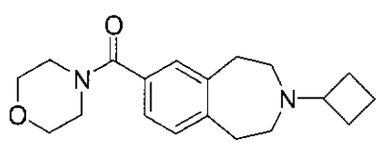


(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)(pirrolidin-1-il)metanona

^{1}H NMR (400 MHz, DMSO-d_6) 7.04 - 7.42 (m, 3H), 3.39 (br. s., 4H), 2.81 - 3.13 (m, 4H), 2.47-2.52 (br. s.,4H), 2.10 (br. s., 2H), 1.75 - 1.96 (m, 6H), 1.53 - 1.74 (m, 2H)

Espectro de Masa: ES^+ 299

2.32 Ejemplo 32

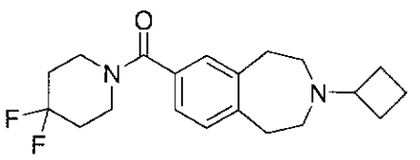


(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)(morfolino)metanona

^{1}H NMR (400 MHz, MeOD) 7.06 - 7.35 (m, 3H), 3.54 - 3.85 (m, 6H), 3.40 - 3.53 (m, 2H), 2.97 - 3.16 (m, 5H), 2.58 - 2.83 (m, 4H), 2.13 - 2.25 (m, 2H), 1.98 - 2.13 (m, 2H), 1.64 - 1.86 (m, 2H)

Espectro de Masa: ES^- 315

2.33 Ejemplo 33

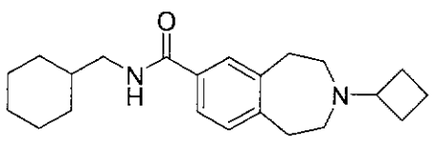


(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)(4,4-difluoropiperidin-1-il)metanona

1H NMR (400 MHz, DMSO-d6) □ 7.04 - 7.29 (m, 3H), 3.57 (br. s., 4H), 2.88 (br. s., 6H), 2.40 (br. s., 3H), 2.02 (br. s., 6H), 1.71 - 1.92 (m, 2H), 1.50 - 1.68 (m, 2H)

Espectro de Masa: ES^+ 349

2.34 Ejemplo 34

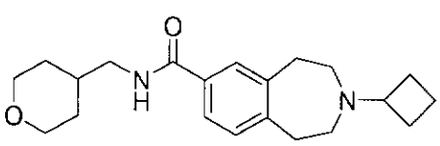


3-Ciclobutil-N-(ciclohexilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

1H NMR (400 MHz, $CDCl_3$) □ 7.52 - 7.62 (m, 3H), 7.17 - 7.23 (m, 1H), 6.24 - 6.35 (m, 1H), 3.72 - 3.84 (m, 2H), 3.53 - 3.65 (m, 2H), 3.27 - 3.41 (m, 3H), 2.92 - 3.06 (m, 2H), 2.58 - 2.73 (m, 2H), 2.42 - 2.57 (m, 2H), 2.22 - 2.35 (m, 2H), 1.88 - 2.00 (m, 1H), 1.65 - 1.84 (m, 6H), 1.54 - 1.65 (m, 1H), 1.12 - 1.33 (m, 2H), 0.94 - 1.08 (m, 2H)

Espectro de Masa: ES^+ 341

2.35 Ejemplo 35

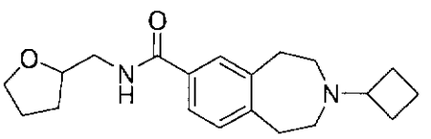


3-Ciclobutil-N-((tetrahidro-2H-piran-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.18 - 8.27 (m, 1H), 7.53 - 7.63 (m, 2H), 7.12 - 7.21 (m, 1H), 3.78 - 3.89 (m, 2H), 3.22 - 3.31 (m, 2H), 3.11 - 3.17 (m, 2H), 2.75 - 2.92 (m, 5H), 2.37 (br. s., 4H), 1.95 - 2.06 (m, 2H), 1.72 - 1.86 (m, 3H), 1.51 - 1.68 (m, 4H), 1.10 - 1.28 (m, 2H)

Espectro de Masa: ES$^+$ 350

2.36 Ejemplo 36

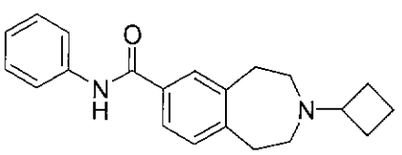


3-ciclobutil-N-((tetrahidrofuran-2-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.49 - 7.77 (m, 2H), 7.13 - 7.39 (m, 1H), 4.00 - 4.18 (m, 1H), 3.84 - 3.95 (m, 1H), 3.71 - 3.82 (m, 1H), 3.36 - 3.53 (m, 2H), 2.93 - 3.13 (m, 5H), 2.66 (br. s., 4H), 2.11 - 2.26 (m, 2H), 1.84 - 2.11 (m, 5H), 1.59 - 1.84 (m, 3H)

Espectro de Masa: ES$^-$ 329

2.37 Ejemplo 37



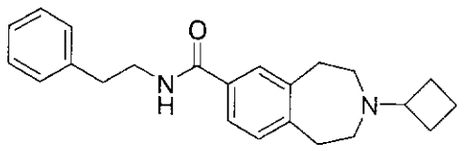
3-Ciclobutil-N-fenil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 10.13 (s, 1H), 7.74 - 7.81 (m, 2H), 7.68 - 7.73 (m, 2H), 7.31 - 7.38 (m, 2H), 7.23 - 7.29 (m, 1H), 7.06 - 7.13 (m, 1H), 2.86 - 2.98 (m, 4H), 2.72 - 2.83 (m, 1H), 2.38 (br. s., 4H), 1.96 - 2.07 (m, 2H), 1.73 - 1.87 (m, 2H), 1.51 - 1.68 (m, 2H)

Espectro de Masa: ES$^+$ 321

2.38 Ejemplo 38

000291

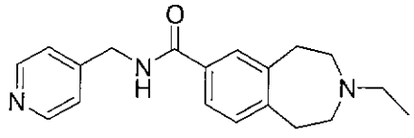


3-Ciclobutil-N-fenetil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.45 - 7.59 (m, 2H), 7.13 - 7.34 (m, 6H), 3.52 - 3.63 (m, 2H), 2.74 - 3.04 (m, 7H), 2.47 (br. s., 4H), 2.03 - 2.17 (m, 2H), 1.85 - 2.02 (m, 2H), 1.60 - 1.81 (m, 2H)

Espectro de Masa: ES$^+$ 349

2.39 Ejemplo 39

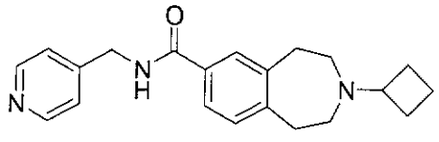


3-Etil-N-(piridin-4-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 8.44 - 8.51 (m, 2H), 7.62 - 7.70 (m, 2H), 7.36 - 7.44 (m, 2H), 7.20 - 7.29 (m, 1H), 4.62 (s, 2H), 3.03 (br. s., 4H), 2.56 - 2.80 (m, 6H), 1.15 (m, 3H)

Espectrode Masa: ES$^+$ 310

2.40 Ejemplo 40

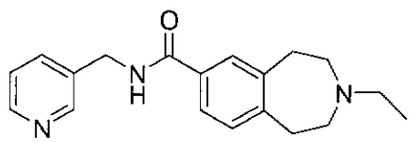


3-Ciclobutil-N-(piridin-4-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 8.40 - 8.50 (m, 2H), 7.58 - 7.69 (m, 2H), 7.34 - 7.45 (m, 2H), 7.17 - 7.30 (m, 1H), 4.61 (s, 2H), 2.99 (br. s., 4H), 2.77 - 2.90 (m, 1H), 2.48 (br. s., 4H), 2.05 - 2.17 (m, 2H), 1.85 - 2.02 (m, 2H), 1.60 - 1.81 (m, 2H)

Espectro de Masa: ES$^+$ 336

2.41 Ejemplo 41

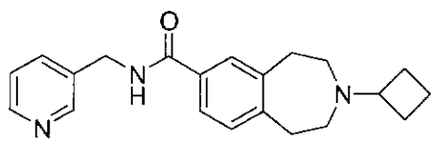


3-Etil-N-(piridin-3-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) δ 8.54 - 8.60 (m, 1H), 8.42 - 8.49 (m, 1H), 7.82 - 7.92 (m, 1H), 7.59 - 7.68 (m, 2H), 7.39 - 7.48 (m, 1H), 7.19 - 7.29 (m, 1H), 4.62 (s, 2H), 2.96 - 3.10 (m, 4H), 2.52 - 2.78 (m, 6H), 1.07 - 1.23 (m, 3H)

Espectro de Masa: ES$^+$ 310

2.42 Ejemplo 42

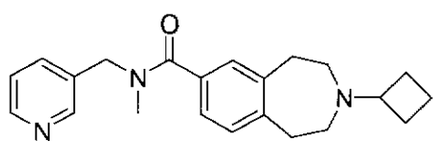


3-Ciclobutil-N-(piridin-3-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) δ 8.55 (s, 1H), 8.37 - 8.50 (m, 1H), 7.78 - 7.94 (m, 1H), 7.56 - 7.67 (m, 2H), 7.35 - 7.50 (m, 1H), 7.13 - 7.31 (m, 1H), 4.59 (s, 2H), 2.99 (br. s., 4H), 2.77 - 2.91 (m, 1H), 2.50 (br. s., 4H), 2.05 - 2.18 (m, 2H), 1.85 - 2.03 (m, 2H), 1.60 - 1.81 (m, 2H)

Espectro de Masa: ES$^+$ 336

2.43 Ejemplo 43

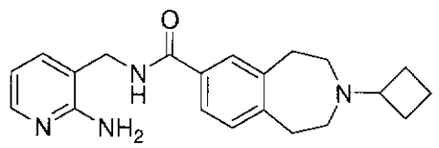


3-ciclobutil-N-metil-N-(piridin-3-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) δ 8.93 (br. s., 1H), 8.78 - 8.86 (m, 1H), 8.62 - 8.72 (m, 1H), 8.05 - 8.18 (m, 1H), 7.29 - 7.47 (m, 3H), 4.94 (br. s., 2H), 3.64 - 3.79 (m, 4H), 3.06 - 3.22 (m, 5H), 2.77 - 2.90 (m, 2H), 2.31 - 2.44 (m, 4H), 1.75 - 1.99 (m, 2H)

Espectro de Masa: ES^+ 350

2.44 Ejemplo 44

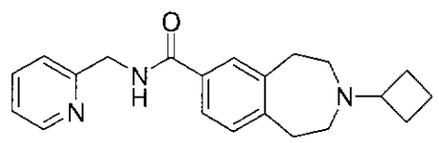


N-((2-Aminopiridin-3-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1H} NMR (400 MHz, MeOD) □ 7.77 - 7.91 (m, 1H), 7.53 - 7.65 (m, 2H), 7.40 - 7.52 (m, 1H), 7.15 - 7.29 (m, 1H), 6.53 - 6.72 (m, 1H), 4.44 (s, 2H), 2.98 (br. s., 4H), 2.77 - 2.92 (m, 1H), 2.50 (br. s., 4H), 2.04 - 2.20 (m, 2H), 1.84 - 2.03 (m, 2H), 1.57 - 1.82 (m, 2H)

Espectro de Masa: ES^+ 351

2.45 Ejemplo 45

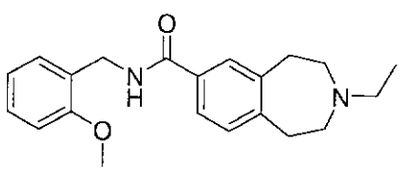


3-Ciclobutil-N-(piridin-2-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 8.36 - 8.55 (m, 1H), 7.73 - 7.87 (m, 1H), 7.55 - 7.72 (m, 2H), 7.36 - 7.51 (m, 1H), 7.26 - 7.36 (m, 1H), 7.16 - 7.26 (m, 1H), 4.68 (s, 2H), 2.99 (br. s., 4H), 2.76 - 2.90 (m, 1H), 2.49 (br. s., 4H), 2.05 - 2.18 (m, 2H), 1.86 - 2.00 (m, 2H), 1.59 - 1.82 (m, 2H)

Espectro de Masa: ES^+ 336

2.46 Ejemplo 46

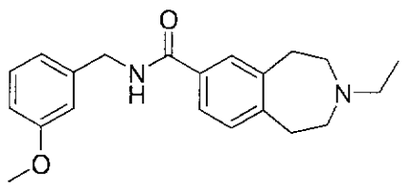


3-Etil-N-(2-metoxibenzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.56 - 7.64 (m, 2H), 7.16 - 7.27 (m, 3H), 6.93 - 6.99 (m, 1H), 6.86 - 6.93 (m, 1H), 4.56 (s, 2H), 3.86 (s, 3H), 2.93 - 3.06 (m, 4H), 2.52 - 2.75 (m, 6H), 1.07 - 1.19 (m, 3H)

Espectro de Masa: ES$^+$ 339

2.47 Ejemplo 47

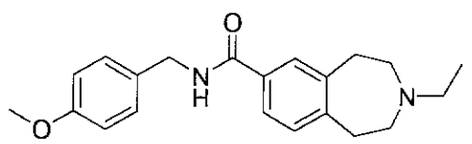


3-Etil-N-(3-metoxibenzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.56 - 7.65 (m, 2H), 7.18 - 7.26 (m, 2H), 6.88 - 6.95 (m, 2H), 6.77 - 6.85 (m, 1H), 4.55 (s, 2H), 3.79 (s, 3H), 2.89 - 3.12 (m, 4H), 2.49 - 2.79 (m, 6H), 1.03 - 1.27 (m, 3H)

Espectro de Masa: ES$^+$ 339

2.48 Ejemplo 48

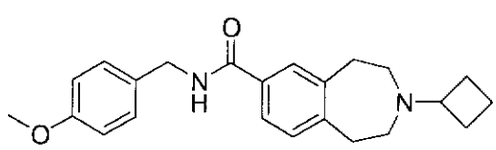


3-Etil-N-(4-metoxibenzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.54 - 7.64 (m, 2H), 7.58 (nuno, 2H), 7.21 - 7.31 (m, 2H), 7.13 - 7.20 (m, 1H), 6.81 - 6.92 (m, 2H), 4.48 (s, 2H), 3.75 (s, 3H), 2.89 - 3.05 (m, 4H), 2.48 - 2.73 (m, 6H), 1.03 - 1.19 (m, 3H)

Espectro de Masa: ES$^+$ 336

2.49 Ejemplo 49



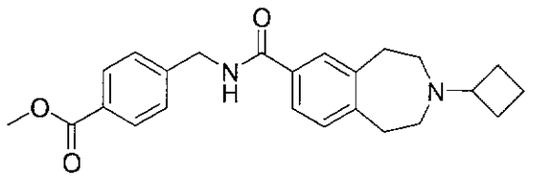
000295

3-Ciclobutil-N-(4-metoxibenzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.47 - 7.56 (m, 2H), 7.24 - 7.32 (m, 2H), 7.09 - 7.18 (m, 1H), 6.85 - 6.93 (m, 2H), 6.29 (br. s., 1H), 4.53 - 4.63 (m, 2H), 3.81 (s, 3H), 2.95 (br. s., 4H), 2.78 (t, *J* = 7.71 Hz, 1H), 2.44 (br. s., 4H), 2.02 - 2.15 (m, 2H), 1.83 - 1.98 (m, 2H), 1.57 - 1.77 (m, 2H)

Espectro de Masa: ES^+ 356

2.50 Ejemplo 50

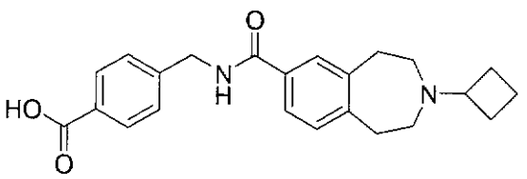


Metil 4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamido)metil)benzoato

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.97 - 8.08 (m, 2H), 7.49 - 7.62 (m, 2H), 7.38 - 7.47 (m, 2H), 7.11 - 7.21 (m, 1H), 6.25 - 6.59 (m, 1H), 4.63 - 4.79 (m, 2H), 3.92 (s, 3H), 2.97 (br. s., 4H), 2.72 - 2.85 (m, 1H), 2.45 (br. s., 4H), 2.01 - 2.16 (m, 2H), 1.82 - 1.97 (m, 2H), 1.55 - 1.78 (m, 2H)

Espectro de Masa: ES+ 393

2.51 Ejemplo 51

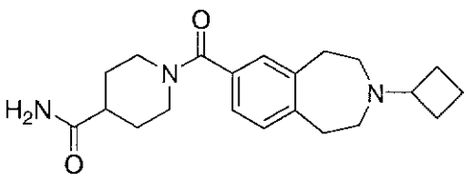


Ácido 4-((3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamido)metil)benzoico

^{1}H NMR (400 MHz, MeOD) □ 7.89 - 7.96 (m, 2H), 7.65 - 7.71 (m, 2H), 7.32 - 7.39 (m, 2H), 7.23 - 7.31 (m, 1H), 4.60 (s, 2H), 3.11 (br. s., 4H), 2.91 (br. s., 4H), 2.09 - 2.32 (m, 4H), 1.67 - 1.88 (m, 2H)

Espectro de Masa: ES^+ 379

2.52 Ejemplo 52

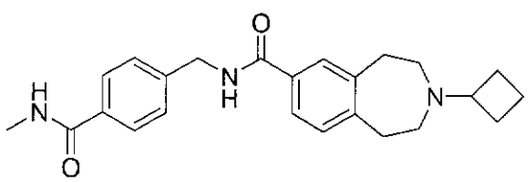


1-(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carbonil)piperidina-4-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.03 - 7.31 (m, 7H), 4.49 - 4.75 (m, 2H), 3.78 (br. s., 2H), 2.77 - 3.03 (m, 5H), 2.34 - 2.62 (m, 4H), 2.04 - 2.19 (m, 2H), 1.84 - 2.02 (m, 2H), 1.57 - 1.82 (m, 2H)

Espectro de Masa: ES^+ 356

2.53 Ejemplo 53

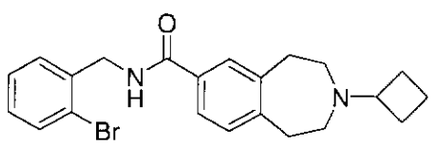


3-Ciclobutil-N-(4-(metilcarbamoil)benzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) 8.85 - 9.13 (m, 1H), 8.28 - 8.53 (m, 1H), 7.68 - 7.89 (m, 2H), 7.54 - 7.71 (m, 2H), 7.29 - 7.47 (m, 2H), 7.08 - 7.28 (m, 1H), 4.42 - 4.59 (m, 2H), 2.88 (br. s., 4H), 2.71 - 2.83 (m, 4H), 2.36 (br. s., 4H), 1.94 - 2.06 (m, 2H), 1.72 - 1.87 (m, 2H), 1.50 - 1.68 (m, 2H)

Espectro de Masa: ES^+ 392

2.54 Ejemplo 54



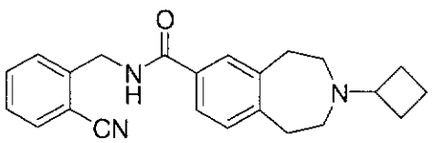
000297

N-(2-Bromobenzil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.45 - 7.62 (m, 4H), 7.28 - 7.34 (m, 1H), 7.12 - 7.21 (m, 2H), 6.57 (br. s., 1H), 4.65 - 4.79 (m, 2H), 2.90 - 3.07 (m, 4H), 2.74 - 2.86 (m, 1H), 2.47 (br. s., 4H), 2.03 - 2.15 (m, 2H), 1.87 - 2.00 (m, 2H), 1.55 - 1.78 (m, 2H)

Espectro de Masa: ES^+ 413, 415

2.55 Ejemplo 55

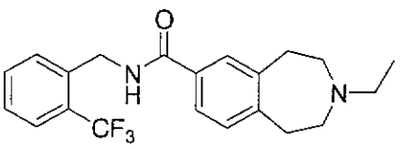


N-(2-Cianobenzil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.51 - 7.74 (m, 5H), 7.33 - 7.43 (m, 1H), 7.11 - 7.19 (m, 1H), 6.72 - 6.90 (m, 1H), 4.73 - 4.89 (m, 2H), 2.96 (br. s., 4H), 2.70 - 2.84 (m, 1H), 2.44 (br. s., 4H), 2.01 - 2.14 (m, 2H), 1.82 - 1.99 (m, 2H), 1.56 - 1.79 (m, 2H)

Espectro de Masa: ES^+ 360

2.56 Ejemplo 56

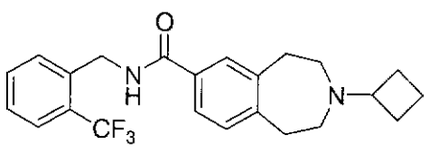


3-Etil-N-(2-(trifluorometil)benzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.68 - 7.74 (m, 1H), 7.62 - 7.68 (m, 2H), 7.50 - 7.62 (m, 2H), 7.39 - 7.48 (m, 1H), 7.19 - 7.27 (m, 1H), 4.75 - 4.81 (m, 2H), 3.01 (br. s., 4H), 2.54 - 2.75 (m, 6H), 1.09 - 1.17 (m, 3H)

Espectro de Masa: ES^+ 377

2.57 Ejemplo 57

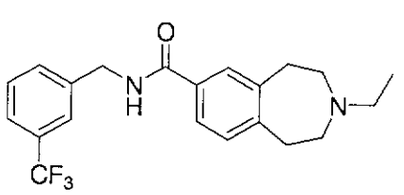


3-Ciclobutil-N-(2-(trifluorometil)benzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) δ 7.67 - 7.73 (m, 1H), 7.62 - 7.67 (m, 2H), 7.50 - 7.61 (m, 2H), 7.38 - 7.47 (m, 1H), 7.18 - 7.25 (m, 1H), 4.74 - 4.81 (m, 2H), 2.98 (d, *J* = 4.04 Hz, 4H), 2.76 - 2.90 (m, 1H), 2.48 (br. s., 4H), 2.05 - 2.16 (m, 2H), 1.86 - 2.00 (m, 2H), 1.59 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 403

2.58 Ejemplo 58

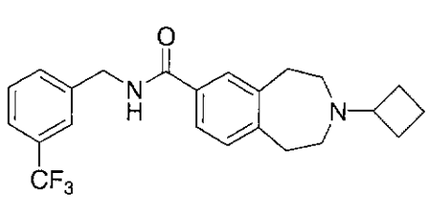


3-Etil-N-(3-(trifluorometil)benzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) δ 7.58 - 7.68 (m, 4H), 7.49 - 7.58 (m, 2H), 7.18 - 7.26 (m, 1H), 4.63 (s, 2H), 3.00 (br. s., 4H), 2.54 - 2.75 (m, 6H), 1.06 - 1.19 (m, 3H)

Espectro de Masa: ES$^+$ 377

2.59 Ejemplo 59

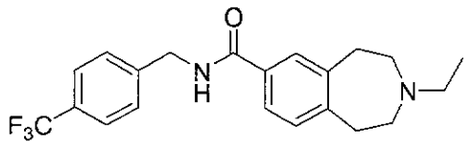


3-Ciclobutil-N-(3-(trifluorometil)benzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.58 - 7.68 (m, 4H), 7.49 - 7.58 (m, 2H), 7.17 - 7.25 (m, 1H), 4.62 (s, 2H), 2.98 (br. s., 4H), 2.77 - 2.91 (m, 1H), 2.49 (br. s., 4H), 2.03 - 2.18 (m, 2H), 1.85 - 2.01 (m, 2H), 1.60 - 1.80 (m, 2H)

Espectro de Masa: ES$^+$ 403

2.60 Ejemplo 60

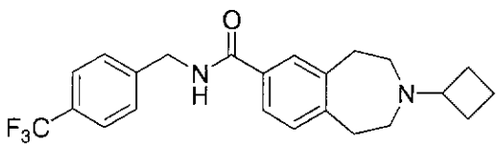


3-Etil-N-(4-(trifluorometil)benzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) ¨ 10.13 (s, 1H), 7.74 - 7.81 (m, 2H), 7.68 - 7.73 (m, 2H), 7.31 - 7.38 (m, 2H), 7.23 - 7.29 (m, 1H), 7.06 - 7.13 (m, 1H), 2.86 - 2.98 (m, 4H), 2.72 - 2.83 (m, 1H), 2.38 (br. s., 4H), 1.96 - 2.07 (m, 2H), 1.73 - 1.87 (m, 2H), 1.51 - 1.68 (m, 2H)

Espectro de Masa: ES$^+$ 377

2.61 Ejemplo 61

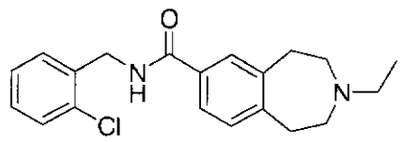


3-Ciclobutil-N-(4-(trifluorometil)benzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) ¨ 7.58 - 7.66 (m, 4H), 7.48 - 7.57 (m, 2H), 7.17 - 7.25 (m, 2H), 4.63 (s, 2H), 2.98 (br. s., 4H), 2.76 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.04 - 2.17 (m, 2H), 1.86 - 2.01 (m, 2H), 1.60 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 403

2.62 Ejemplo 62

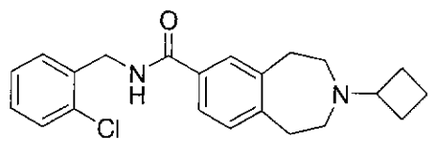


N-(2-Clorobenzil)-3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.58 - 7.69 (m, 2H), 7.34 - 7.44 (m, 2H), 7.19 - 7.32 (m, 3H), 4.65 (s, 2H), 3.01 (br. s., 4H), 2.54 - 2.77 (m, 6H), 1.08 - 1.19 (m, 3H)

Espectro de Masa: ES$^+$ 343

2.63 Ejemplo 63

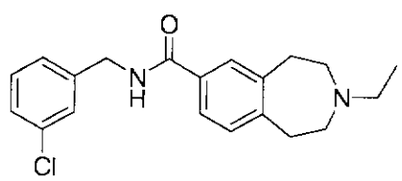


N-(2-Clorobenzil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.59 - 7.67 (m, 2H), 7.34 - 7.43 (m, 2H), 7.17 - 7.31 (m, 3H), 4.65 (s, 2H), 2.90 - 3.05 (m, 4H), 2.76 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.04 - 2.16 (m, 2H), 1.86 - 2.00 (m, 2H), 1.61 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 369

2.64 Ejemplo 64

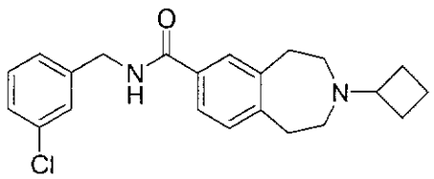


N-(3-Clorobenzil)-3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.58 - 7.66 (m, 2H), 7.18 - 7.40 (m, 5H), 4.54 (s, 2H), 3.01 (br. s., 4H), 2.54 - 2.75 (m, 6H), 1.09 - 1.18 (m, 3H)

Espectro de Masa: ES$^+$ 343

2.65 Ejemplo 65

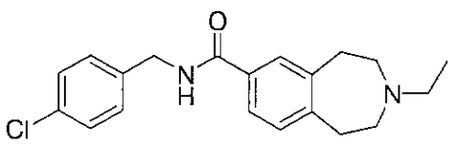


N-(3-Clorobenzil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.57 - 7.65 (m, 2H), 7.15 - 7.37 (m, 5H), 4.56 (s, 2H), 2.89 - 3.04 (m, 4H), 2.75 - 2.87 (m, 1H), 2.46 (br. s., 4H), 2.02 - 2.15 (m, 2H), 1.84 - 2.00 (m, 2H), 1.58 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 369

2.66 Ejemplo 66

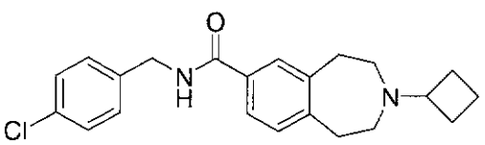


N-(4-Clorobenzil)-3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.57 - 7.64 (m, 2H), 7.27 - 7.36 (m, 4H), 7.16 - 7.23 (m, 1H), 4.52 (s, 2H), 2.90 - 3.04 (m, 4H), 2.53 - 2.72 (m, 6H), 1.06 - 1.16 (m, 3H)

Espectro de Masa: ES$^+$ 343

2.67 Ejemplo 67

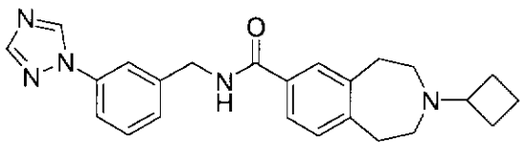


N-(4-Clorobenzil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.55 - 7.64 (m, 2H), 7.27 - 7.37 (m, 4H), 7.17 - 7.24 (m, 1H), 4.53 (s, 2H), 2.98 (br. s., 4H), 2.76 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.02 - 2.17 (m, 2H), 1.86 - 2.00 (m, 2H), 1.58 - 1.80 (m, 2H)

Espectro de Masa: ES$^-$ 369

2.68 Ejemplo 68

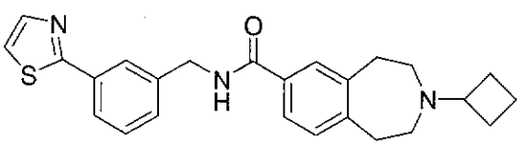


N-(3-(1H-1,2,4-Triazol-1-il)benzil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) 9.28 (s, 1H), 8.95 - 9.07 (m, 1H), 8.17 - 8.28 (m, 1H), 7.82 (s, 1H), 7.70 - 7.78 (m, 1H), 7.62 - 7.70 (m, 2H), 7.47 - 7.56 (m, 1H), 7.32 - 7.42 (m, 1H), 7.16 - 7.26 (m, 1H), 4.50 - 4.60 (m, 2H), 2.89 (br. s., 4H), 2.71 - 2.82 (m, 1H), 2.36 (br. s., 4H), 2.01 (d, *J* = 6.57 Hz, 2H), 1.71 - 1.89 (m, 2H), 1.50 - 1.69 (m, 2H)

Espectro de Masa: ES$^+$ 402

2.69 Ejemplo 69

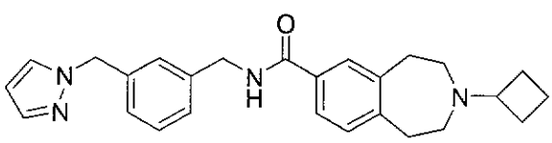


3-Ciclobutil-N-(3-(tiazol-2-il)benzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.95 (s, 1H), 7.81 - 7.88 (m, 2H), 7.61 - 7.66 (m, 2H), 7.58 - 7.61 (m, 1H), 7.43 - 7.50 (m, 2H), 7.18 - 7.25 (m, 1H), 4.64 (s, 2H), 2.98 (br. s., 4H), 2.77 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.05 - 2.16 (m, 2H), 1.87 - 2.00 (m, 2H), 1.62 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 418

2.70 Ejemplo 70



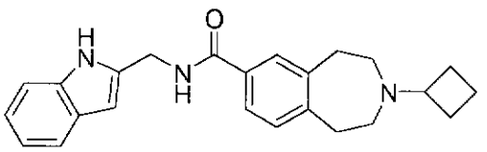
N-(3-((1H-Pirazol-1-il)metil)benzil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) 8.85 - 8.97 (m, 1H), 7.76 - 7.85 (m, 1H), 7.58 - 7.68 (m, 2H), 7.39 - 7.49 (m, 1H), 7.13 - 7.32 (m, 4H), 7.03 - 7.10 (m, 1H), 6.21 - 6.34 (m, 1H), 5.31

(s, 2H), 4.35 - 4.51 (m, 2H), 2.68 - 3.04 (m, 5H), 2.37 (br. s., 4H), 1.94 - 2.10 (m, 2H), 1.71 - 1.89 (m, 2H), 1.49 - 1.69 (m, 2H)

Espectro de Masa: ES^+ 415

2.71 Ejemplo 71

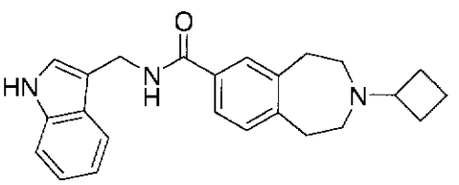


N-((1H-Indol-2-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.63 (br. s., 3H), 7.41 - 7.48 (m, 1H), 7.28 - 7.34 (m, 1H), 7.16 - 7.24 (m, 1H), 7.01 - 7.08 (m, 1H), 6.92 - 6.99 (m, 1H), 6.34 (s, 1H), 4.70 (s, 2H), 2.98 (br. s., 4H), 2.80 - 2.92 (m, 1H), 2.51 (br. s., 4H), 2.05 - 2.17 (m, 2H), 1.88 - 2.01 (m, 2H), 1.60 - 1.79 (m, 2H)

Espectro de Masa: ES^+ 374

2.72 Ejemplo 72



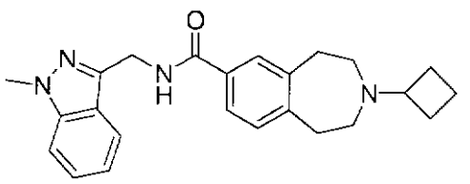
N-((1H-Indol-3-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.61 - 7.67 (m, 1H), 7.53 - 7.58 (m, 2H), 7.32 - 7.36 (m, 1H), 7.24 (s, 1H), 7.13 - 7.17 (m, 1H), 7.07 - 7.12 (m, 1H), 6.97 - 7.04 (m, 1H), 4.73 (s, 2H), 2.93 (br. s., 4H), 2.75 - 2.85 (m, 1H), 2.44 (br. s., 4H), 2.02 - 2.13 (m, 2H), 1.85 - 1.98 (m, 2H), 1.60 - 1.76 (m, 2H)

Espectro de Masa: ES^+ 374

2.73 Ejemplo 73

000304

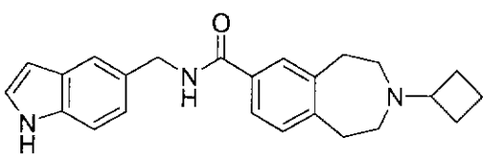


3-Ciclobutil-N-((1-metil-1H-indazol-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.79 - 7.85 (m, 1H), 7.57 - 7.62 (m, 2H), 7.45 - 7.51 (m, 1H), 7.36 - 7.44 (m, 1H), 7.15 - 7.21 (m, 1H), 7.08 - 7.15 (m, 1H), 4.02 (s, 3H), 2.89 - 3.01 (m, 4H), 2.76 - 2.87 (m, 1H), 2.46 (br. s., 4H), 2.03 - 2.15 (m, 2H), 1.84 - 2.01 (m, 2H), 1.61 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 389

2.74 Ejemplo 74

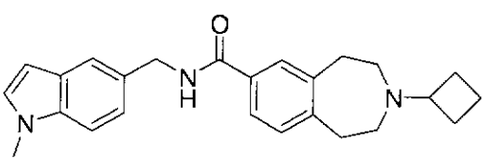


N-((1H-Indol-5-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.58 - 7.64 (m, 2H), 7.53 (s, 1H), 7.31 - 7.37 (m, 1H), 7.17 - 7.24 (m, 2H), 7.09 - 7.15 (m, 1H), 6.38 - 6.43 (m, 1H), 4.63 (s, 3H), 2.97 (br. s., 4H), 2.78 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.05 - 2.15 (m, 2H), 1.86 - 2.00 (m, 2H), 1.62 - 1.77 (m, 2H)

Espectro de Masa: ES$^+$ 374

2.75 Ejemplo 75

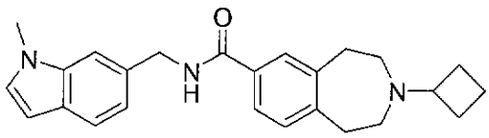


3-Ciclobutil-N-((1-metil-1H-indol-5-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.56 - 7.64 (m, 2H), 7.52 (br. s., 1H), 7.29 - 7.36 (m, 1H), 7.19 (m, 2H), 7.09 - 7.14 (m, 1H), 6.34 - 6.41 (m, 1H), 4.64 (s, 2H), 3.79 (s, 3H), 2.91 - 3.03 (m, 4H), 2.76 - 2.89 (m, 1H), 2.47 (br. s., 4H), 2.04 - 2.15 (m, 2H), 1.86 - 1.99 (m, 2H), 1.60 - 1.77 (m, 2H)

Espectro de Masa: ES$^+$ 388

2.76 Ejemplo 76

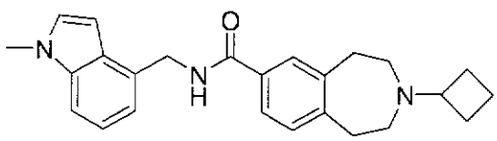


3-Ciclobutil-N-((1-metil-1H-indol-6-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.85 - 8.98 (m, 1H), 7.60 - 7.70 (m, 2H), 7.44 - 7.53 (m, 1H), 7.36 (s, 1H), 7.25 - 7.31 (m, 1H), 7.15 - 7.23 (m, 1H), 6.98 - 7.08 (m, 1H), 6.34 - 6.42 (m, 1H), 4.52 - 4.64 (m, 2H), 3.78 (s, 3H), 2.87 (br. s., 4H), 2.67 - 2.80 (m, 1H), 2.34 (br. s., 4H), 1.96-2.10 (m, 2H), 1.69 - 1.86 (m, 2H), 1.48 - 1.69 (m, 2H)

Espectro de Masa: ES$^+$ 388

2.77 Ejemplo 77

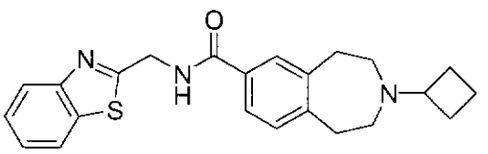


3-Ciclobutil-N-((1-metil-1H-indol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

1H NMR (400 MHz, DMSO-d6) □ 8.80 - 8.94 (m, 1H), 7.58 - 7.74 (m, 2H), 7.27 - 7.37 (m, 2H), 7.15 - 7.23 (m, 1H), 7.06 - 7.14 (m, 1H), 6.91 - 6.99 (m, 1H), 6.52 - 6.60 (m, 1H), 4.66 - 4.77 (m, 2H), 3.35 (s, 3H), 2.87 (br. s., 4H), 2.75 (br. s., 1H), 2.26 - 2.42 (m, 4H), 1.94 - 2.07 (m, 2H), 1.71 - 1.86 (m, 2H), 1.50 - 1.66 (m, 2H)

Espectro de Masa: ES^+ 388

2.78 Ejemplo 78

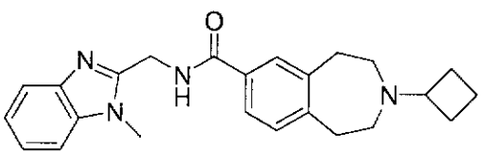


N-(Benzo[d]tiazol-2-ilmetil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.92 - 7.98 (m, 2H), 7.65 - 7.70 (m, 2H), 7.47 - 7.54 (m, 1H), 7.38 - 7.45 (m, 1H), 7.22 - 7.28 (m, 1H), 4.96 (s, 2H), 2.96 - 3.06 (m, 4H), 2.81 - 2.91 (m, 1H), 2.51 (br. s., 4H), 2.07 - 2.17 (m, 2H), 1.88 - 2.02 (m, 2H), 1.62 - 1.79 (m, 2H)

Espectro de Masa: ES^+ 392

2.79 Ejemplo 79

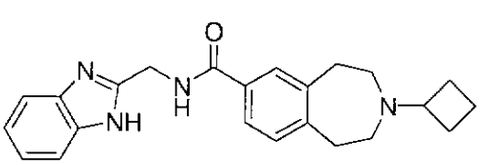


3-Ciclobutil-N-((1-metil-1H-benzo[d]imidazol-2-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.93 - 9.05 (m, 1H), 7.62 - 7.71 (m, 2H), 7.55 - 7.61 (m, 1H), 7.49 - 7.55 (m, 1H), 7.13 - 7.29 (m, 3H), 4.69 - 4.82 (m, 2H), 3.32 (s, 3H), 2.88 (br. s., 4H), 2.70 - 2.82 (m, 1H), 2.35 (br. s., 4H), 1.93 - 2.07 (m, 2H), 1.70 - 1.86 (m, 2H), 1.48 - 1.68 (m, 2H)

Espectro de Masa: ES^+ 389

2.80 Ejemplo 80

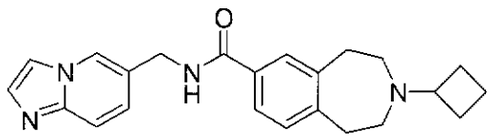


N-((1H-Benzo[d]imidazol-2-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.63 - 7.78 (m, 2H), 7.52 (br. s., 2H), 7.13 - 7.31 (m, 4H), 4.81 (s, 2H), 2.99 (br. s., 4H), 2.77 - 2.91 (m, 1H), 2.50 (br. s., 4H), 2.05 - 2.19 (m, 2H), 1.84 - 2.03 (m, 2H), 1.58 - 1.81 (m, 2H)

Espectro de Masa: ES$^+$ 375

2.81 Ejemplo 81

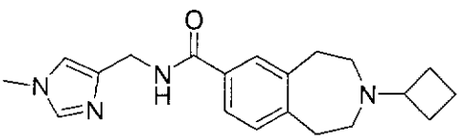


3-Ciclobutil-N-(imidazo[1,2-a]piridin-6-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.89 - 9.00 (m, 1H), 8.46 (s, 1H), 7.95 (s, 1H), 7.59 - 7.70 (m, 2H), 7.49 - 7.57 (m, 2H), 7.16 - 7.26 (m, 2H), 4.38 - 4.52 (m, 2H), 2.88 (br. s., 4H), 2.70 - 2.81 (m, 1H), 2.35 (br. s., 4H), 1.93 - 2.07 (m, 2H), 1.70 - 1.86 (m, 2H), 1.47 - 1.68 (m, 2H)

Espectro de Masa: ES$^+$ 375

2.82 Ejemplo 82

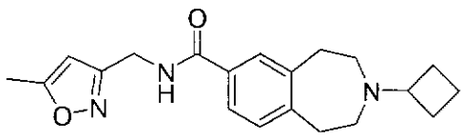


3-Ciclobutil-N-((1-metil-1H-imidazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.57 - 7.62 (m, 2H), 7.53 (s, 1H), 7.17 - 7.22 (m, 1H), 6.99 (s, 1H), 4.45 (s, 2H), 3.68 (s, 3H), 2.98 (br. s., 4H), 2.78 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.05 - 2.18 (m, 2H), 1.87 - 2.01 (m, 2H), 1.62 - 1.78 (m, 2H)

Espectro de Masa: ES^+ 338

2.83 Ejemplo 83

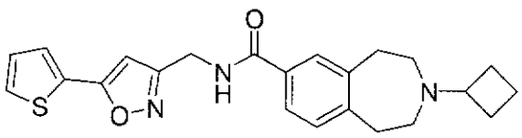


3-Ciclobutil-N-((5-metilisoxazol-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^1H NMR (400 MHz, MeOD) □ 7.58 - 7.64 (m, 2H), 7.18 - 7.25 (m, 1H), 6.12 (s, 1H), 4.55 (s, 2H), 2.99 (br. s., 4H), 2.81 - 2.93 (m, 1H), 2.44 - 2.61 (m, 4H), 2.39 (s, 3H), 2.06 - 2.18 (m, 2H), 1.88 - 2.02 (m, 2H), 1.63 - 1.79 (m, 2H)

Espectro de Masa: ES^+ 340

2.84 Ejemplo 84

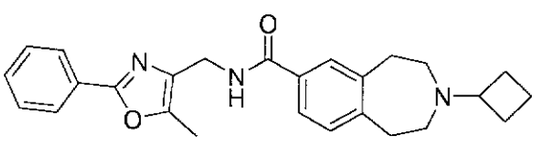


3-Ciclobutil-N-((5-(tiofen-2-il)isoxazol-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^1H NMR (400 MHz, MeOD) □ 7.60 - 7.66 (m, 3H), 7.56 - 7.59 (m, 1H), 7.20 - 7.25 (m, 1H), 7.14 - 7.19 (m, 1H), 6.60 (s, 1H), 4.63 (s, 2H), 2.99 (br. s., 4H), 2.81 - 2.92 (m, 1H), 2.51 (br. s., 4H), 2.07 - 2.17 (m, 2H), 1.88 - 2.01 (m, 2H), 1.60 - 1.79 (m, 2H)

Espectro de Masa: ES^+ 408

2.85 Ejemplo 85

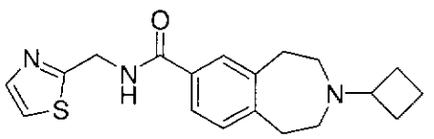


3-Ciclobutil-N-((5-metil-2-feniloxazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.94 - 8.01 (m, 2H), 7.61 (br. s., 2H), 7.41 - 7.52 (m, 3H), 7.15 - 7.24 (m, 1H), 4.46 (s, 2H), 2.98 (br. s., 4H), 2.78 - 2.91 (m, 1H), 2.47 (s, 7H), 2.05 - 2.17 (m, 2H), 1.86 - 2.01 (m, 2H), 1.60 - 1.79 (m, 2H)

Espectro de Masa: ES$^+$ 416

2.86 Ejemplo 86

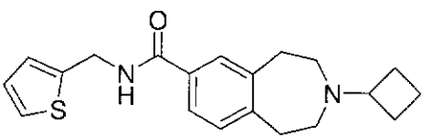


3-Ciclobutil-N-(tiazol-2-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 9.21 - 9.33 (m, 1H), 7.69 - 7.78 (m, 1H), 7.58 - 7.70 (m, 3H), 7.18 - 7.28 (m, 1H), 4.67 - 4.79 (m, 2H), 2.89 (br. s., 4H), 2.78 (br. s., 1H), 2.37 (br. s., 4H), 1.94 - 2.08 (m, 2H), 1.70 - 1.87 (m, 2H), 1.46 - 1.69 (m, 2H)

Espectro de Masa: ES$^+$ 342

2.87 Ejemplo 87

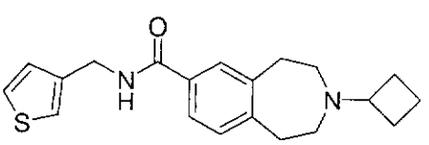


3-Ciclobutil-N-(tiofen-2-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.55 - 7.62 (m, 2H), 7.25 - 7.29 (m, 1H), 7.16 - 7.22 (m, 1H), 7.01 - 7.04 (m, 1H), 6.91 - 6.96 (m, 1H), 4.71 (s, 2H), 2.92 - 3.02 (m, 4H), 2.77 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.05 - 2.15 (m, 2H), 1.86 - 2.00 (m, 2H), 1.61 - 1.77 (m, 2H)

Espectro de Masa: ES$^+$ 341

2.88 Ejemplo 88

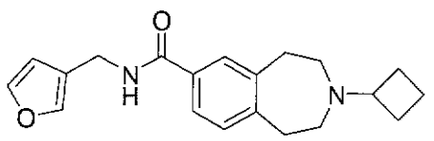


3-Ciclobutil-N-(tiofen-3-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.55 - 7.63 (m, 2H), 7.33 - 7.37 (m, 1H), 7.22 - 7.27 (m, 1H), 7.17 - 7.22 (m, 1H), 7.06 - 7.11 (m, 1H), 4.55 (s, 2H), 2.97 (br. s., 4H), 2.77 - 2.87 (m, 1H), 2.38 - 2.58 (m, 4H), 2.02 - 2.16 (m, 2H), 1.86 - 2.00 (m, 2H), 1.59 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 341

2.89 Ejemplo 89

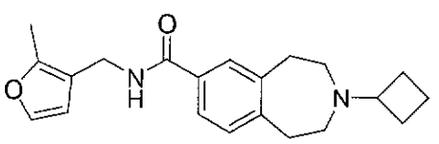


3-Ciclobutil-N-(furan-3-ilmetil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.54 - 7.61 (m, 2H), 7.47 (s, 1H), 7.43 (s, 1H), 7.15 - 7.24 (m, 1H), 6.45 (s, 1H), 4.39 (s, 2H), 2.97 (br. s., 4H), 2.77 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.04 - 2.15 (m, 2H), 1.87 - 2.00 (m, 2H), 1.61 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 325

2.90 Ejemplo 90

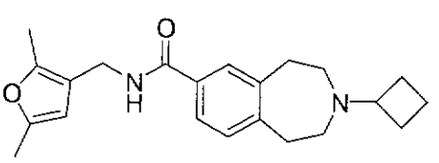


3-ciclobutil-N-((2-metilfuran-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.60 - 8.73 (m, 1H), 7.55 - 7.64 (m, 2H), 7.37 - 7.44 (m, 1H), 7.15 - 7.23 (m, 1H), 6.31 - 6.38 (m, 1H), 4.15 - 4.25 (m, 2H), 2.87 (br. s., 5H), 2.22 - 2.45 (m, 7H), 1.94 - 2.07 (m, 2H), 1.72 - 1.87 (m, 2H), 1.48 - 1.67 (m, 2H)

Espectro de Masa: ES$^+$ 339

2.91 Ejemplo 91

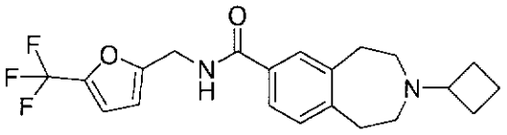


3-ciclobutil-N-((2,5-dimetilfuran-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) □ 8.58 - 8.65 (m, 1H), 7.54 - 7.62 (m, 2H), 7.15 - 7.20 (m, 1H), 5.93 (s, 1H), 4.10 - 4.15 (m, 2H), 2.82 - 2.90 (m, 4H), 2.72 - 2.79 (m, 1H), 2.34 (br. s., 4H), 2.21 (s, 3H), 2.16 (s, 3H), 1.96 - 2.05 (m, 2H), 1.72 - 1.84 (m, 2H), 1.51 - 1.66 (m, 2H)

Espectro de Masa: ES$^+$ 353

2.92 Ejemplo 92

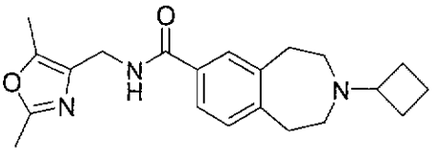


3-ciclobutil-N-((5-(trifluorometil)furan-2-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) □ 8.95 - 9.04 (m, 1H), 7.57 - 7.67 (m, 2H), 7.18 - 7.25 (m, 1H), 7.13 - 7.18 (m, 1H), 6.48 - 6.53 (m, 1H), 4.46 - 4.56 (m, 2H), 2.88 (br. s., 4H), 2.70 - 2.82 (m, 1H), 2.26 - 2.43 (m, 4H), 2.00 (br. s., 2H), 1.70 - 1.88 (m, 2H), 1.49 - 1.67 (m, 2H)

Espectro de Masa: ES$^+$ 393

2.93 Ejemplo 93

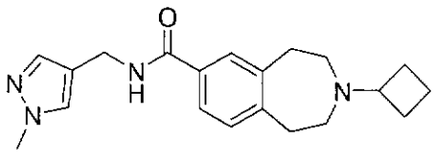


3-ciclobutil-N-((2,5-dimetiloxazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) □ 8.65 - 8.75 (m, 1H), 7.54 - 7.66 (m, 2H), 7.12 - 7.22 (m, 1H), 4.15 - 4.25 (m, 2H), 2.81 - 2.93 (m, 4H), 2.69 - 2.80 (m, 1H), 2.22 - 2.43 (m, 10H), 1.94 - 2.07 (m, 2H), 1.71 - 1.86 (m, 2H), 1.50 - 1.67 (m, 2H)

Espectro de Masa: ES$^+$ 354

2.94 Ejemplo 94

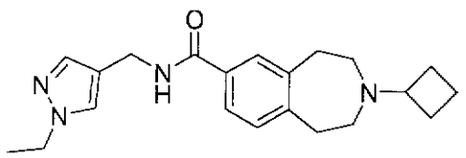


3-Ciclobutil-N-((1-metil-1H-pirazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) ¯ 7.54 - 7.59 (m, 3H), 7.45 (s, 1H), 7.16 - 7.22 (m, 1H), 4.39 (s, 2H), 3.84 (s, 3H), 2.97 (br. s., 4H), 2.77 - 2.89 (m, 1H), 2.47 (br. s., 4H), 2.05 - 2.15 (m, 2H), 1.87 - 2.00 (m, 2H), 1.62 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 339

2.95 Ejemplo 95

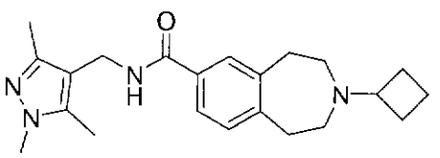


3-Ciclobutil-N-((1-etil-1H-pirazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) ¯ 8.62 - 8.72 (m, 1H), 7.55 - 7.65 (m, 3H), 7.34 (s, 1H), 7.14 - 7.20 (m, 1H), 4.21 - 4.31 (m, 2H), 4.00 - 4.12 (m, 2H), 2.80 - 2.91 (m, 4H), 2.68 - 2.79 (m, 1H), 2.33 (br. s., 4H), 1.94 - 2.05 (m, 2H), 1.70 - 1.84 (m, 2H), 1.49 - 1.66 (m, 2H), 1.32 (t, 3H)

Espectro de Masa: ES$^+$ 353

2.96 Ejemplo 96

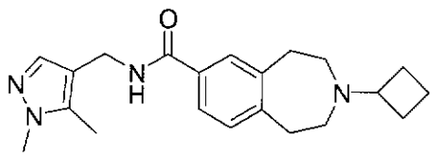


3-Ciclobutil-N-((1,3,5-trimetil-1H-pirazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.39 - 8.50 (m, 1H), 7.53 - 7.63 (m, 2H), 7.12 - 7.21 (m, 1H), 4.12 - 4.22 (m, 2H), 3.35 (s, 3H), 2.80 - 2.92 (m, 4H), 2.67 - 2.79 (m, 1H), 2.33 (br. s., 4H), 2.20 (s, 3H), 2.10 (s, 3H), 1.94 - 2.05 (m, 2H), 1.70 - 1.84 (m, 2H), 1.47 - 1.67 (m, 2H)

Espectro de Masa: ES$^+$ 367

2.97 Ejemplo 97

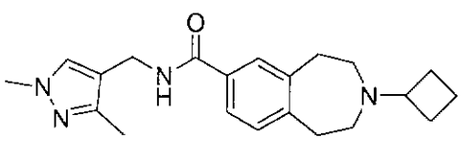


3-Ciclobutil-N-((1,5-dimetil-1H-pirazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.54 - 8.65 (m, 1H), 7.52 - 7.65 (m, 2H), 7.25 (s, 1H), 7.12 - 7.21 (m, 1H), 4.16 - 4.26 (m, 2H), 3.34 (s, 3H), 2.86 (br. s., 4H), 2.68 - 2.79 (m, 1H), 2.39 (br. s., 4H), 2.19 - 2.25 (m, 3H), 1.94 - 2.07 (m, 2H), 1.69 - 1.85 (m, 2H), 1.50 - 1.67 (m, 2H)

Espectro de Masa: ES$^-$ 353

2.98 Ejemplo 98

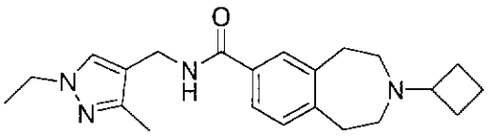


3-Ciclobutil-N-((1,3-dimetil-1H-pirazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.54 - 8.63 (m, 1H), 7.54 - 7.66 (m, 2H), 7.46 (s, 1H), 7.13 - 7.20 (m, 1H), 4.16 - 4.26 (m, 2H), 3.69 (s, 3H), 2.81 - 2.95 (m, 4H), 2.68 - 2.80 (m, 1H), 2.24 - 2.43 (m, 4H), 2.09 (s, 3H), 1.94 - 2.06 (m, 2H), 1.71 - 1.85 (m, 2H), 1.49 - 1.67 (m, 2H)

Espectro de Masa: ES$^+$ 353

2.99 Ejemplo 99

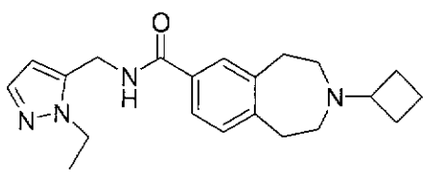


3-Ciclobutil-N-((1-etil-3-metil-1H-pirazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) □ 8.53 - 8.64 (m, 1H), 7.57 - 7.66 (m, 2H), 7.51 (s, 1H), 7.17 (d, *J* = 7.58 Hz, 1H), 4.18 - 4.26 (m, 2H), 3.92 - 4.03 (m, 2H), 2.87 (br. s., 4H), 2.70 - 2.81 (m, 1H), 2.27 - 2.43 (m, 4H), 2.13 (s, 3H), 1.95 - 2.07 (m, 2H), 1.78 (br. s., 2H), 1.49 - 1.68 (m, 2H), 1.26 - 1.34 (m, 3H)

Espectro de Masa: ES$^+$ 367

2.100 Ejemplo 100

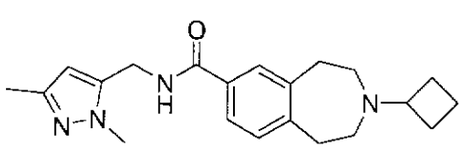


3-ciclobutil-N-((1-etil-1H-pirazol-5-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) □ 8.82 - 8.93 (m, 1H), 7.55 - 7.70 (m, 2H), 7.29 - 7.38 (m, 1H), 7.15 - 7.23 (m, 1H), 6.09 - 6.18 (m, 1H), 4.46 - 4.55 (m, 2H), 4.09 - 4.19 (m, 2H), 2.81 - 2.95 (m, 4H), 2.68 - 2.80 (m, 1H), 2.34 (br. s., 4H), 1.93 - 2.10 (m, 2H), 1.70 - 1.85 (m, 2H), 1.49 - 1.67 (m, 2H), 1.24 - 1.34 (m, 3H)

Espectro de Masa: ES$^+$ 353

2.101 Ejemplo 101

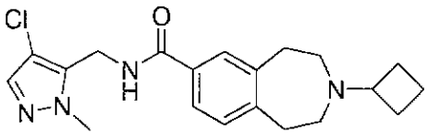


3-Ciclobutil-N-((1,3-dimetil-1H-pirazol-5-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.77 - 8.89 (m, 1H), 7.54 - 7.71 (m, 2H), 7.17 - 7.27 (m, 1H), 5.92 (s, 1H), 4.36 - 4.49 (m, 2H), 3.71 (s, 3H), 2.89 (br. s., 4H), 2.70 - 2.83 (m, 1H), 2.34 (br. s., 4H), 1.96 - 2.11 (m, 5H), 1.80 (br. s., 2H), 1.49 - 1.69 (m, 2H)

Espectro de Masa: ES$^+$ 353

2.102 Ejemplo 102

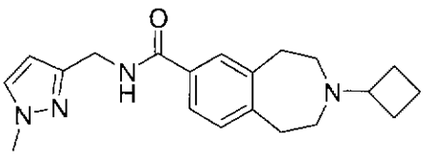


N-((4-cloro-1-metil-1H-pirazol-5-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) □ 8.76 - 8.92 (m, 1H), 7.58 - 7.65 (m, 2H), 7.49 (s, 1H), 7.17 - 7.22 (m, 1H), 4.47 - 4.54 (m, 2H), 3.84 (s, 3H), 2.88 (br. s., 4H), 2.70 - 2.81 (m, 1H), 2.34 (br. s., 4H), 1.95 - 2.07 (m, 2H), 1.78 (br. s., 2H), 1.51 - 1.67 (m, 2H)

Espectro de Masa: ES$^+$ 373

2.103 Ejemplo 103

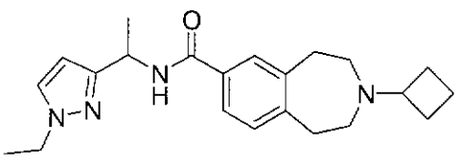


3-Ciclobutil-N-((1-metil-1H-pirazol-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) □ 8.70 - 8.82 (m, 1H), 7.50 - 7.70 (m, 3H), 7.12 - 7.24 (m, 1H), 6.07 - 6.14 (m, 1H), 4.32 - 4.44 (m, 2H), 3.78 (s, 3H), 2.66 - 2.98 (m, 5H), 2.24 - 2.44 (m, 4H), 2.01 (br. s., 2H), 1.79 (br. s., 2H), 1.48 - 1.69 (m, 2H)

Espectro de Masa: ES$^+$ 339

2.104 Ejemplo104

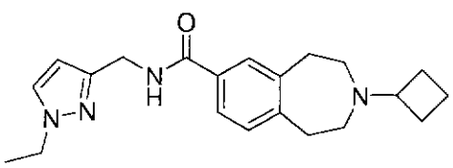


3-ciclobutil-N-(1-(1-etil-1H-pirazol-3-il)etil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) 8.45 - 8.61 (m, 1H), 7.53 - 7.67 (m, 3H), 7.11 - 7.21 (m, 1H), 6.08 - 6.19 (m, 1H), 5.13 - 5.26 (m, 1H), 3.99 - 4.10 (m, 2H), 2.86 (br. s., 4H), 2.66 - 2.78 (m, 1H), 2.33 (br. s., 4H), 1.98 (d, *J* = 7.33 Hz, 2H), 1.70 - 1.84 (m, 2H), 1.48 - 1.66 (m, 2H), 1.39 - 1.47 (m, 3H), 1.33 (m, 3H)

Espectro de Masa: ES$^+$ 367

2.105 Ejemplo 105

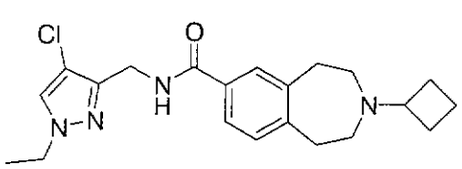


3-Ciclobutil-N-((1-etil-1H-pirazol-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) 8.69 - 8.84 (m, 1H), 7.55 - 7.70 (m, 3H), 7.13 - 7.23 (m, 1H), 6.06 - 6.16 (m, 1H), 4.33 - 4.46 (m, 2H), 4.02 - 4.11 (m, 2H), 2.87 (br. s., 4H), 2.69 - 2.82 (m, 1H), 2.35 (br. s., 4H), 1.93 - 2.09 (m, 2H), 1.70 - 1.87 (m, 2H), 1.48 - 1.68 (m, 2H), 1.28 - 1.39 (m, 3H)

Espectro de Masa: ES$^+$ 353

2.106 Ejemplo 106



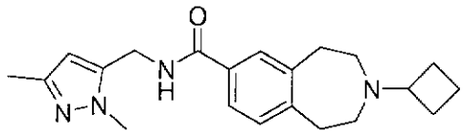
000317

N-((4-Cloro-1-etil-1H-pirazol-3-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) □ 8.64 - 8.75 (m, 1H), 7.95 (s, 1H), 7.58 - 7.69 (m, 2H), 7.14 - 7.22 (m, 1H), 4.37 - 4.48 (m, 2H), 3.99 - 4.12 (m, 2H), 2.87 (br. s., 5H), 2.36 (br. s., 4H), 1.95 - 2.07 (m, 2H), 1.79 (br. s., 2H), 1.48 - 1.68 (m, 2H), 1.28 - 1.39 (m, 3H)

Espectro de Masa: ES$^+$ 387

2.107 Ejemplo 107

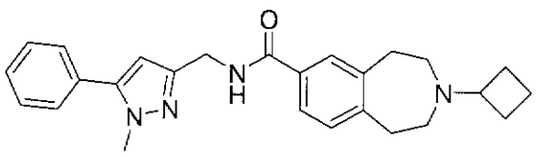


3-Ciclobutil-N-((1,5-dimetil-1H-pirazol-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.67 - 8.80 (m, 1H), 7.55 - 7.68 (m, 2H), 7.13 - 7.25 (m, 1H), 5.90 (s, 1H), 4.24 - 4.36 (m, 2H), 3.63 (s, 3H), 2.70 - 2.81 (m, 1H), 2.88 (br. s., 4H), 2.34 (br. s., 4H), 2.19 (s, 3H), 2.02 (br. s., 2H), 1.79 (br. s., 2H), 1.60 (br. s., 2H)

Espectro de Masa: ES$^+$ 353

2.108 Ejemplo 108

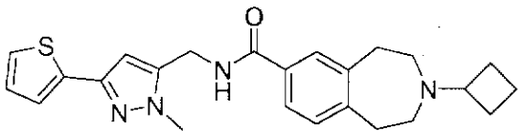


3-Ciclobutil-N-((1-metil-5-fenil-1H-pirazol-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.77 - 8.86 (m, 1H), 7.58 - 7.70 (m, 2H), 7.36 - 7.55 (m, 5H), 7.14 - 7.23 (m, 1H), 6.26 - 6.33 (m, 1H), 4.36 - 4.49 (m, 2H), 3.80 (s, 3H), 2.87 (br. s., 4H), 2.68 - 2.79 (m, 1H), 2.34 (br. s., 4H), 1.93 - 2.08 (m, 2H), 1.70 - 1.86 (m, 2H), 1.49 - 1.67 (m, 2H)

Espectro de Masa: ES^+ 415

2.109 Ejemplo 109

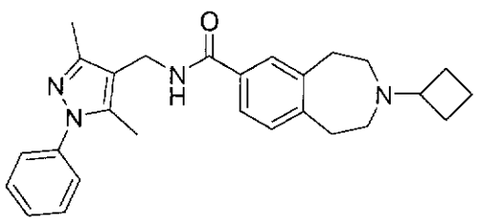


3-Ciclobutil-N-((1-metil-3-(tiofen-2-il)-1H-pirazol-5-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ 8.87 - 8.97 (m, 1H), 7.58 - 7.69 (m, 2H), 7.37 - 7.44 (m, 1H), 7.30 - 7.37 (m, 1H), 7.17 - 7.26 (m, 1H), 7.00 - 7.08 (m, 1H), 6.49 (s, 1H), 4.45 - 4.57 (m, 2H), 3.83 (s, 3H), 2.88 (br. s., 4H), 2.70 - 2.82 (m, 1H), 2.35 (br. s., 4H), 1.93 - 2.08 (m, 2H), 1.70 - 1.88 (m, 2H), 1.49 - 1.68 (m, 2H)

Espectro de Masa: ES^- 421

2.110 Ejemplo 110

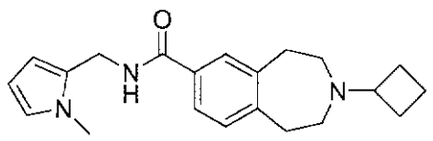


3-Ciclobutil-N-((3,5-dimetil-1-fenil-1H-pirazol-4-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.55 - 7.60 (m, 2H), 7.47 - 7.55 (m, 2H), 7.37 - 7.47 (m, 3H), 7.16 - 7.22 (m, 1H), 4.43 (s, 2H), 2.91 - 3.03 (m, 4H), 2.77 - 2.88 (m, 1H), 2.38 - 2.56 (m, 4H), 2.27 - 2.35 (m, 6H), 2.05 - 2.16 (m, 2H), 1.86 - 1.99 (m, 2H), 1.60 - 1.78 (m, 2H)

Espectro de Masa: ES^+ 429

2.111 Ejemplo 111

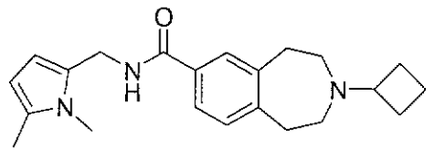


3-Ciclobutil-N-((1-metil-1H-pirrol-2-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^1H NMR (400 MHz, MeOD) □ 7.51 - 7.60 (m, 2H), 7.11 - 7.25 (m, 1H), 6.56 - 6.66 (m, 1H), 6.02 - 6.09 (m, 1H), 5.91 - 5.99 (m, 1H), 4.53 (s, 2H), 3.61 (s, 3H), 2.89 - 3.04 (m, 4H), 2.76 - 2.88 (m, 1H), 2.47 (br. s., 4H), 2.04 - 2.16 (m, 2H), 1.84 - 2.00 (m, 2H), 1.59 - 1.78 (m, 2H)

Espectro de Masa: ES^+ 338

2.112 Ejemplo 112

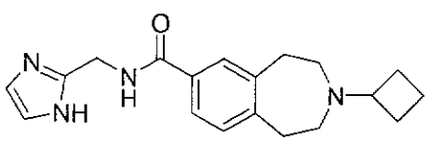


3-ciclobutil-N-((1,5-dimetil-1H-pirrol-2-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^1H NMR (400 MHz, DMSO-d_6) ¯ 8.52 - 8.62 (m, 1H), 7.56 - 7.68 (m, 2H), 7.14 - 7.21 (m, 1H), 5.81 - 5.88 (m, 1H), 5.64 - 5.70 (m, 1H), 4.34 - 4.45 (m, 2H), 3.41 (s, 3H), 2.81 - 2.94 (m, 4H), 2.70 - 2.81 (m, 1H), 2.34 (br. s., 4H), 2.14 (s, 3H), 1.95 - 2.07 (m, 2H), 1.70 - 1.85 (m, 2H), 1.51 - 1.67 (m, 2H)

Espectro de Masa: ES^+ 352

2.113 Ejemplo 113

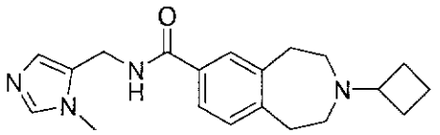


N-((1H-Imidazol-2-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.58 - 7.69 (m, 2H), 7.17 - 7.24 (m, 1H), 6.97 (s, 2H), 4.60 (s, 2H), 2.98 (br. s., 4H), 2.77 - 2.89 (m, 1H), 2.48 (br. s., 4H), 2.06 - 2.16 (m, 2H), 1.87 - 2.00 (m, 2H), 1.62 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 325

2.114 Ejemplo 114

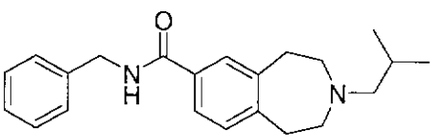


3-Ciclobutil-N-((1-metil-1H-imidazol-5-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.57 - 7.63 (m, 3H), 7.18 - 7.25 (m, 1H), 6.96 (s, 1H), 4.60 (s, 2H), 3.72 (s, 3H), 2.94 - 3.04 (m, 4H), 2.79 - 2.91 (m, 1H), 2.50 (br. s., 4H), 2.07 - 2.18 (m, 2H), 1.88 - 2.02 (m, 2H), 1.62 - 1.80 (m, 2H)

Espectro de Masa: ES$^+$ 338

2.115 Ejemplo 115

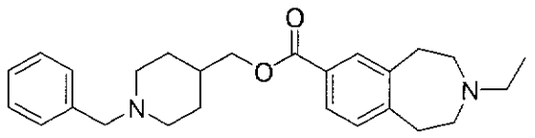


N-benzil-3-isobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida.

MS ES$^+$: 337 (M+H)

^{1}H NMR (400 MHz, $CDCl_3$): □ 7.49 - 7.57 (m, 2H), 7.28 - 7.40 (m, 5H), 7.11 - 7.16 (m, 1H), 4.63 - 4.68 (m, 2H), 2.91 - 2.98 (m, 4H), 2.55 - 2.64 (m, 4H), 2.16 - 2.22 (m, 2H), 1.74 - 1.86 (m, 1H), 0.89 - 0.96 (m, 6H)

2.116 Ejemplo 116

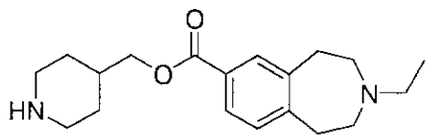


(1-Benzilpiperidin-4-il)metil 3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato

^{1}H NMR (400 MHz, DMSO-d6) □ 7.60 - 7.67 (m, 2H), 7.14 - 7.29 (m, 6H), 4.01 - 4.08 (m, 2H), 3.38 (s, 2H), 2.81 - 2.89 (m, 4H), 2.71 - 2.79 (m, 2H), 2.37 - 2.49 (m, 6H), 1.81 - 1.91 (m, 2H), 1.58 - 1.69 (m, 3H), 1.15 - 1.29 (m, 2H), 0.89 - 0.97 (m, 3H)

Espectro de Masa: ES$^+$ 407

2.117 Ejemplo 117

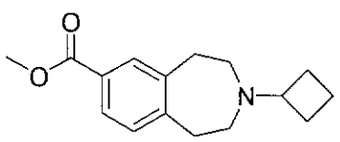


Piperidin-4-ilmetil 3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato

^{1}H NMR (400 MHz, D_2O) ¯ 7.84 - 7.92 (m, 2H), 7.34 - 7.42 (m, 1H), 4.21 - 4.30 (m, 2H), 3.70 - 3.82 (m, 2H), 3.43 - 3.51 (m, 2H), 3.13 - 3.34 (m, 6H), 2.98 - 3.12 (m, 4H), 2.13 - 2.26 (m, 1H), 2.02 - 2.11 (m, 2H), 1.52 - 1.66 (m, 2H), 1.28 - 1.37 (m, 3H)

Espectro de Masa: ES$^+$ 316

2.118 Ejemplo 118

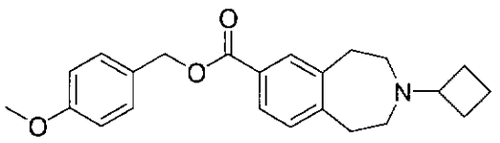


Metil 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato

^{1}H NMR (400 MHz, MeOD) □ 7.71 - 7.81 (m, 2H), 7.17 - 7.25 (m, 1H), 3.88 (s, 3H), 2.98 (br. s., 4H), 2.78 - 2.89 (m, 1H), 2.39 - 2.59 (m, 4H), 2.05 - 2.16 (m, 2H), 1.87 - 2.00 (m, 2H), 1.60 - 1.78 (m, 2H)

Espectro de Masa: ES$^+$ 260

2.119 Ejemplo 119

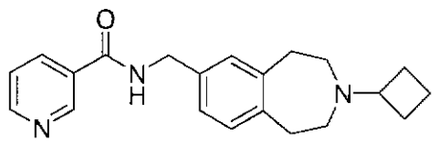


4-Metoxibenzil 3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxilato

1H NMR (400 MHz, $CDCl_3$) □ 7.81 - 7.87 (m, 1H), 7.80 (s, 1H), 7.35 - 7.41 (m, 2H), 7.13 - 7.19 (m, 1H), 6.88 - 6.94 (m, 2H), 5.28 (s, 2H), 3.82 (s, 3H), 3.08 (br. s., 4H), 2.90 - 3.01 (m, 1H), 2.67 (br. s., 4H), 2.07 - 2.24 (m, 4H), 1.56 - 1.81 (m, 2H)

Espectro de Masa: ES^+ 366

2.120 Ejemplo 120

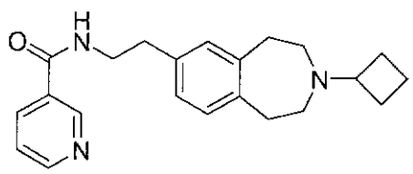


N-((3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)nicotinamida

MS ES^+: 336 (M+H)

^{1}H NMR (400 MHz, MeOD): □ 8.96 - 9.02 (m, 1H), 8.65 - 8.71 (m, 1H), 8.21 - 8.30 (m, 1H), 7.50 - 7.58 (m, 1H), 7.02 - 7.14 (m, 3H), 4.53 (s, 2H), 2.87 - 2.96 (m, 4H), 2.76 - 2.86 (m, 1H), 2.36 - 2.53 (m, 4H), 2.05 - 2.14 (m, 2H), 1.86 - 1.99 (m, 2H), 1.61 - 1.78 (m, 2H)

2.121 Ejemplo 121

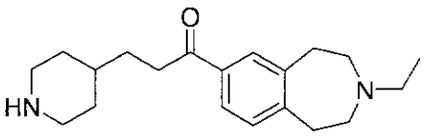


N-(2-(3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)etil)nicotinamida

^{1}H NMR (400 MHz, MeOD) □ 8.78 - 8.98 (m, 1H), 8.58 - 8.71 (m, 1H), 8.08 - 8.27 (m, 1H), 7.39 - 7.64 (m, 1H), 6.92 - 7.14 (m, 3H), 3.49 - 3.72 (m, 2H), 2.71 - 3.01 (m, 7H), 2.44 (br. s., 4H), 2.01 - 2.19 (m, 2H), 1.82 - 2.01 (m, 2H), 1.54 - 1.82 (m, 2H)

Espectro de Masa: ES^+ 350

2.122 Ejemplo 122

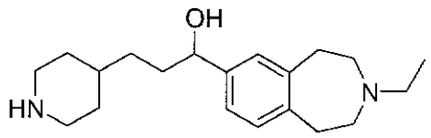


Hidrocloruro de 1-(3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(piperidin-4-il)propan-1-ona

NMR: ^{1}H NMR (400 MHz, D_2O) = 7.74 - 7.86 (m, 2H), 7.31 - 7.39 (m, 1H), 3.65 - 3.78 (m, 2H), 3.31 - 3.41 (m, 2H), 2.85 - 3.31 (m, 12H), 1.86 - 1.99 (m, 2H), 1.55 - 1.70 (m, 3H), 1.33 (ninguno, 6H), 1.22 - 1.44 (m, 5H)

Espectro de Masa: ES^+ 315

2.123 Ejemplo 123

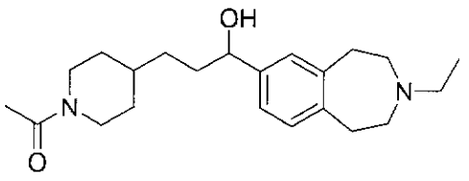


Formiato de 1-(3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(piperidin-4-il)propan-1-ol

NMR: ^{1}H NMR (400 MHz, MeOD) 8.47 (br. s., 2H), 7.11 - 7.29 (m, 3H), 4.50 - 4.65 (m, 1H), 3.43 - 3.55 (m, 2H), 3.06 - 3.41 (m, 10H), 2.89 - 2.99 (m, 2H), 1.83 - 2.01 (m, 2H), 1.63 - 1.83 (m, 2H), 1.51 - 1.66 (m, 1H), 1.12 - 1.50 (m, 9H)

Espectro de Masa: ES^+ 317

2.124 Ejemplo 124

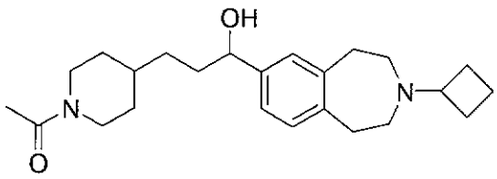


1-(4-(3-(3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-hidroxipropil)piperidin-1-il)etanona

NMR: ^{1}H NMR (400 MHz, MeOD) □ 6.98 - 7.15 (m, 3H), 4.34 - 4.63 (m, 2H), 3.76 - 3.95 (m, 1H), 3.00 - 3.13 (m, 1H), 2.85 - 2.99 (m, 4H), 2.48 - 2.75 (m, 7H), 2.05 (s, 3H), 1.61 - 1.89 (m, 4H), 1.43 - 1.58 (m, 1H), 1.29 - 1.44 (m, 1H), 0.91 - 1.26 (m, 6H)

Espectro de Masa: ES$^+$ 359

2.125 Ejemplo 125

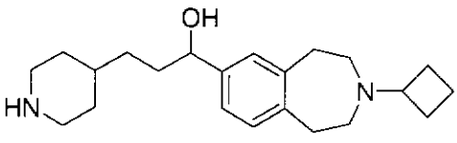


1-(4-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-il)-3-hidroxipropil)piperidina-1-il)etanouno

NMR: ^{1}H NMR (400 MHz, DMSO-d_6) □ 6.95 - 7.08 (m, 3H), 4.99 - 5.10 (m, 1H), 4.22 - 4.47 (m, 2H), 3.64 - 3.82 (m, 1H), 2.85 - 3.02 (m, 1H), 2.65 - 2.86 (m, 5H), 2.21 - 2.47 (m, 5H), 1.88 - 2.06 (m, 5H), 1.69 - 1.86 (m, 2H), 1.47 - 1.68 (m, 6H), 1.35 - 1.45 (m, 1H), 1.20 - 1.34 (m, 1H), 1.05 - 1.19 (m, 1H), 0.90 - 1.04 (m, 1H), 0.74 - 0.90 (m, 1H)

Espectro de Masa: ES$^+$ 385

2.126 Ejemplo 126

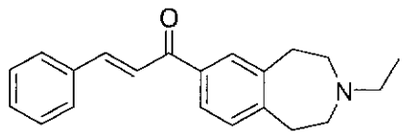


1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(piperidin-4-il)propan-1-ol

NMR: ^{1}H NMR (400 MHz, DMSO-d_6) □ 6.86 - 7.13 (m, 3H), 4.99 (br. s., 1H), 4.28 - 4.45 (m, 1H), 2.59 - 2.94 (m, 7H), 2.16 - 2.44 (m, 5H), 1.88 - 2.12 (m, 2H), 1.68 - 1.86 (m, 2H), 1.40 - 1.66 (m, 7H), 1.14 - 1.36 (m, 2H), 0.98 - 1.13 (m, 2H), 0.76 - 0.98 (m, 2H)

Espectro de Masa: ES$^+$ 343

2.127 Ejemplo127

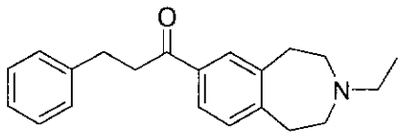


(E)-1-(3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-fenilprop-2-en-1-ona

NMR: ^{1}H NMR (400 MHz, MeOD) □ 7.83 - 7.93 (m, 2H), 7.70 - 7.81 (m, 4H), 7.40 - 7.50 (m, 3H), 7.31 (d, *J* = 7.83 Hz, 1H), 2.99 - 3.16 (m, 4H), 2.53 - 2.86 (m, 6H), 1.07 - 1.22 (m, 3H)

Espectro de Masa: ES$^+$ 306

2.128 Ejemplo 128

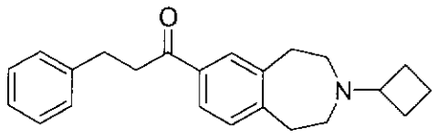


Hidrocloruro de 1-(3-etil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-fenilpropan-1-ona

NMR: ^{1}H NMR (400 MHz, D_2O) □ 7.65 - 7.73 (m, 1H), 7.62 (s, 1H), 7.13 - 7.33 (m, 6H), 3.60 - 3.76 (m, 4H), 2.83 - 3.33 (m, 10H), 1.23 - 1.39 (m, 3H)

Espectro de Masa: ES$^+$ 308

2.129 Ejemplo 129

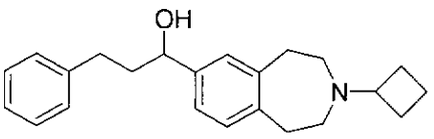


1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-fenilpropan-1-ona

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) □ ppm 1.55 - 1.79 (m, 2 H) 1.82 - 2.01 (m, 2 H) 2.01 - 2.15 (m, 2 H) 2.46 (br. s., 4 H) 2.72 - 2.86 (m, 1 H) 2.92 - 3.03 (m, 4 H) 3.01 - 3.14 (m, 2 H) 3.20 - 3.36 (m, 2 H) 7.09 - 7.42 (m, 6 H) 7.64 - 7.80 (m, 2 H)

Espectro de Masa: ES$^+$ 334

2.130 Ejemplo 130

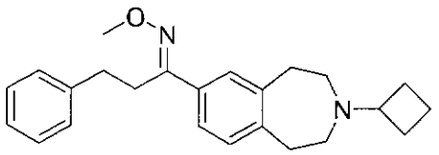


Formiato de 1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-fenilpropan-1-ol

NMR: ^{1}H NMR (400 MHz, MeOD) □ 8.52 (s, 1H), 6.98 - 7.42 (m, 8H), 4.49 - 4.67 (m, 1H), 3.51 - 3.69 (m, 1H), 2.92 - 3.26 (m, 8H), 2.51 - 2.80 (m, 2H), 2.19 - 2.42 (m, 4H), 1.66 - 2.13 (m, 4H)

Espectro de Masa: ES$^+$ 336

2.131 Ejemplo 131

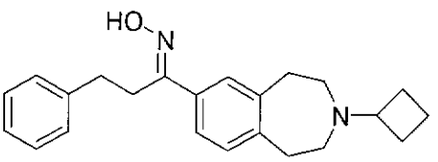


1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-il)-3-fenilpropan-1-ona O-metil oxima

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) □ ppm 1.54 - 1.81 (m, 4 H) 1.93 (br. s., 2 H) 2.01 - 2.18 (m, 2 H) 2.45 (br. s., 3 H) 2.73 - 3.06 (m, 6 H) 3.07 - 3.22 (m, 2 H) 3.61 (s, 3 H) 6.69 (s, 1 H) 6.76 - 6.90 (m, 1 H) 7.04 - 7.13 (m, 1 H) 7.13 - 7.21 (m, 3 H) 7.21 - 7.34 (m, 2 H)

Espectro de Masa: ES$^+$ 363

2.132 Ejemplo 132

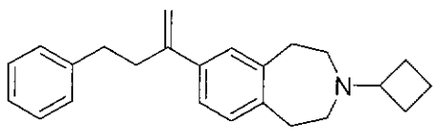


1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-fenilpropan-1-ona oxima

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) □ 7.03 - 7.61 (m, 9H), 3.02 - 3.12 (m, 2H), 2.85 - 3.01 (m, 6H), 2.73 - 2.85 (m, 1H), 2.47 (br. s., 4H), 2.02 - 2.17 (m, 2H), 1.84 - 2.02 (m, 2H), 1.48 - 1.79 (m, 2H)

Espectro de Masa: ES^+ 349

2.133 Ejemplo 133

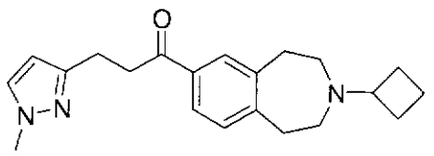


3-ciclobutil-7-(4-fenilbut-1-en-2-il)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) □ 7.13 - 7.40 (m, 7H), 7.02 - 7.13 (m, 1H), 5.22 - 5.38 (m, 1H), 5.04 (s, 1H), 2.93 (br. s., 4H), 2.68 - 2.86 (m, 5H), 2.47 (br. s., 4H), 1.99 - 2.17 (m, 2H), 1.82 - 2.00 (m, 2H), 1.51 - 1.79 (m, 2H)

Espectro de Masa: ES^+ 332

2.134 Ejemplo 134

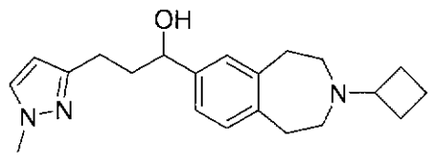


1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(1-metil-1H-pirazol-3-il)propan-1-ona

NMR: ^{1}H NMR (400 MHz, $CDCl_3$) □ 7.67 - 7.82 (m, 2H), 7.22 - 7.31 (m, 1H), 7.12 - 7.22 (m, 1H), 6.04 - 6.14 (m, 1H), 3.85 (s, 3H), 3.29 - 3.41 (m, 2H), 3.07 (t, J = 7.58 Hz, 2H), 2.97 (br. s., 4H), 2.71 - 2.84 (m, 1H), 2.45 (br. s., 4H), 2.02 - 2.16 (m, 2H), 1.82 - 2.01 (m, 2H), 1.53 - 1.79 (m, 2H)

Espectro de Masa: ES^+ 338

2.135 Ejemplo 135

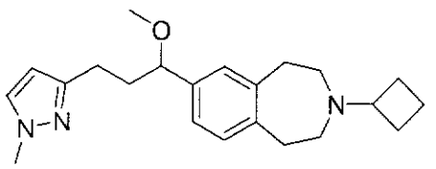


1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(1-metil-1H-pirazol-3-il)propan-1-ol

NMR: ^{1}H NMR (400 MHz, MeOD) □ 7.35 - 7.54 (m, 1H), 6.94 - 7.24 (m, 3H), 5.94 - 6.21 (m, 1H), 4.46 - 4.71 (m, 1H), 3.69 - 3.90 (m, 3H), 2.75 - 3.04 (m, 5H), 2.29 - 2.73 (m, 6H), 1.84 - 2.28 (m, 5H), 1.55 - 1.82 (m, 3H)

Espectro de Masa: ES$^+$ 323 (M-16)

2.136 Ejemplo 136



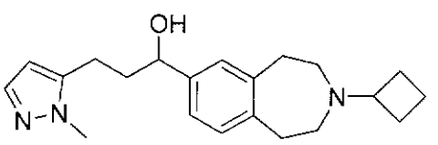
Hidrocloruro de 3-ciclobutil-7-(1-metoxi-3-(1-metil-1H-pirazol-3-il)propil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

NMR: ^{1}H NMR (400 MHz, MeOD) □ 7.74 - 8.08 (m, 1H), 6.98 - 7.38 (m, 3H), 6.31 - 6.53 (m, 1H), 4.10 - 4.26 (m, 1H), 3.93 - 4.09 (m, 3H), 3.60 - 3.85 (m, 4H), 3.33 - 3.50 (m, 2H), 2.98 - 3.24 (m, 4H), 2.65 - 2.96 (m, 4H), 2.26 - 2.62 (m, 4H), 1.68 - 2.22 (m, 4H)

Espectro de Masa: ES$^+$ 322 (M-32)

2.137 Ejemplo 137

1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(1-metil-1H-pirazol-5-il)propan-1-ol

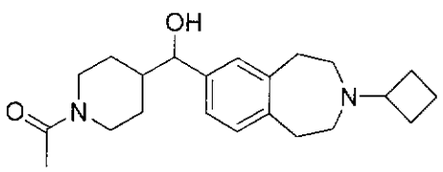


^{1}H NMR: (400 MHz, MeOD) 7.34 (s, 1H), 7.06 - 7.18 (m, 3H), 6.09 (s, 1H), 4.52 - 4.70 (m, 1H), 3.66 - 3.79 (m, 3H), 2.79 - 3.01 (m, 5H), 2.61 - 2.79 (m, 2H), 2.49 (br. s., 4H), 1.87 - 2.19 (m, 6H), 1.59 - 1.82 (m, 2H)

MS ES$^+$: 340

2.138 Ejemplo138

1-(4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)(hidroxi)metil)piperidin-1-il)etanona

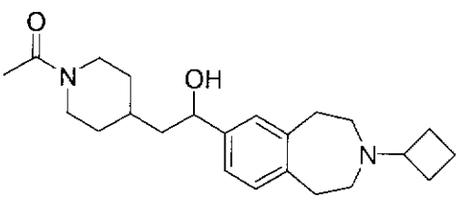


^{1}H NMR: (400 MHz, MeOD) 7.00 - 7.16 (m, 3H), 4.42 - 4.64 (m, 1H), 4.27 - 4.34 (m, 1H), 3.80 - 4.01 (m, 1H), 2.78 - 3.12 (m, 6H), 2.36 - 2.63 (m, 5H), 1.61 - 2.21 (m, 10H), 1.05 - 1.44 (m, 4H)

MS ES$^+$: 357

2.139 Ejemplo 139

1-(4-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxietil)piperidin-1-il)etanona

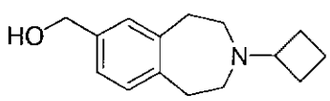


^{1}H NMR: (400 MHz, MeOD) 7.00 - 7.18 (m, 3H), 4.66 - 4.74 (m, 1H), 4.42 - 4.55 (m, 1H), 3.84 - 3.96 (m, 1H), 3.01 - 3.16 (m, 1H), 2.86 - 3.01 (m, 5H), 2.46 - 2.69 (m, 5H), 2.05 -

2.20 (m, 5H), 1.91 - 2.05 (m, 2H), 1.62 - 1.91 (m, 6H), 1.48 - 1.62 (m, 1H), 1.03 - 1.31 (m, 2H)

MS ES$^+$: 371

2.140 Ejemplo 140

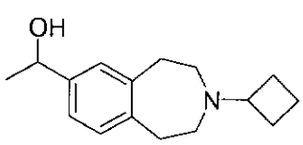


(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metanol

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) 7.01 - 7.15 (m, 3H), 4.55 (s, 2H), 2.72 - 3.03 (m, 5H), 2.30 - 2.61 (m, 4H), 2.05 - 2.19 (m, 2H), 1.86 - 2.04 (m, 2H), 1.59 - 1.81 (m, 2H)

MS ES$^+$: 232

2.141 Ejemplo 141

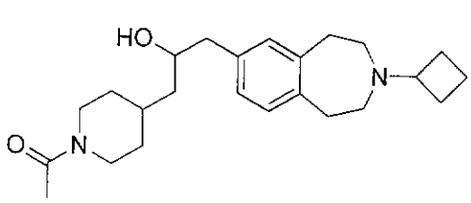


1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)etanol

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) 7.04 - 7.16 (m, 3H), 4.75 - 4.81 (m, 1H), 2.81 - 2.98 (m, 5H), 2.41 - 2.59 (m, 4H), 2.07 - 2.17 (m, 2H), 1.89 - 2.03 (m, 2H), 1.63 - 1.79 (m, 2H), 1.39 - 1.46 (m, 3H)

MS ES$^+$: 246

2.142 Ejemplo 142 racémico

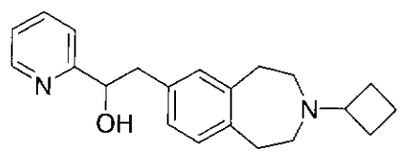


1-(4-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)etanona

^{1}H NMR (400 MHz, MeOD) □ 6.92 - 7.09 (m, 3H), 4.38 - 4.54 (m, 1H), 3.81 - 3.96 (m, 2H), 3.01 - 3.17 (m, 1H), 2.81 - 2.98 (m, 5H), 2.38 - 2.76 (m, 7H), 2.05 - 2.18 (m, 5H), 1.90 - 2.04 (m, 2H), 1.61 - 1.89 (m, 5H), 1.28 - 1.48 (m, 2H), 0.83 - 1.27 (m, 2H)

MS ES+ :385

2.143 Ejemplo 143



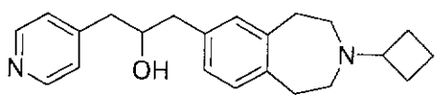
2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-(piridin-2-il)etanol

^{1}H NMR (400 MHz, MeOD) □ 8.41 - 8.53 (m, 1H), 7.75 - 7.87 (m, 1H), 7.41 - 7.57 (m, 1H), 7.26 - 7.37 (m, 1H), 6.85 - 7.02 (m, 3H), 4.86 - 4.97 (m, 1H), 3.04 - 3.14 (m, 1H), 2.77 - 2.98 (m, 6H), 2.46 (br. s., 4H), 2.04 - 2.20 (m, 2H), 1.87 - 2.03 (m, 2H), 1.57 - 1.82 (m, 2H)

MS ES+ :323

2.144 Ejemplo 144 racémico

1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(piridin-4-il)propan-2-ol

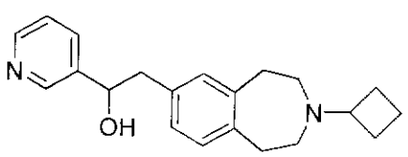


^{1}H NMR (400 MHz, MeOD) □ 8.29 - 8.36 (m, 2H), 7.19 - 7.28 (m, 2H), 6.88 - 7.02 (m, 3H), 3.94 - 4.03 (m, 1H), 2.75 - 2.91 (m, 6H), 2.59 - 2.73 (m, 3H), 2.43 (br. s., 4H), 1.99 - 2.12 (m, 2H), 1.82 - 1.98 (m, 2H), 1.55 - 1.75 (m, 2H)

MS ES+ :337

2.145 Ejemplo 145

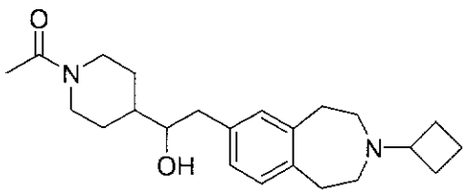
2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-(piridin-3-il)etanol



^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.61 – 8.62 (m, 1H), 8.53 – 8.55 (m, 1H), 7.73 – 7.75 (m, 1H), 7.28 – 7.31 (m, 1H), 7.03 – 7.05 (m, 1H), 6.96 – 6.98 (m, 2H), 4.92 – 4.95 (m, 1H), 2.88 – 3.04 (m, 2H), 2.86 (s, 4H), 2.78 (s, 1H), 2.53 (s, 1H), 2.44 (s, 4H), 2.04 – 2.10 (m, 2H), 1.63 (s, 2H), 1.58 – 1.72 (m, 2H).

MS ES$^+$: 323

2.146 Ejemplo 146 racémico



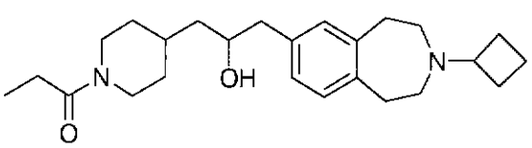
1-(4-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-hidroxietil)piperidin-1-il)etanona

^{1}H NMR (400 MHz, MeOD) ¯ 6.95 - 7.09 (m, 3H), 4.51 - 4.66 (m, 1H), 3.97 (br. s., 1H), 3.54 - 3.69 (m, 1H), 3.01 - 3.13 (m, 1H), 2.73 - 2.99 (m, 6H), 2.34 - 2.69 (m, 6H), 2.05 - 2.20 (m, 5H), 1.84 - 2.05 (m, 3H), 1.56 - 1.82 (m, 4H), 1.16 - 1.56 (m, 2H)

MS ES+ :371

2.147 Ejemplo 147

1-(4-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)propan-1-ona - racémico

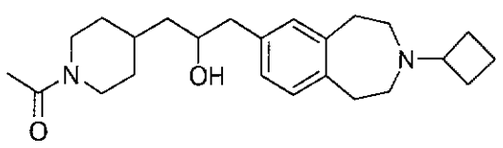


^{1}H NMR: (400 MHz, MeOD) ¯ 6.92 - 7.06 (m, 3 H), 4.42 - 4.53 (m, 1 H), 3.80 - 3.98 (m, 2 H), 2.98 - 3.17 (m, 1 H), 2.79 - 2.97 (m, 5 H), 2.34 - 2.76 (m, 9 H), 2.06 - 2.18 (m, 2 H), 1.89 - 2.04 (m, 2 H), 1.59 - 1.89 (m, 5 H), 1.26 - 1.48 (m, 2 H), 1.11 (m, 5 H)

MS ES$^+$: 399

2.148 Ejemplo 148

1-(4-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)etanona – enantiómero único

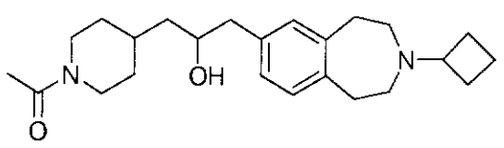


^{1}H NMR: (400 MHz, MeOD)]

MS ES$^+$:

2.149 Ejemplo 149

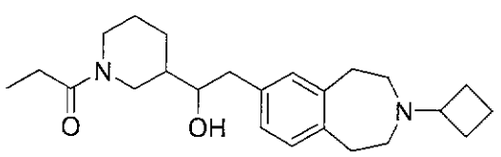
1-(4-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)etanona – enantiómero único



^{1}H NMR: (400 MHz, MeOD)]

MS ES$^+$:

2.150 Ejemplo 150 (racémico)

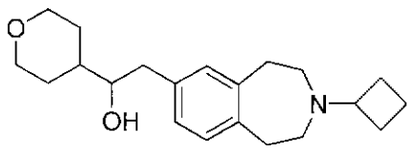


1-(4-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-hidroxietil)piperidin-1-il)propan-1-ona

^{1}H NMR (400 MHz, MeOD) □ 6.72 - 6.88 (m, 3H), 4.38 (br. s., 1H), 3.79 (br. s., 1H), 3.32 - 3.44 (m, 1H), 2.76 - 2.90 (m, 1H), 2.52 - 2.76 (m, 6H), 2.12 - 2.48 (m, 8H), 1.90 (br. s., 2H), 1.63 - 1.84 (m, 3H), 1.33 - 1.59 (m, 4H), 1.13 (br. s., 2H), 0.85 - 0.96 (m, 3H)

MS ES+ :385

2.151 Ejemplo 151 racémico

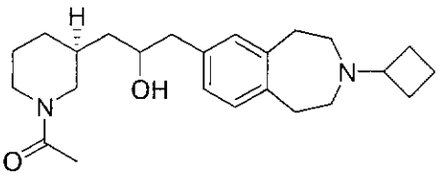


2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-(tetrahidro-2H-piran-4-il)etanol

^{1}H NMR (400 MHz, MeOD) □ 6.92 - 7.08 (m, 3H), 3.90 - 4.06 (m, 2H), 3.49 - 3.62 (m, 1H), 3.37 - 3.45 (m, 1H), 2.75 - 2.99 (m, 7H), 2.32 - 2.66 (m, 5H), 2.05 - 2.19 (m, 2H), 1.87 - 2.04 (m, 2H), 1.38 - 1.85 (m, 7H)

MS ES+ : 330

2.152 Ejemplo 152

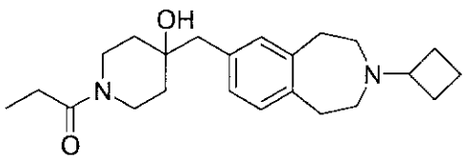


1-((3S)-3-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)etanona

^{1}H NMR (400 MHz, $CDCl_3$) □ ppm 1.11 - 1.31 (m, 1 H) 1.58 (br. s., 13 H) 2.01 - 2.25 (m, 5 H) 2.77 (d, *J*=2.02 Hz, 11 H) 3.61 - 4.04 (m, 2 H) 4.25 - 4.49 (m, 1 H) 6.96 (br. s., 2 H) 7.05 (d, *J*=7.83 Hz, 1 H)

MS ES+ :385

2.153 Ejemplo 153

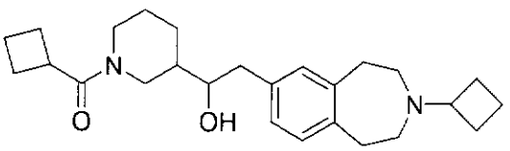


1-(4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-4-hidroxipiperidin-1-il)propan-1-ona

^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 0.81 - 0.96 (m, 3 H) 1.15 - 1.40 (m, 4 H) 1.42 - 1.61 (m, 2 H) 1.62 - 1.80 (m, 2 H) 1.86 - 2.03 (m, 2 H) 2.11 - 2.35 (m, 6 H) 2.54 (s, 2 H) 2.60 - 2.87 (m, 6 H) 3.11 - 3.22 (m, 1 H) 3.44 - 3.57 (m, 1 H) 3.93 - 4.08 (m, 1 H) 4.29 (s, 1 H) 6.80 - 6.96 (m, 3 H)

MS ES+ :371

2.154 Ejemplo 154

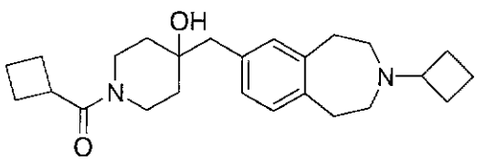


ciclobutil(3-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-hidroxietil)piperidin-1-il)metanona

^{1}H NMR (400 MHz, MeOD) δ 6.84 - 7.09 (m, 3 H) 4.43 - 4.66 (m, 1 H) 3.76 - 3.94 (m, 1 H) 3.52 - 3.66 (m, 1 H) 3.35 - 3.47 (m, 1 H) 2.93 - 3.02 (m, 1 H) 2.85 - 2.93 (m, 4 H) 2.76 - 2.83 (m, 1 H) 2.57 - 2.65 (m, 1 H) 2.52 - 2.59 (m, 1 H) 2.47 (s, 4 H) 2.06 - 2.35 (m, 6 H) 1.78 - 2.05 (m, 5 H) 1.52 - 1.78 (m, 4 H) 1.16 - 1.43 (m, 3 H).

MS ES$^+$ 411

2.155 Ejemplo 155

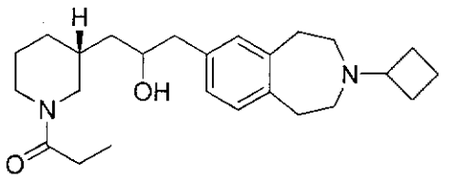


ciclobutil(4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-4-hidroxipiperidin-1-il)metanona

^{1}H NMR (400 MHz, DMSO-d_6) ppm 1.12 - 1.36 (m, 4 H) 1.42 - 1.85 (m, 6 H) 1.87 - 2.10 (m, 6 H) 2.15 - 2.39 (m, 4 H) 2.53 (s, 2 H) 2.59 - 2.89 (m, 6 H) 3.03 - 3.23 (m, 2 H) 3.28 - 3.39 (m, 1 H) 3.87 - 4.03 (m, 1 H) 4.27 (s, 1 H) 6.75 - 6.99 (m, 3 H)

MS ES+ :397

2.156 Ejemplo 156

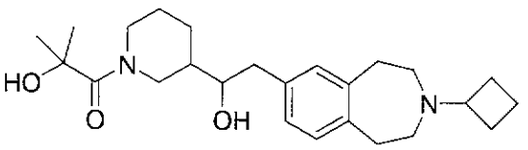


1-((3R)-3-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)etanona

^{1}H NMR (400 MHz, MeOD) δ 6.85 - 7.11 (m, 3 H) 4.19 - 4.43 (m, 1 H) 3.68 - 3.98 (m, 2 H) 2.58 - 3.19 (m, 9 H) 2.28 - 2.57 (m, 5 H) 1.55 - 2.18 (m, 9 H) 1.01 - 1.55 (m, 8 H)

MS ES$^+$ 399

2.157 Ejemplo 157



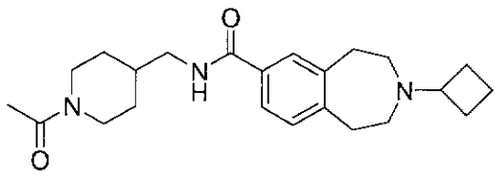
1-(4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-4-hidroxipiperidin-1-il)-2-hidroxi-2-metilpropan-1-ona

^{1}H NMR (400 MHz, DMSO-d_6) d ppm 1.28 (s, 6 H) 1.31 - 1.47 (m, 4 H) 1.49 - 1.68 (m, 2 H) 1.68 - 1.86 (m, 2 H) 1.91 - 2.07 (m, 2 H) 2.23 - 2.43 (m, 4 H) 2.60 (s, 2 H) 2.67 - 2.86 (m, 5 H) 4.33 (s, 1 H) 5.27 (s, 1 H) 6.84 - 7.06 (m, 3 H) 4H no fueron asignados.

MS ES+ :401

2.158 Ejemplo 158

000337

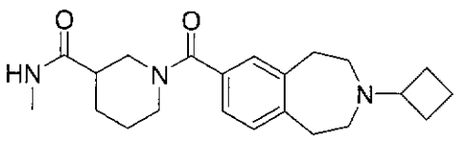


N-((1-acetilpiperidin-4-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, CLOROFORMO-d) □ 7.36 - 7.49 (m, 2H), 7.04 - 7.14 (m, 1H), 6.06 - 6.18 (m, 1H), 4.48 - 4.64 (m, 1H), 3.69 - 3.83 (m, 1H), 3.30 - 3.41 (m, 1H), 3.17 - 3.29 (m, 1H), 2.81 - 3.04 (m, 5H), 2.64 - 2.79 (m, 1H), 2.23 - 2.56 (m, 5H), 1.94 - 2.08 (m, 6H), 1.43 - 1.90 (m, 4H), 0.98 - 1.27 (m, 4H)

MS ES$^+$ 384

2.159 Ejemplo 159

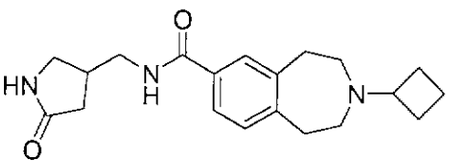


1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carbonil)-N-metilpiperidina-3-carboxamida

NMR: ^{1}H NMR (400 MHz, METANOL-d_4) □ 7.00 - 7.47 (m, 3H), 4.38 - 4.65 (m, 1H), 3.61 - 3.86 (m, 1H), 2.25 - 3.21 (m, 15H), 2.06 - 2.22 (m, 2H), 1.40 - 2.04 (m, 8H)

MS ES$^-$ 370

2.160 Ejemplo 160

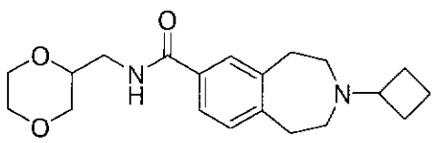


3-ciclobutil-N-((5-oxopirrolidin-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.52 - 7.68 (m, 2H), 7.17 - 7.29 (m, 1H), 3.39 - 3.59 (m, 3H), 3.18 - 3.28 (m, 1H), 2.93 - 3.08 (m, 4H), 2.76 - 2.92 (m, 2H), 2.36 - 2.63 (m, 5H), 2.06 - 2.26 (m, 3H), 1.87 - 2.04 (m, 2H), 1.61 - 1.82 (m, 2H)

MS ES$^+$ 342

2. 161 Ejemplo 161

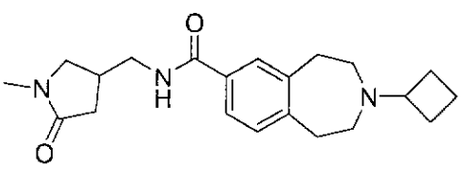


N-((1,4-dioxan-2-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.38 - 7.54 (m, 2H), 7.02 - 7.16 (m, 1H), 3.53 - 3.76 (m, 5H), 3.41 - 3.52 (m, 1H), 3.23 - 3.34 (m, 3H), 2.81 - 2.96 (m, 4H), 2.67 - 2.80 (m, 1H), 2.25 - 2.51 (m, 4H), 1.93 - 2.07 (m, 2H), 1.76 - 1.90 (m, 2H), 1.50 - 1.69 (m, 2H)

MS ES$^+$ 345

2.162 Ejemplo 162

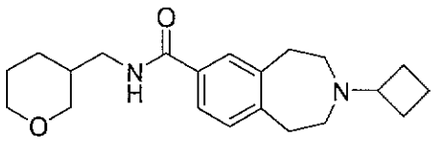


3-ciclobutil-N-((1-metil-5-oxopirrolidin-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.43 - 7.57 (m, 2H), 7.12 - 7.21 (m, 1H), 6.24 - 6.39 (m, 1H), 3.40 - 3.65 (m, 3H), 3.19 - 3.28 (m, 1H), 2.90 - 3.03 (m, 4H), 2.67 - 2.89 (m, 5H), 2.35 - 2.64 (m, 5H), 2.15 - 2.28 (m, 1H), 2.03 - 2.15 (m, 2H), 1.85 - 1.99 (m, 2H), 1.58 - 1.77 (m, 2H)

MS ES$^-$ 356

2.163 Ejemplo 163

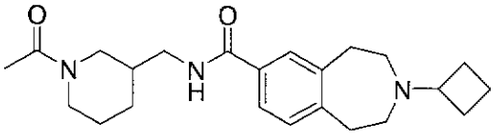


3-ciclobutil-N-((tetrahidro-2H-piran-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.52 - 7.64 (m, 2H), 7.16 - 7.26 (m, 1H), 3.77 - 3.94 (m, 2H), 3.37 - 3.52 (m, 2H), 3.21 - 3.29 (m, 2H), 2.94 - 3.05 (m, 4H), 2.78 - 2.92 (m, 1H), 2.36 - 2.61 (m, 4H), 2.06 - 2.19 (m, 2H), 1.84 - 2.01 (m, 4H), 1.54 - 1.80 (m, 5H)

MS ES$^+$ 343

2.164 Ejemplo 164

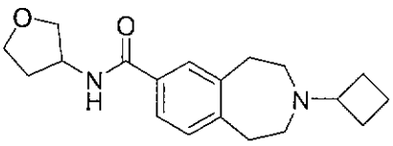


N-((1-acetilpiperidin-3-il)metil)-3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.53 - 7.69 (m, 2H), 7.16 - 7.28 (m, 1H), 4.23 - 4.41 (m, 1H), 3.74 - 3.92 (m, 1H), 3.13 - 3.27 (m, 2H), 2.74 - 3.09 (m, 6H), 2.39 - 2.73 (m, 4H), 2.05 - 2.18 (m, 5H), 1.64 - 2.05 (m, 7H), 1.28 - 1.61 (m, 2H), 0.83 - 0.95 (m, 1H)

MS ES$^+$ 384

2.165 Ejemplo 165



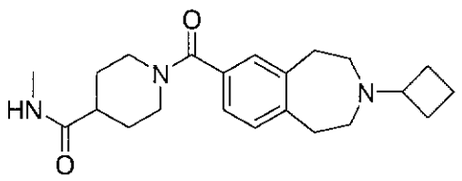
3-ciclobutil-N-(tetrahidrofuran-3-il)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.53 - 7.67 (m, 2H), 7.16 - 7.26 (m, 1H), 4.52 - 4.65 (m, 1H), 3.92 - 4.07 (m, 2H), 3.78 - 3.91 (m, 1H), 3.65 - 3.77 (m, 1H), 2.93 - 3.07 (m, 4H), 2.79 -

2.93 (m, 1H), 2.38 - 2.67 (m, 4H), 2.24 - 2.38 (m, 1H), 2.06 - 2.20 (m, 2H), 1.87 - 2.07 (m, 3H), 1.59 - 1.82 (m, 2H)

MS ES^+ 315

2.166 Ejemplo 166

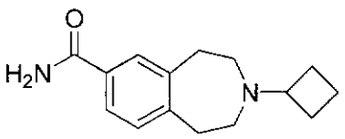


1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carbonil)-N-metilpiperidina-4-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.14 - 7.25 (m, 3H), 4.53 - 4.76 (m, 1H), 3.74 - 3.91 (m, 1H), 2.79 - 3.21 (m, 7H), 2.67 - 2.78 (m, 4H), 2.36 - 2.63 (m, 4H), 2.06 - 2.21 (m, 2H), 1.83 - 2.03 (m, 3H), 1.55 - 1.82 (m, 5H)

MS ES^+ 370

2.167 Ejemplo 167

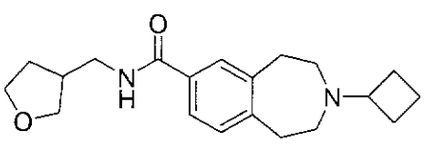


3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) 7.64 (br. s., 2H), 7.22 (d, *J* = 7.83 Hz, 1H), 2.76 - 3.09 (m, 5H), 2.50 (br. s., 4H), 2.12 (br. s., 2H), 1.86 - 2.04 (m, 2H), 1.57 - 1.86 (m, 2H)

MS ES^- 245

2.168 Ejemplo 168

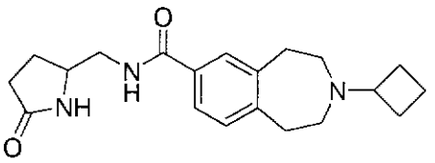


3-ciclobutil-N-((tetrahidrofuran-3-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.48 - 7.67 (m, 2H), 7.12 - 7.29 (m, 1H), 3.66 - 3.96 (m, 3H), 3.53 - 3.66 (m, 1H), 3.35 - 3.45 (m, 2H), 2.91 - 3.06 (m, 4H), 2.74 - 2.92 (m, 1H), 2.28 - 2.68 (m, 5H), 1.84 - 2.19 (m, 5H), 1.57 - 1.81 (m, 3H)

MS ES$^+$ 329

2.169 Ejemplo 169

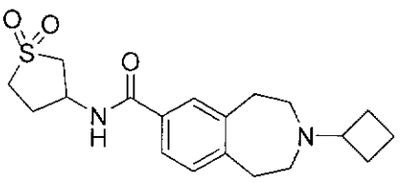


3-ciclobutil-N-((5-oxopirrolidin-2-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, MeOD) □ 7.42 - 7.54 (m, 2H), 7.02 - 7.16 (m, 1H), 3.74 - 3.86 (m, 1H), 3.26 - 3.43 (m, 2H), 2.81 - 2.93 (m, 4H), 2.64 - 2.80 (m, 1H), 2.28 - 2.51 (m, 4H), 2.10 - 2.29 (m, 3H), 1.92 - 2.05 (m, 2H), 1.74 - 1.90 (m, 3H), 1.50 - 1.68 (m, 2H)

MS ES$^+$ 342

2.170 Ejemplo 170



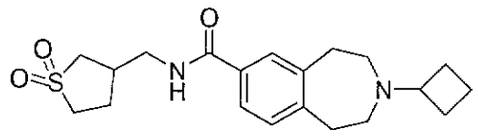
3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-ácido carboxílico(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-amida

^{1}H NMR (400 MHz, $CDCl_3$) □ 7.46 - 7.58 (m, 2H), 7.09 - 7.22 (m, 1H), 6.64 - 6.80 (m, 1H), 4.95 - 5.09 (m, 1H), 3.39 - 3.53 (m, 1H), 3.05 - 3.36 (m, 3H), 2.87 - 3.03 (m, 4H), 2.72 -

2.87 (m, 1H), 2.56 - 2.69 (m, 1H), 2.31 - 2.54 (m, 4H), 2.02 - 2.15 (m, 2H), 1.81 - 1.99 (m, 2H), 1.65 - 1.78 (m, 2H)

MS ES^+ 363

2.171 Ejemplo 171

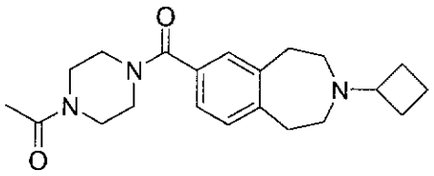


3-Ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-ácido carboxílico(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-ilmetil)-amida

^1H NMR (400 MHz, MeOD) □ 7.55 - 7.66 (m, 2H), 7.19 - 7.26 (m, 1H), 3.45 - 3.60 (m, 2H), 3.18 - 3.29 (m, 2H), 3.05 - 3.17 (m, 1H), 2.95 - 3.05 (m, 4H), 2.74 - 2.95 (m, 3H), 2.31 - 2.62 (m, 5H), 2.06 - 2.19 (m, 2H), 1.88 - 2.04 (m, 3H), 1.62 - 1.80 (m, 2H)

MS ES^+ 377

2.172 Ejemplo 172

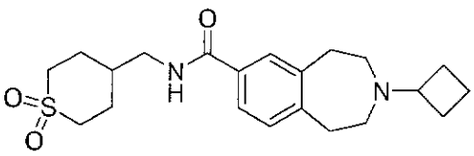


1-(4-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carbonil)piperazin-1-il)etanona

^1H NMR (400 MHz, MeOD) ¯ ppm 1.67 - 2.01 (m, 2 H) 2.07 - 2.28 (m, 3 H) 2.40 (br. s., 4 H) 2.70 - 2.95 (m, 2 H) 3.04 - 3.27 (m, 2 H) 3.41 - 4.00 (m, 13 H) 7.17 - 7.45 (m, 3 H)

MS ES+ 356

2.173 Ejemplo 173

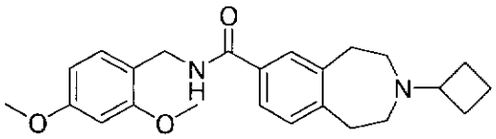


1,1-Dioxo-tetrahidro-1lambda*6*-tiopiran-4-ácido carboxílico(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-ilmetil)-amida

^{1}H NMR (400 MHz, MeOD) □ 7.00 - 7.11 (m, 3H), 4.27 - 4.35 (m, 2H), 3.06 - 3.23 (m, 5H), 2.86 - 3.00 (m, 5H), 2.42 - 2.62 (m, 4H), 2.08 - 2.36 (m, 6H), 1.90 - 2.06 (m, 2H), 1.63 - 1.81 (m, 2H)

MS ES$^+$ 391

2.174 Ejemplo 174



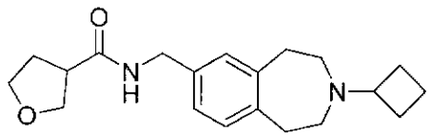
3-ciclobutil-N-(2,4-dimetoxibenzil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-carboxamida

^{1}H NMR (400 MHz, DMSO) □ 8.63 (t, 1H), 7.64 (d, 1H), 7.62 (d, 1H), 7.19 (d, 1H), 7.07 (d, 1H), 6.55 (d, 1H), 6.47 (dd, 1H), 4.35 (d, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 2.81-2.91 (m, 4H), 2.71-2.81 (m, 1H), 2.28-2.43 (bs, 4H), 1.96-2.05 (m, 2H), 1.71-1.84 (m, 2H), 1.51-1.66 (m, 2H)

MS ES$^+$ 395

2.175 Ejemplo 175

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)tetrahidrofuran-3-carboxamida

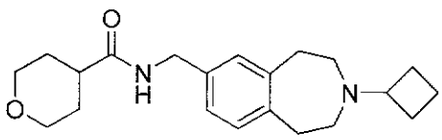


^{1}H NMR: (400 MHz, MeOD) □ 6.96 - 7.13 (m, 3H), 4.25 - 4.39 (m, 2H), 3.85 - 4.02 (m, 2H), 3.74 - 3.85 (m, 2H), 3.00 - 3.13 (m, 1H), 2.79 - 2.99 (m, 5H), 2.49 (br. s., 4H), 2.05 - 2.21 (m, 4H), 1.87 - 2.04 (m, 2H), 1.59 - 1.84 (m, 2H)

MS ES$^+$ 329

2.176 Ejemplo 176

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)tetrahidro-2H-piran-4-carboxamida

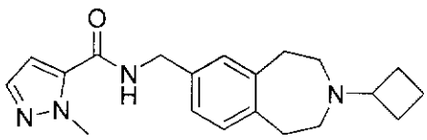


^{1}H NMR: (400 MHz, MeOD) □ 6.99 - 7.12 (m, 3H), 4.31 (s, 2H), 3.95 - 4.02 (m, 2H), 3.39 - 3.53 (m, 2H), 2.77 - 3.01 (m, 5H), 2.33 - 2.59 (m, 4H), 2.06 - 2.20 (m, 2H), 1.88 - 2.04 (m, 2H), 1.64 - 1.87 (m, 6H)

MS ES$^+$ 343

2.177 Ejemplo 177

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-1-metil-1H-pirazol-5-carboxamida

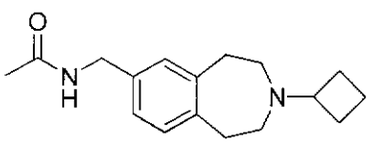


^{1}H NMR: (400 MHz, MeOD) □ 7.39 - 7.55 (m, 1H), 7.04 - 7.19 (m, 3H), 6.76 - 6.86 (m, 1H), 4.48 (s, 2H), 4.09 - 4.21 (m, 3H), 2.79 - 3.00 (m, 5H), 2.50 (br. s., 4H), 2.06 - 2.22 (m, 2H), 1.86 - 2.04 (m, 2H), 1.58 - 1.84 (m, 2H)

MS ES$^+$ 339

2.178 Ejemplo 178

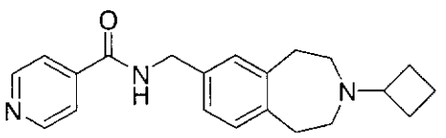
1-(4-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxietil)piperidin-1-il)etanona



^{1}H NMR: (400 MHz, MeOD) □ 6.93 - 7.24 (m, 3H), 4.30 (br. s., 2H), 2.77 - 3.03 (m, 5H), 2.48 (br. s., 4H), 2.06 - 2.21 (m, 2H), 1.88 - 2.05 (m, 5H), 1.61 - 1.82 (m, 2H)

MS ES$^+$ 273

2.179 Ejemplo 2.179

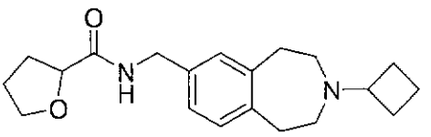


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)isonicotinamida

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) 8.55 - 8.80 (m, 2H), 7.74 - 7.90 (m, 2H), 7.01 - 7.22 (m, 3H), 4.40 - 4.65 (m, 2H), 2.71 - 3.03 (m, 5H), 2.25 - 2.68 (m, 4H), 2.03 - 2.18 (m, 2H), 1.85 - 2.02 (m, 2H), 1.59 - 1.80 (m, 2H)

MS ES$^+$ 336

2.180 Ejemplo 180

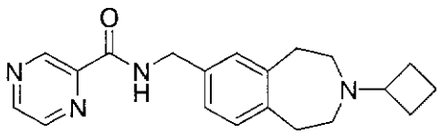


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)tetrahidrofuran-2-carboxamida

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) 6.93 - 7.12 (m, 3H), 4.24 - 4.41 (m, 3H), 3.93 - 4.07 (m, 1H), 3.78 - 3.93 (m, 1H), 2.70 - 3.00 (m, 5H), 2.19 - 2.59 (m, 5H), 2.03 - 2.18 (m, 2H), 1.79 - 2.04 (m, 5H), 1.58 - 1.80 (m, 2H)

MS ES$^+$ 329

2.181 Ejemplo 181

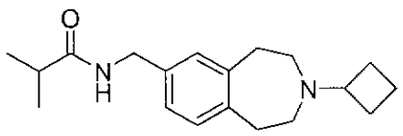


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)pirazina-2-carboxamida

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) □ 9.20 - 9.34 (m, 1H), 8.76 - 8.87 (m, 1H), 8.61 - 8.74 (m, 1H), 7.12 - 7.27 (m, 3H), 4.50 - 4.69 (m, 2H), 3.22 - 3.61 (m, 5H), 3.02 - 3.18 (m, 4H), 2.09 - 2.43 (m, 4H), 1.71 - 1.96 (m, 2H)

MS ES$^+$ 337

2.182 Ejemplo 182

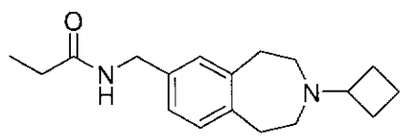


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)isobutiramida

^{1}H NMR: ^{1}H NMR (400 MHz, $CDCl_3$) □ 6.84 - 6.99 (m, 3H), 5.43 - 5.62 (m, 1H), 4.21 - 4.34 (m, 2H), 2.73 - 2.88 (m, 4H), 2.60 - 2.73 (m, 1H), 2.19 - 2.45 (m, 4H), 1.89 - 2.02 (m, 2H), 1.73 - 1.88 (m, 2H), 1.44 - 1.65 (m, 3H), 1.01 - 1.12 (m, 6H)

MS ES$^+$ 301

2.183 Ejemplo183

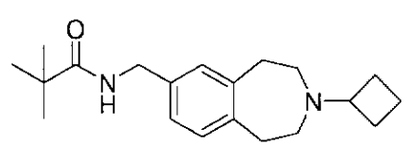


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)propionamida

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) □6.98 - 7.11 (m, 3H), 4.28 - 4.36 (m, 2H), 2.77 - 2.98 (m, 5H), 2.37 - 2.57 (m, 4H), 2.21 - 2.30 (m, 2H), 2.05 - 2.18 (m, 2H), 1.87 - 2.02 (m, 2H), 1.63 - 1.80 (m, 2H), 1.10 - 1.21 (m, 3H)

MS ES$^+$ 287

2.184 Ejemplo184

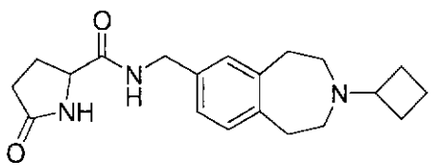


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)pivalamida

^{1}H NMR: ^{1}H NMR (400 MHz, MeOD) 6.95 - 7.11 (m, 3H), 4.26 - 4.35 (m, 2H), 2.80 - 2.96 (m, 5H), 2.39 - 2.57 (m, 4H), 2.06 - 2.18 (m, 2H), 1.89 - 2.02 (m, 2H), 1.61 - 1.81 (m, 2H), 1.22 (s, 9H)

MS ES$^+$ 315

2.185 Ejemplo 185

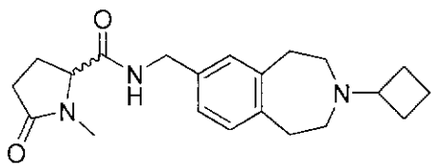


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-5-oxopirrolidina-2-carboxamida

^{1}H NMR (400 MHz, MeOD) ppm 1.59 - 1.81 (m, 2 H) 1.85 - 2.03 (m, 2 H) 2.05 - 2.20 (m, 3 H) 2.24 - 2.62 (m, 7 H) 2.76 - 3.05 (m, 5 H) 4.21 (s, 1 H) 4.28 - 4.41 (m, 2 H) 7.07 (d, 3 H)

MS ES+ 342

2.186 Ejemplo 186



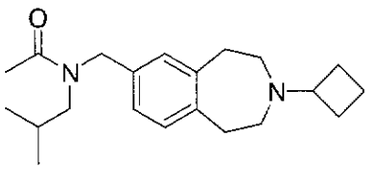
N-((3-ciclobutil-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepin-7-il)metil)-1-metil-5-oxopirrolidina-2-carboxamida

^{1}H NMR (400 MHz, MeOD) ppm 1.50 - 1.85 (m, 2 H) 1.87 - 2.21 (m, 4 H) 2.49 (br. s., 6 H) 2.78 (s, 3 H) 2.93 (br. s., 5 H) 4.05 - 4.25 (m, 1 H) 4.37 (s, 2 H) 7.01 - 7.20 (m, 3 H)

MS ES$^+$ 326

000348

2.187 Ejemplo 187

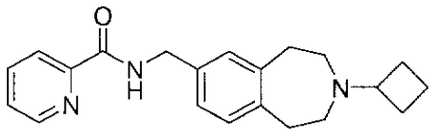


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-N-isobutilacetamida

^{1}H NMR (400 MHz, MeOD) □ 7.04 - 7.15 (m, 1H), 6.92 - 7.02 (m, 2H), 4.56 - 4.62 (m, 2H), 3.19 - 3.23 (m, 1H), 3.10 - 3.16 (m, 1H), 2.81 - 2.99 (m, 5H), 2.49 (br. s., 4H), 2.19 (s, 2H), 2.07 - 2.17 (m, 6H), 1.88 - 2.07 (m, 5H), 1.61 - 1.79 (m, 3H)

MS ES$^+$ 329

2.188 Ejemplo 188

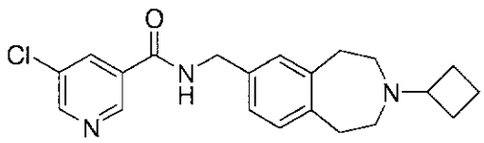


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)picolinamida

^{1}H NMR (400 MHz, DMSO) d ppm 1.41 - 1.83 (m, 2 H) 1.86 - 2.27 (m, 3 H) 2.53 - 2.76 (m, 4 H) 2.75 - 3.13 (m, 3 H) 4.33 - 4.56 (m, 2 H) 6.97 - 7.24 (m, 3 H) 7.51 - 7.69 (m, 1 H) 7.89 - 8.14 (m, 2 H) 8.56 - 8.72 (m, 1 H) 9.09 - 9.33 (m, 1 H)

MS ES+ 336

2.189 Ejemplo 189

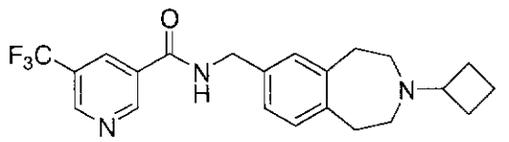


5-Cloro-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)nicotinamida

^{1}H NMR (400 MHz, DMSO) □ ppm 1.44 - 1.68 (m, 2 H) 1.69 - 1.87 (m, 2 H) 1.93 - 2.08 (m, 2 H) 2.18 - 2.45 (m, 4 H) 2.82 (br. s., 5 H) 4.44 (d, 2 H) 6.98 - 7.17 (m, 3 H) 8.34 (t, 1 H) 8.79 (d, 1 H) 8.99 (d, 1 H) 9.17 - 9.30 (m, 1 H)

MS ES+ 370

2.190 Ejemplo 190

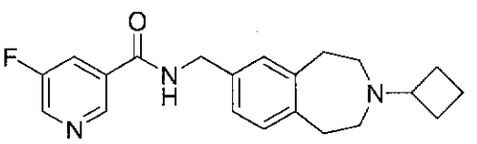


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-5-(trifluorometil)nicotinamida

^{1}H NMR (400 MHz, DMSO) ppm 1.47 - 1.70 (m, 2 H) 1.70 - 1.93 (m, 2 H) 1.93 - 2.12 (m, 2 H) 2.18 - 2.46 (m, 4 H) 2.63 - 3.03 (m, 5 H) 4.39 - 4.54 (m, 2 H) 7.10 (br. s., 3 H) 8.61 (br. s., 1 H) 9.14 (s, 1 H) 9.32 (s, 2 H)

MS ES+ 404

2.191 Ejemplo 191

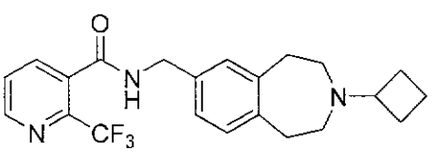


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-5-fluoronicotinamida

^{1}H NMR (400 MHz, DMSO) ppm 1.56 (m, 2 H) 1.69 - 1.87 (m, 2 H) 1.92 - 2.08 (m, 2 H) 2.17 - 2.43 (m, 4 H) 2.82 (br. s., 5 H) 4.41 (s, 2 H) 7.00 - 7.16 (m, 3 H) 7.42 - 7.51 (m, 1 H) 8.12 - 8.26 (m, 1 H) 8.29 - 8.42 (m, 1 H) 8.95 - 9.11 (m, 1 H)

MS ES$^+$ 354

2.192 Ejemplo 192

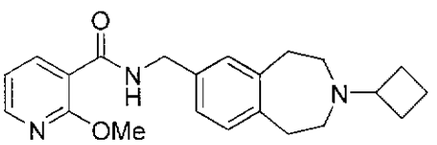


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-(trifluorometil)nicotinamida

^{1}H NMR (400 MHz, DMSO) □ ppm 1.44 - 1.68 (m, 2 H) 1.69 - 1.87 (m, 2 H) 1.92 - 2.07 (m, 2 H) 2.22 - 2.43 (m, 4 H) 2.66 - 2.90 (m, 5 H) 4.32 - 4.46 (m, 2 H) 6.99 - 7.15 (m, 3 H) 7.72 - 7.86 (m, 1 H) 7.98 - 8.12 (m, 1 H) 8.75 - 8.85 (m, 1 H) 9.06 - 9.19 (m, 1 H)

MS ES$^+$ 404

2.193 Ejemplo 193

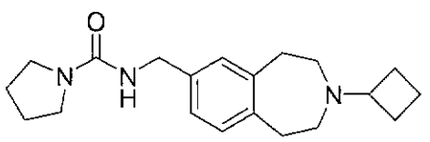


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-metoxinicotinamida

^{1}H NMR (400 MHz, DMSO) □ ppm 1.49 - 1.66 (m, 2 H) 1.69 - 1.86 (m, 2 H) 1.93 - 2.05 (m, 2 H) 2.20 - 2.43 (m, 4 H) 2.67 - 2.86 (m, 5 H) 3.97 (s, 3 H) 4.38 - 4.48 (m, 2 H) 7.02 - 7.08 (m, 3 H) 7.09 - 7.16 (m, 1 H) 8.09 - 8.16 (m, 1 H) 8.27 - 8.34 (m, 1 H) 8.67 - 8.81 (m, 1 H)

MS ES$^+$ 366

2.194 Ejemplo 194

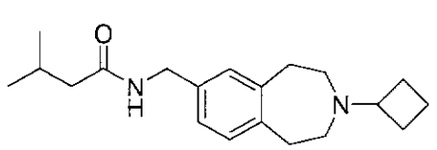


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)pirrolidine-1-carboxamida

^{1}H NMR (400 MHz, DMSO-d6) □ ppm 1.43 - 1.69 (m, 2 H) 1.79 (t, 5 H) 1.92 - 2.10 (m, 2 H) 2.13 - 2.47 (m, 4 H) 2.81 (br. s., 5 H) 3.22 (t, 4 H) 3.28 - 3.55 (m, 1 H) 4.16 (d, 2 H) 6.51 - 6.67 (m, 1 H) 7.00 (br. s., 3 H)

MS ES+ 328

2.195 Ejemplo 195



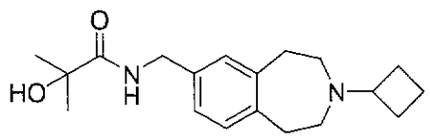
000351

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3-metilbutanamida

^{1}H NMR (400 MHz, METANOL-d4) □ ppm 0.96 (d, 6 H) 1.55 - 1.81 (m, 2 H) 1.84 - 2.01 (m, 2 H) 2.03 - 2.19 (m, 5 H) 2.27 - 2.62 (m, 4 H) 2.72 - 3.03 (m, 5 H) 4.26 - 4.38 (m, 2 H) 7.05 (s, 3 H)

MS ES+ 315

2.196 Ejemplo 196

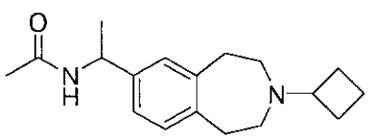


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-hidroxi-2-metilpropanamida

^{1}H NMR (400 MHz, METANOL-d4) □ ppm 1.15 (s, 6 H) 1.35 - 1.57 (m, 2 H) 1.61 - 1.79 (m, 2 H) 1.79 - 1.96 (m, 2 H) 2.06 - 2.38 (m, 4 H) 2.50 - 2.75 (m, 5 H) 4.05 - 4.14 (m, 2 H) 6.81 (d, 3 H)

MS ES+ 317

2.197 Ejemplo 197



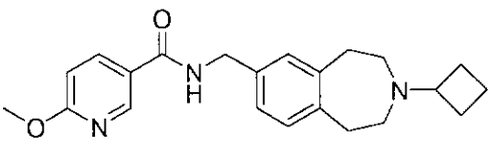
N-(1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)etil)acetamida

^{1}H NMR (400 MHz, METANOL-d_4) □ 7.01 - 7.11 (m, 3H), 2.79 - 2.97 (m, 5H), 2.36 - 2.58 (m, 4H), 2.06 - 2.18 (m, 3H), 1.89 - 2.01 (m, 5H), 1.61 - 1.78 (m, 2H), 1.37 - 1.46 (m, 3H)

MS ES$^+$ 287

2.198 Ejemplo 198

000352

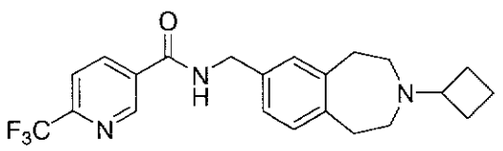


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-metoxinicotinamida

^{1}H NMR (400 MHz, METANOL-d_4) □ ppm 1.72 (nuno, 2 H) 1.87 - 2.10 (m, 2 H) 2.08 - 2.28 (m, 2 H) 2.35 - 2.76 (m, 4 H) 2.95 (br. s., 5 H) 3.98 (s, 3 H) 4.53 (s, 2 H) 6.87 (d, 1 H) 7.05 - 7.21 (m, 3 H) 8.06 - 8.19 (m, 1 H) 8.67 (d, 1 H)

MS ES$^+$ 366

2.199 Ejemplo 199

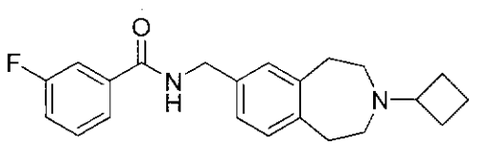


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(trifluorometil)nicotinamida

^{1}H NMR (400 MHz, METANOL-d_4) □ ppm 1.55 (nuno, 2 H) 1.75 - 1.91 (m, 2 H) 1.93 - 2.12 (m, 2 H) 2.18 - 2.60 (m, 4 H) 2.82 (d, 5 H) 4.45 (s, 2 H) 7.01 (d, 3 H) 7.75 - 7.91 (m, 1 H) 8.26 - 8.44 (m, 1 H) 9.02 (s, 1 H)

MS ES$^+$ 404

2.200 Ejemplo 200



N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3-fluorobenzamida

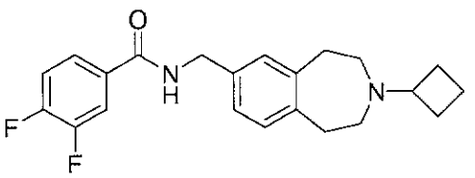
^{1}H NMR (400 MHz, DMSO) □ ppm 1.49 - 1.65 (m, 2 H) 1.69 - 1.84 (m, 2 H) 1.92 - 2.05 (m, 2 H) 2.17 - 2.44 (m, 4 H) 2.68 - 2.86 (m, 5 H) 4.34 - 4.49 (m, 2 H) 6.98 - 7.11 (m, 3 H) 7.34

000353

- 7.43 (m, 1 H) 7.48 - 7.57 (m, 1 H) 7.64 - 7.72 (m, 1 H) 7.72 - 7.79 (m, 1 H) 9.02 - 9.15 (m, 1 H)

MS ES^+ 353

2.201 Ejemplo 201

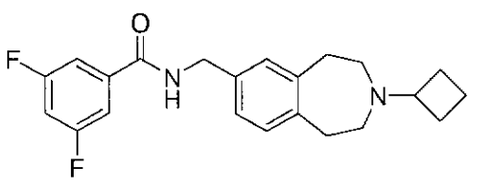


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3,4-difluorobenzamida

^{1}H NMR (400 MHz, METANOL-d_4) □ ppm 1.69 (nuno, 2 H) 1.95 (br. s., 2 H) 2.11 (br. s., 2 H) 2.49 (br. s., 4 H) 2.93 (br. s., 5 H) 4.52 (s, 2 H) 7.11 (br. s., 3 H) 7.30 - 7.52 (m, 1 H) 7.65 - 7.88 (m, 2 H)

MS ES^+ 371

2.202 Ejemplo 202

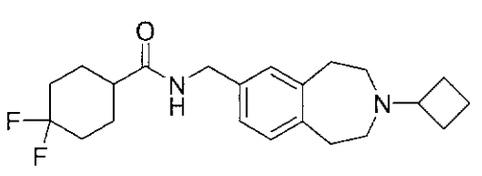


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3,5-difluorobenzamida

^{1}H NMR (400 MHz, METANOL-d_4) □ ppm 1.55 - 1.86 (m, 2 H) 1.86 - 2.07 (m, 2 H) 2.07 - 2.27 (m, 2 H) 2.33 - 2.75 (m, 4 H) 2.95 (br. s., 5 H) 4.52 (s, 2 H) 7.04 - 7.27 (m, 4 H) 7.48 (dd, 2 H)

MS ES^+ 371

2.203 Ejemplo 203

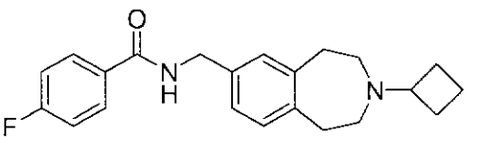


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-4,4-difluorociclohexanocarboxamida

^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.61 (br. s., 4 H) 1.79 (t, 6 H) 2.01 (br. s., 4 H) 2.33 (d, 4 H) 2.80 (br. s., 5 H) 4.19 (d, 2 H) 6.87 - 7.00 (m, 2 H) 7.04 (d, *J*=7.33 Hz, 1 H) 8.30 (br. s., 1 H)

MS ES$^+$ 377

2.204 Ejemplo 204

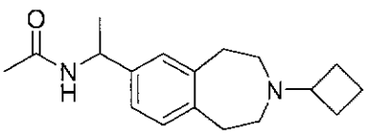


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-4-fluorobenzamida

^{1}H NMR (400 MHz, METANOL-d_4) □ ppm 1.70 (nuno, 2 H) 1.83 - 2.04 (m, 2 H) 2.05 - 2.18 (m, 2 H) 2.34 - 2.65 (m, 4 H) 2.93 (br. s., 5 H) 4.53 (s, 2 H) 7.02 - 7.16 (m, 3 H) 7.16 - 7.26 (m, 2 H) 7.92 (d, 2 H)

MS ES$^+$ 353

2.205 Ejemplo 205

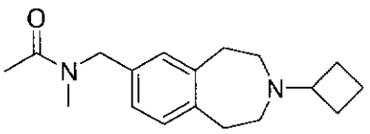


N-(1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)etil)acetamida

NMR: ^{1}H NMR (400 MHz, METANOL-d$_4$) □ 7.00 - 7.15 (m, 3H), 4.90 - 5.03 (m, 1H), 2.81 - 2.98 (m, 5H), 2.42 - 2.57 (m, 4H), 2.05 - 2.19 (m, 2H), 1.90 - 2.03 (m, 5H), 1.62 - 1.79 (m, 2H), 1.37 - 1.48 (m, 3H)

MS ES$^-$ 287

2.206 Ejemplo 206

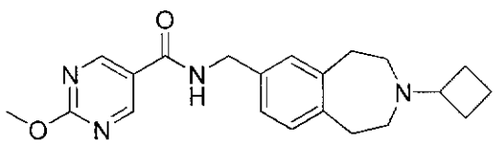


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepina-7-il)metil)-N-metilacetamida

NMR: ^{1}H NMR (400 MHz, METANOL-d_4) □ 7.04 - 7.17 (m, 1H), 6.92 - 7.04 (m, 2H), 4.49 - 4.60 (m, 2H), 2.80 - 3.01 (m, 8H), 2.38 - 2.57 (m, 4H), 2.07 - 2.20 (m, 5H), 1.88 - 2.03 (m, 2H), 1.60 - 1.80 (m, 2H)

MS ES$^+$ 287

2.207 Ejemplo 207

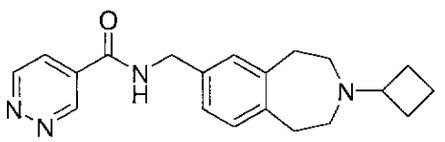


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-metoxipirimidina-5-carboxamida

NMR: ^{1}H NMR (400 MHz, DMSO)□ 9.11 (t, 1H), 9.03 (s, 2H), 7.03-7.10 (m, 3H), 4.43 (d, 2H), 3.98 (s, 3H), 2.70-2.85 (m, 5H), 2.28-2.40 (m, 4H), 1.96-2.04 (m, 2H), 1.72-1.84 (m, 2H), 1.48-1.66 (m, 2H)

MS ES$^+$ 367

2.208 Ejemplo 208

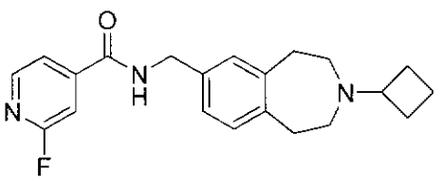


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)piridazina-4-carboxamida

^{1}H NMR (400 MHz, DMSO) 9.56-9.60 (m, 1H), 9.41-9.50 (m, 2H), 8.03 (dd, 1H), 7.04-7.11 (m, 3H), 4.46 (d, 2H), 2.70-2.87 (m, 5H), 2.26-2.42 (m, 4H), 1.95-2.05 (m, 2H), 1.71-1.84 (m, 2H), 1.48-1.66 (m, 2H)

MS ES$^+$ 337

2.209 Ejemplo 209

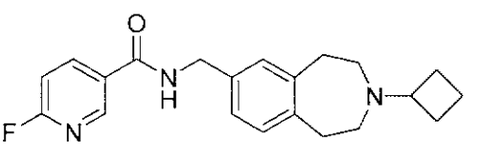


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-fluoroisonicotinamida

^{1}H NMR (400 MHz, DMSO) 9.40 (s, 1H), 8.47 (d, 1H), 7.84 (d, 1H), 7.63 (s, 1H), 7.09-7.17 (m, 3H), 4.50 (d, 2H), 2.87 (bs, 4H), 2.76-2.86 (m, 1H), 2.32-2.47 (bs, 4H), 2.02-2.12 (m, 2H), 1.77-1.90 (m, 2H), 1.57-1.72 (m, 2H)

MS ES$^+$ 354

2.210 Ejemplo 210

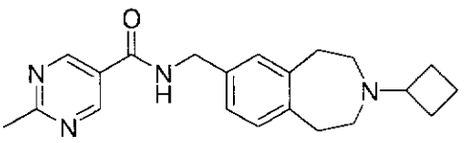


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-fluoronicotinamida

^{1}H NMR (400 MHz, DMSO) 9.12-9.21 (m, 1H), 8.74 (d, 1H), 8.42 (td, 1H), 7.31 (dd, 1H), 7.03-7.09 (m, 3H), 4.43 (d, 2H), 2.70-2.84 (m, 5H), 2.28-2.39 (bs, 4H), 1.95-2.04 (m, 2H), 1.72-1.83 (m, 2H), 1.50-1.66 (m, 2H)

MS ES$^+$ 354

2.211 Ejemplo 211

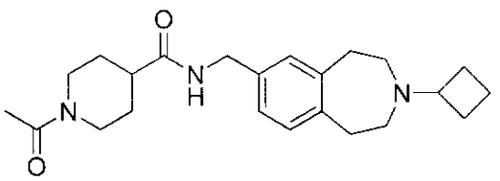


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-metilpirimidina-5-carboxamida

^{1}H NMR (400 MHz, DMSO) 9.23 (t, 1H), 9.09 (s, 2H), 7.03-7.11 (m, 3H), 4.44 (d, 2H), 2.71-2.86 (m, 5H), 2.68 (s, 3H), 2.27-2.42 (m, 4H), 1.95-2.05 (m, 2H), 1.72-1.85 (m, 2H), 1.48-1.66 (m, 2H)

MS ES$^+$ 351

2.212 Ejemplo 212

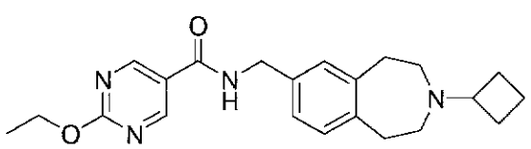


1-acetil-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)piperidina-4-carboxamida

^{1}H NMR (400 MHz, DMSO) 8.10-8.18 (m, 1H), 7.00-7.06 (m, 1H), 6.91-7.00 (m, 2H), 4.28-4.40 (m, 1H), 4.20 (d, 2H), 3.76-3.87 (m, 1H), 2.99-3.09 (m 1H), 2.73-2.86 (m, 5H), 2.53-2.64 (m, 1H), 2.29-2.48 (m, 5H), 1.95-2.07 (m, 5H), 1.67-1.87 (m, 4H), 1.48-1.67 (m, 3H), 1.34-1.49 (m, 1H)

MS ES$^+$ 384

2.213 Ejemplo 213



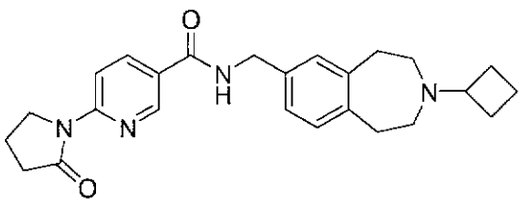
000353

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-etoxipirimidina-5-carboxamida

^{1}H NMR (400 MHz, DMSO) 9.09 (t, 1H), 9.01 (s, 2H), 7.02-7.11 (m, 3H), 4.38-4.47 (m, 4H), 2.66-2.86 (m, 5H), 2.24-2.40 (m, 4H), 1.95-2.04 (m, 2H), 1.71-1.84 (m, 2H), 1.48-1.65 (m, 2H), 1.35 (t, 3H)

MS ES$^+$ 381

2.214 Ejemplo 214

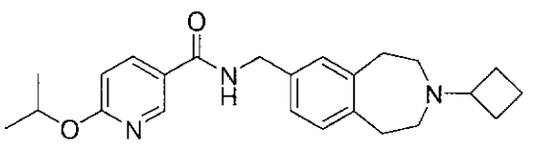


N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(2-oxopirrolidin-1-il)nicotinamida

^{1}H NMR (400 MHz, DMSO) 9.04 (t, 1H), 8.87 (d, 1H), 8.37 (d, 1H), 8.26 (dd, 1H), 7.01-7.10 (m, 3H), 4.43 (d, 2H), 4.03 (t, 2H), 2.66-2.85 (m, 5H), 2.61 (t, 2H), 2.25-2.41 (m, 4H), 1.93-2.12 (m, 4H), 1.70-1.83 (m, 2H), 1.48-1.66 (m, 2H)

MS ES$^+$ 419

2.215 Ejemplo 215



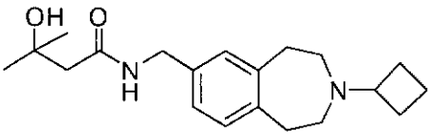
N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-isopropoxinicotinamida

^{1}H NMR (400 MHz, DMSO) 8.94 (t, 1H), 8.68 (d, 1H), 8.13 (dd, 1H), 7.00-7.09 (m, 3H), 6.80 (d, 1H), 5.31 (septet, 1H), 4.41 (d, 2H), 2.72-2.87 (m, 5H), 2.28-2.44 (m, 4H), 1.95-2.05 (m, 2H), 1.73-1.86 (m, 2H), 1.48-1.66 (m, 2H), 1.31 (d, 6H)

MS ES$^+$ 394

2.216 Ejemplo 216

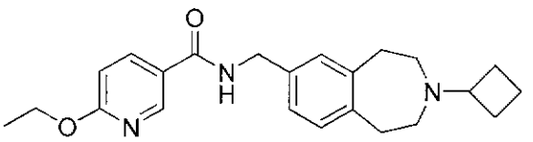
N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3-hidroxi-3-metilbutanamida



^{1}H NMR: (400 MHz, MeOD) □ 6.95 - 7.12 (m, 3 H) 4.34 (s, 2 H) 3.55 (s, 2 H) 2.88 - 2.94 (m, 4 H) 2.78 - 2.88 (m, 1 H) 2.46 (br. s., 4 H) 2.04 - 2.17 (m, 2 H) 1.87 - 2.01 (m, 2 H) 1.58 - 1.79 (m, 2 H) 1.14 - 1.19 (m, 6 H)

MS ES$^+$: 331

2.217 Ejemplo 217



N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-etoxinicotinamida

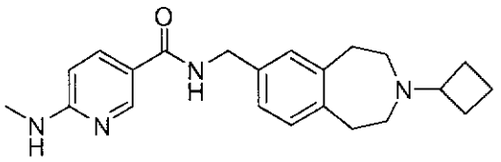
^{1}H NMR (400 MHz, DMSO)□ 8.95 (t, 1H), 8.68 (d, 1H), 8.14 (dd, 1H), 7.01-7.09 (m, 3H), 6.85 (d, 1H), 4.41 (d, 2H), 4.36 (quart, 2H), 2.71-2.86 (m, 5H), 2.26-2.45 (m, 4H), 1.94-2.05 (m, 2H), 1.70-1.86 (m, 2H), 1.47-1.67 (m, 2H), 1.33 (t, 3H)

MS ES$^+$ 380

2.218 Ejemplo 218

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(metilamino)nicotinamida

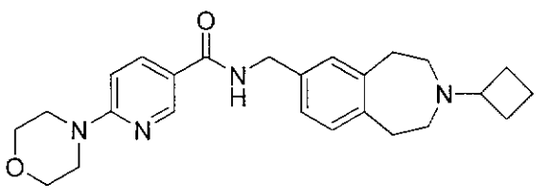
000360



^{1}H NMR: (400 MHz, DMSO-d_6) 8.43 - 8.58 (m, 2 H), 7.77 (m, 1 H), 6.85 - 7.03 (m, 4 H), 6.36 (m, 1 H), 4.22 - 4.36 (m, 2 H), 2.73 (m, 8 H), 2.13 - 2.34 (m, 4 H), 1.85 - 2.01 (m, 2 H), 1.61 - 1.79 (m, 2 H), 1.49 (m, 2 H)

MS ES$^+$: 365

2.219 Ejemplo 219



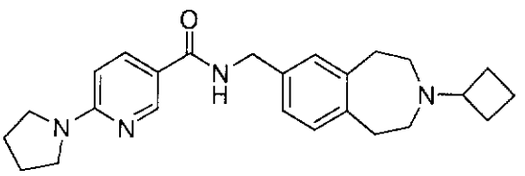
N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-morfolinonicotinamida

^{1}H NMR (400 MHz, DMSO) 8.72 - 8.85 (m, 1H), 8.67 (s, 1H), 7.92 - 8.11 (m, 1H), 6.95 - 7.14 (m, 3H), 6.79 - 6.92 (m, 1H), 4.17 - 4.77 (m, 2H), 3.64 - 3.81 (m, 4H), 3.46 - 3.62 (m, 4H), 2.67 - 2.90 (m, 5H), 2.19 - 2.44 (m, 4H), 1.90 - 2.09 (m, 2H), 1.68 - 1.89 (m, 2H), 1.46 - 1.68 (m, 2H)

MS ES$^+$ 421

2.220 Ejemplo 220

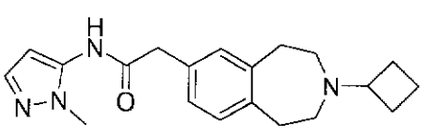
N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(pirrolidin-1-il)nicotinamida



^{1}H NMR: (400 MHz, DMSO-d_6) 8.51 - 8.75 (m, 2 H), 7.95 (m, 1 H), 7.03 (br. s., 3 H), 6.45 (m, 1 H), 4.28 - 4.44 (m, 2 H), 3.38 - 3.53 (m, 4 H), 2.65 - 2.89 (m, 5 H), 2.19 - 2.42 (m, 4 H), 1.95 (br. s., 6 H), 1.66 - 1.85 (m, 2 H), 1.57 (m, 2 H)

MS ES$^+$: 404

2.221 Ejemplo 221

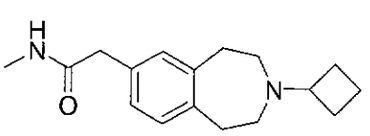


2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-N-(1-metil-1H-pirazol-5-il)acetamida

^{1}H NMR (400 MHz, MeOD) ppm 1.60 - 1.81 (m, 2 H) 1.87 - 2.05 (m, 2 H) 2.06 - 2.20 (m, 2 H) 2.36 - 2.63 (m, 4 H) 2.81 - 3.02 (m, 5 H) 3.62 - 3.71 (m, 5 H) 6.21 (d, 1 H) 7.12 (d, 3 H) 7.34 - 7.44 (m, 1 H)

MS ES$^+$ 339

2.222 Ejemplo 222



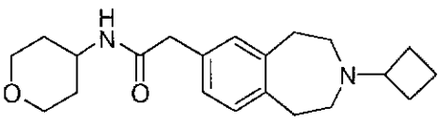
2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-N-metilacetamida

^{1}H NMR (400 MHz, MeOD) ppm 1.59 - 1.81 (m, 2 H) 1.86 - 2.03 (m, 2 H) 2.05 - 2.20 (m, 2 H) 2.35 - 2.60 (m, 4 H) 2.73 (s, 3 H) 2.80 - 2.99 (m, 5 H) 3.44 (s, 2 H) 7.04 (s, 3 H)

MS ES$^+$ 273

2.223 Ejemplo 223

2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-N-(tetrahidro-2H-piran-4-il)acetamida

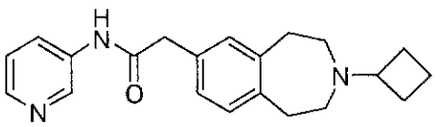


^{1}H NMR: (400 MHz, MeOD) □ 7.05 (s, 3 H), 3.79 - 4.00 (m, 3 H), 3.43 (s, 4 H), 2.77 - 2.98 (m, 5 H), 2.34 - 2.59 (m, 4 H), 2.03 - 2.19 (m, 2 H), 1.86 - 2.04 (m, 2 H), 1.59 - 1.88 (m, 4 H), 1.40 - 1.60 (m, 2 H)

MS ES$^+$: 365

2.224 Ejemplo 224

2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-*N*-(piridin-3-il)acetamida

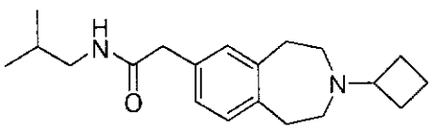


^{1}H NMR: (400 MHz, MeOD) □ 8.74 (m, 1 H), 8.22 - 8.30 (m, 1 H), 8.08 - 8.17 (m, 1 H), 7.35 - 7.44 (m, 1 H), 7.03 - 7.19 (m, 3 H), 3.67 (s, 2 H), 2.77 - 3.00 (m, 5 H), 2.30 - 2.66 (m, 4 H), 2.04 - 2.19 (m, 2 H), 1.85 - 2.04 (m, 2 H), 1.71 (m, 2 H)

MS ES$^+$: 336

2.225 Ejemplo 225

2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-*N*-isobutilacetamida

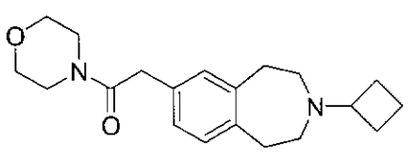


^{1}H NMR: (400 MHz, MeOD) 7.06 (s, 3 H), 3.42 - 3.48 (m, 2 H), 2.97 - 3.04 (m, 2 H), 2.79 - 2.96 (m, 5 H), 2.35 - 2.62 (m, 4 H), 2.06 - 2.19 (m, 2 H), 1.89 - 2.06 (m, 2 H), 1.60 - 1.86 (m, 3 H), 0.89 (m, 6 H)

MS ES$^+$: 337

2.226 Ejemplo 226

2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-morfolinoetanona

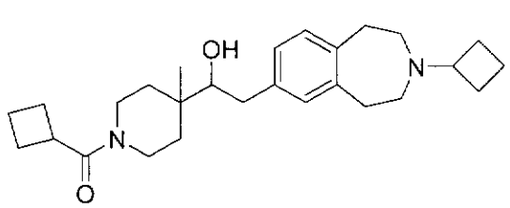


^{1}H NMR (400 MHz, MeOD) 6.95 - 7.15 (m, 3H), 3.74 (s, 2H), 3.57 - 3.68 (m, 4H), 3.45 - 3.56 (m, 4H), 2.77 - 2.98 (m, 5H), 2.48 (br. s., 4H), 2.06 - 2.23 (m, 2H), 1.87 - 2.05 (m, 2H), 1.60 - 1.85 (m, 2H)

MS ES$^+$: 329

2.227 Ejemplo 227

Ciclobutil(4-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-hidroxietil)-4-metilpiperidina-1-il)metanona

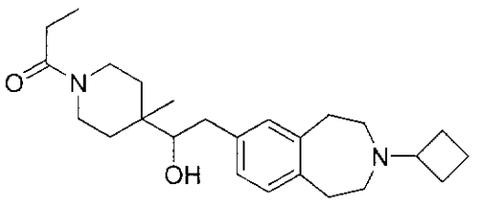


^{1}H NMR (400 MHz, DICLOROMETANO-d_2) δ 6.93 (br. s., 3H), 4.13 - 4.32 (m, 1H), 3.46 - 3.59 (m, 1H), 3.36 - 3.46 (m, 1H), 3.06 - 3.33 (m, 2H), 2.66 - 3.02 (m, 7H), 2.21 - 2.51 (m, 7H), 1.83 (br. s., 8H), 1.42 - 1.76 (m, 6H), 1.30 - 1.43 (m, 1H), 1.05 (s, 3H)

MS ES$^+$: 425

2.228 Ejemplo 228 (racémico)

1-(4-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-hidroxietil)-4-metilpiperidin-1-il)propan-1-ona

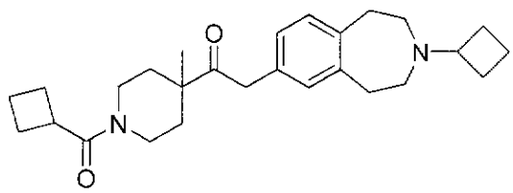


^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.09 (s, 3 H) 1.12 - 1.21 (m, 3 H) 1.35 - 1.46 (m, 1 H) 1.46 - 1.52 (m, 1 H) 1.52 - 1.79 (m, 7 H) 1.83 - 2.01 (m, 1 H) 2.02 - 2.18 (m, 2 H) 2.29 - 2.56 (m, 6 H) 2.72 - 3.04 (m, 6 H) 3.18 - 3.33 (m, 1 H) 3.39 - 3.48 (m, 1 H) 3.63 - 3.76 (m, 1 H) 4.29 - 4.42 (m, 1 H) 6.95 (br. s., 2 H) 7.03 - 7.09 (m, 1 H)

MS ES$^+$: 399

2.229 Ejemplo 229

1-(1-(ciclobutanocarbonil)-4-metilpiperidin-4-il)-2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)etanona



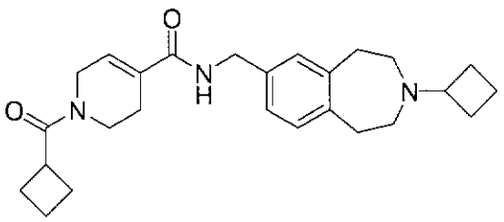
^{1}H NMR (400 MHz, DICLOROMETANO-d_2) δ 7.00 - 7.05 (m, 1H), 6.85 - 6.91 (m, 2H), 3.77 - 3.86 (m, 1H), 3.66 - 3.76 (m, 2H), 3.31 - 3.41 (m, 1H), 3.22 (quin, *J* = 8.59 Hz, 1H), 3.06 - 3.17 (m, 2H), 2.71 - 2.92 (m, 5H), 2.39 (br. s., 4H), 2.18 - 2.33 (m, 2H), 2.00 - 2.16

(m, 6H), 1.74 - 1.99 (m, 3H), 1.53 - 1.73 (m, 2H), 1.42 - 1.53 (m, 1H), 1.31 - 1.42 (m, 1H), 1.22 (s, 3H)

MS ES$^+$: 423

2.230 Ejemplo 230

1-(ciclobutanocarbonil)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-1,2,3,6-tetrahidropiridina-4-carboxamida

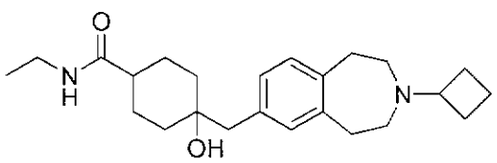


^{1}H NMR (400 MHz, DMSO-*d*6) ppm 8.24 - 8.44 (m, 1H), 6.90 - 7.06 (m, 3H), 6.46 - 6.58 (m, 1H), 4.20 - 4.30 (m, 2H), 3.93 - 4.08 (m, 2H), 3.48 - 3.58 (m, 1H), 3.33 - 3.44 (m, 2H), 2.64 - 2.86 (m, 5H), 2.20 - 2.40 (m, 6H), 2.04 - 2.20 (m, 4H), 1.83 - 2.04 (m, 3H), 1.67 - 1.83 (m, 3H), 1.49 - 1.66 (m, 2H)

MS ES$^+$: 422

2.231 Ejemplo 231

4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-N-etil-4-hidroxiciclohexanocarboxamida

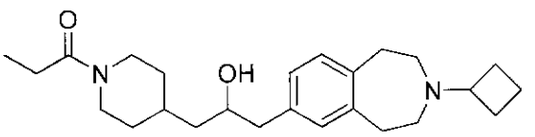


^{1}H NMR (400 MHz, DMSO-d_6) ppm 0.72 - 0.85 (m, 3 H) 0.98 - 1.08 (m, 2 H) 1.11 - 1.32 (m, 4 H) 1.33 - 1.74 (m, 7 H) 1.76 - 1.89 (m, 2 H) 2.05 - 2.23 (m, 4 H) 2.35 - 2.41 (m, 2 H) 2.48 - 2.68 (m, 5 H) 2.75 - 2.92 (m, 2 H) 3.73 - 3.82 (m, 1 H) 6.59 - 6.88 (m, 3 H) 7.29 - 7.45 (m, 1 H)

MS ES$^+$: 385

2.232 Ejemplo 232 (enantiómero del Ejemplo 142)

1-(4-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)propan-1-ona

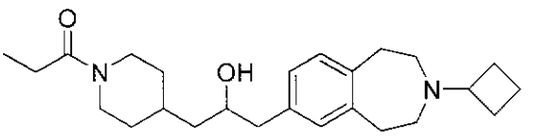


^{1}H NMR (400 MHz, MeOD) □ 6.92 - 7.09 (m, 3H), 4.38 - 4.54 (m, 1H), 3.81 - 3.96 (m, 2H), 3.01 - 3.17 (m, 1H), 2.81 - 2.98 (m, 5H), 2.38 - 2.76 (m, 7H), 2.05 - 2.18 (m, 5H), 1.90 - 2.04 (m, 2H), 1.61 - 1.89 (m, 5H), 1.28 - 1.48 (m, 2H), 0.83 - 1.27 (m, 2H)

MS ES$^+$: 385

2.233 Ejemplo 233 (enantiómero del Ejemplo 142)

1-(4-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)propan-1-ona

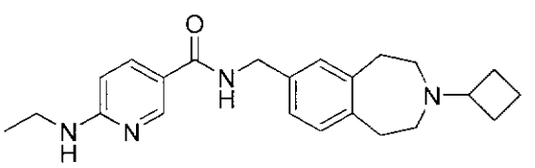


^{1}H NMR (400 MHz, MeOD) □ 6.92 - 7.09 (m, 3H), 4.38 - 4.54 (m, 1H), 3.81 - 3.96 (m, 2H), 3.01 - 3.17 (m, 1H), 2.81 - 2.98 (m, 5H), 2.38 - 2.76 (m, 7H), 2.05 - 2.18 (m, 5H), 1.90 - 2.04 (m, 2H), 1.61 - 1.89 (m, 5H), 1.28 - 1.48 (m, 2H), 0.83 - 1.27 (m, 2H)

MS ES$^+$: 385

2.234 Ejemplo 234

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(etilamino)nicotinamida



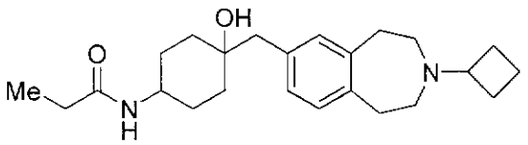
^{1}H NMR (400 MHz, DMSO-*d*6) □ ppm 8.56 - 8.66 (m, 1H), 8.49 - 8.56 (m, 1H), 7.75 - 7.87 (m, 1H), 6.92 - 7.08 (m, 4H), 6.37 - 6.46 (m, 1H), 4.29 - 4.42 (m, 2H), 3.23 - 3.29 (m, 2H),

2.64 - 2.88 (m, 5H), 2.32 (br. s., 4H), 1.91 - 2.06 (m, 2H), 1.67 - 1.84 (m, 2H), 1.45 - 1.66 (m, 2H), 1.03 - 1.19 (m, 3H)

MS ES$^+$: 379

2.235 Ejemplo 235

N-(4-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-4-hidroxiciclohexil)propionamida

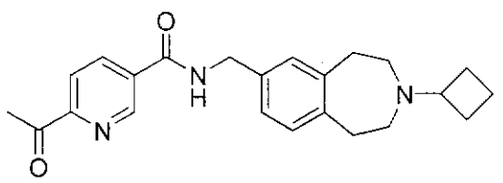


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 0.77 - 0.85 (m, 3 H) 1.08 - 1.20 (m, 2 H) 1.23 - 1.51 (m, 8 H) 1.57 - 1.70 (m, 2 H) 1.80 - 1.92 (m, 4 H) 2.12 - 2.26 (m, 4 H) 2.38 - 2.44 (m, 2 H) 2.53 - 2.70 (m, 5 H) 3.18 - 3.29 (m, 1 H) 3.85 (s, 1 H) 6.72 - 6.78 (m, 2 H) 6.79 - 6.87 (m, 1 H) 7.36 - 7.47 (m, 1 H)

MS ES$^+$: 385

2.236 Ejemplo 236

6-acetil-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)nicotinamida

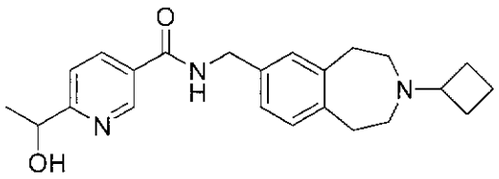


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.47 - 1.66 (m, 2 H) 1.69 - 1.88 (m, 2 H) 1.93 - 2.09 (m, 2 H) 2.23 - 2.41 (m, 4 H) 2.62 - 2.70 (m, 3 H) 2.71 - 2.92 (m, 5 H) 4.34 - 4.56 (m, 2 H) 6.98 - 7.17 (m, 3 H) 7.98 - 8.10 (m, 1 H) 8.32 - 8.45 (m, 1 H) 9.08 - 9.20 (m, 1 H) 9.26 - 9.40 (m, 1 H)

MS ES$^+$: 378

2.237 Ejemplo 237

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(1-hidroxietil)nicotinamida

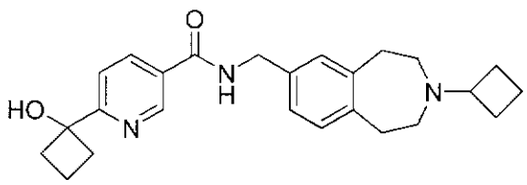


^{1}H NMR (400 MHz, DMSO-d_6) ppm 1.34 - 1.41 (m, 3 H) 1.51 - 1.65 (m, 2 H) 1.71 - 1.84 (m, 2 H) 1.94 - 2.06 (m, 2 H) 2.26 - 2.39 (m, 4 H) 2.71 - 2.84 (m, 5 H) 4.40 - 4.47 (m, 2 H) 4.73 - 4.83 (m, 1 H) 5.44 - 5.49 (m, 1 H) 7.02 - 7.10 (m, 3 H) 7.56 - 7.64 (m, 1 H) 8.19 - 8.27 (m, 1 H) 8.92 - 8.97 (m, 1 H) 9.03 - 9.16 (m, 1 H)

MS ES$^+$: 380

2.238 Ejemplo 238

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(1-hidroxiciclobutil)nicotinamida

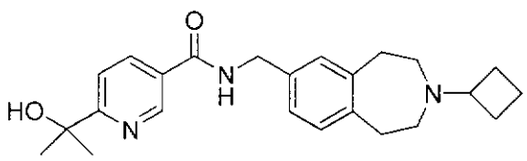


^{1}H NMR (400 MHz, DMSO-d_6) ppm 1.51 - 1.68 (m, 2 H) 1.72 - 2.06 (m, 6 H) 2.18 - 2.44 (m, 6 H) 2.52 - 2.60 (m, 2 H) 2.75 - 2.90 (m, 5 H) 4.39 - 4.48 (m, 2 H) 5.84 (s, 1 H) 7.02 - 7.10 (m, 3 H) 7.62 - 7.69 (m, 1 H) 8.15 - 8.23 (m, 1 H) 8.98 - 9.04 (m, 1 H) 9.06 - 9.15 (m, 1 H)

MS ES$^+$: 406

2.239 Ejemplo 239

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(2-hidroxipropan-2-il)nicotinamida

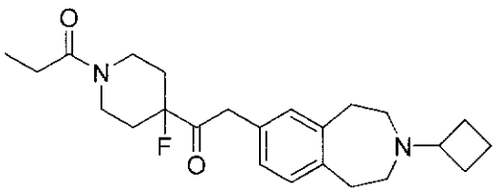


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.45 (s, 6 H) 1.51 - 1.66 (m, 2 H) 1.68 - 1.84 (m, 2 H) 1.93 - 2.06 (m, 2 H) 2.23 - 2.42 (m, 4 H) 2.68 - 2.87 (m, 5 H) 4.36 - 4.50 (m, 2 H) 5.31 (s, 1 H) 7.00 - 7.11 (m, 3 H) 7.71 - 7.79 (m, 1 H) 8.15 - 8.25 (m, 1 H) 8.90 - 8.99 (m, 1 H) 9.02 - 9.15 (m, 1 H)

MS ES$^+$: 394

2.240 Ejemplo 240

1-(4-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)acetil)-4-fluoropiperidin-1-il)propan-1-ona

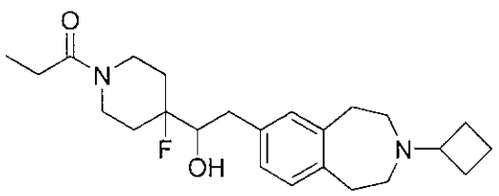


^{1}H NMR (400 MHz, DICLOROMETANO-d_2) □ ppm 0.96 - 1.07 (m, 3 H) 1.43 - 2.03 (m, 11 H) 2.20 - 2.42 (m, 5 H) 2.72 - 2.90 (m, 6 H) 3.17 - 3.34 (m, 1 H) 3.62 - 3.75 (m, 1 H) 3.79 - 3.89 (m, 2 H) 4.35 - 4.48 (m, 1 H) 6.78 - 6.89 (m, 2 H) 6.92 - 7.02 (m, 1 H)

MS ES$^+$: 401

2.241 Ejemplo 241

1-(4-(2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-1-hidroxietil)-4-fluoropiperidin-1-il)propan-1-ona

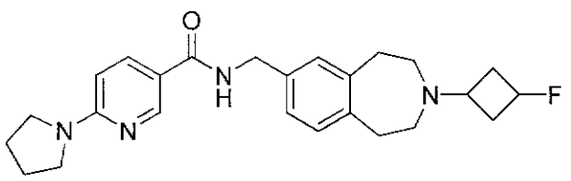


^{1}H NMR (400 MHz, DICLOROMETANO-d_2) □ ppm 1.09 - 1.19 (m, 3 H) 1.53 - 2.17 (m, 12 H) 2.30 - 2.51 (m, 5 H) 2.51 - 2.62 (m, 1 H) 2.72 - 3.00 (m, 6 H) 3.30 - 3.44 (m, 1 H) 3.66 - 3.90 (m, 2 H) 4.52 - 4.67 (m, 1 H) 6.95 - 7.15 (m, 3 H) 1H was not determined

MS ES$^+$: 403

2.242 Ejemplo 242

N-((3-(3-fluorociclobutil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepin-7-il)metil)-6-(pirrolidin-1-il)nicotinamida

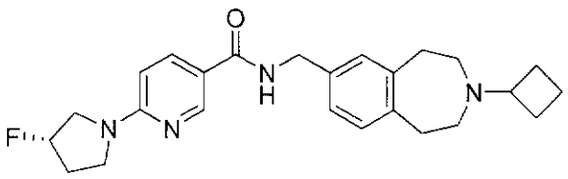


1H NMR (400 MHz, CD_3OD) δ 8.50 - 8.62 (m, 1 H) 7.89 - 8.02 (m, 1 H) 7.00 - 7.14 (m, 3 H) 6.43 - 6.56 (m, 1 H) 4.97 - 5.23 (m, 1 H) 4.49 (s, 2 H) 3.41 - 3.57 (m, 4 H) 3.11 - 3.25 (m, 1 H) 2.84 - 2.99 (m, 4 H) 2.48 (br. s., 4 H) 2.19 - 2.41 (m, 4 H) 1.97 - 2.12 (m, 4 H).

MS ES^+: 423.

2.243 Ejemplo 243

(*S*)-*N*-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(3-fluoropirrolidin-1-il)nicotinamida

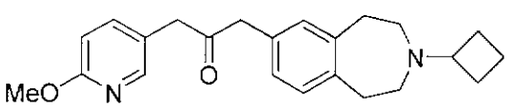


^1H NMR (400 MHz, DMSO-d_6) δ 8.53 - 8.83 (m, 2H), 7.84 - 8.07 (m, 1H), 6.88 - 7.20 (m, 3H), 6.27 - 6.65 (m, 1H), 5.27 - 5.58 (m, 1H), 4.24 - 4.50 (m, 2H), 3.40 - 3.98 (m, 4H), 2.66 - 2.90 (m, 5H), 1.91 (nuno, 12H)

MS ES^+: 423

2.244 Ejemplo 244

1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(6-metoxipiridin-3-il)propan-2-ona



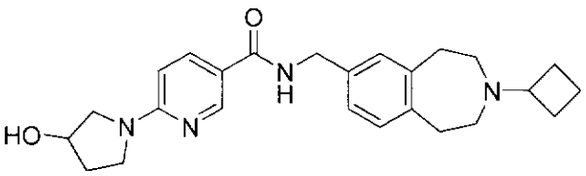
000371

^{1}H NMR (400 MHz, DICLOROMETANO-d_2) □ ppm 1.52 - 1.82 (m, 2 H) 1.77 - 2.00 (m, 2 H) 2.01 - 2.21 (m, 2 H) 2.31 - 2.61 (m, 4 H) 2.74 - 3.02 (m, 5 H) 3.69 (s, 2 H) 3.73 (s, 2 H) 3.92 (s, 3 H) 6.67 - 6.76 (m, 1 H) 6.89 - 7.01 (m, 2 H) 7.04 - 7.14 (m, 1 H) 7.31 - 7.43 (m, 1 H) 7.87 - 7.96 (m, 1 H)

MS ES$^+$: 365

2.245 Ejemplo 245

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(3-hidroxipirrolidin-1-il)nicotinamida

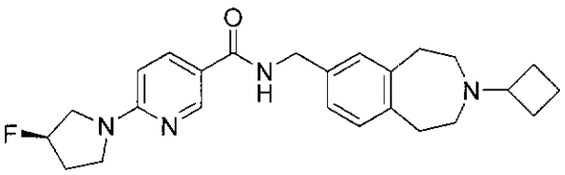


^{1}H NMR (400 MHz, DMSO-d_6) □ 8.48 - 8.78 (m, 2H), 7.84 - 8.12 (m, 1H), 6.83 - 7.15 (m, 3H), 6.22 - 6.58 (m, 1H), 4.81 - 5.08 (m, 1H), 4.17 - 4.54 (m, 3H), 3.33 - 3.65 (m, 4H), 2.64 - 2.90 (m, 5H), 2.16 - 2.41 (m, 4H), 1.76 (nuno, 9H)

MS ES$^+$: 421

2.246 Ejemplo 246

(*R*)-*N*-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(3-fluoropirrolidin-1-il)nicotinamida

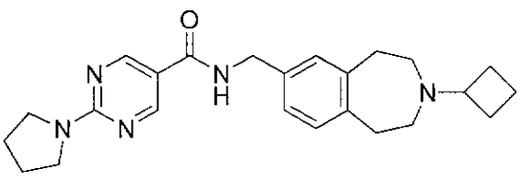


^{1}H NMR (400 MHz, DMSO-d_6) □ 8.53 - 8.83 (m, 2H), 7.84 - 8.07 (m, 1H), 6.88 - 7.20 (m, 3H), 6.27 - 6.65 (m, 1H), 5.27 - 5.58 (m, 1H), 4.24 - 4.50 (m, 2H), 3.40 - 3.98 (m, 4H), 2.66 - 2.90 (m, 5H), 1.91 (nuno, 12H)

MS ES$^+$: 423

2.247 Ejemplo 247

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-(pirrolidin-1-il)pirimidina-5-carboxamida

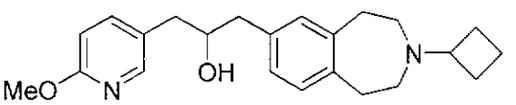


^{1}H NMR (400 MHz, DMSO-d_6) □ 8.79 (s, 3H), 6.82 - 7.23 (m, 3H), 4.24 - 4.59 (m, 2H), 3.41 - 3.65 (m, 4H), 2.63 - 3.04 (m, 4H), 2.6-2.4 (6H, solapado por solvente punta) 2.13 - 2.42 (m, 2H), 1.77 (nuno, 7H)

MS ES$^+$: 407

2.248 Ejemplo 248

1-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-3-(6-metoxipiridin-3-il)propan-2-ol

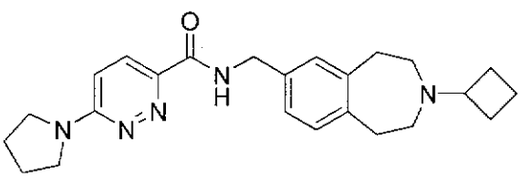


^{1}H NMR (400 MHz, DICLOROMETANO-d_2) □ ppm 1.59 - 1.78 (m, 5 H) 2.00 - 2.21 (m, 2 H) 2.29 - 2.57 (m, 4 H) 2.60 - 2.95 (m, 9 H) 3.92 (s, 3 H) 3.95 - 4.06 (m, 1 H) 6.68 - 6.76 (m, 1 H) 6.95 - 7.11 (m, 3 H) 7.47 - 7.57 (m, 1 H) 7.97 - 8.09 (m, 1 H)

MS ES$^+$: 367

2.249 Ejemplo 249

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(pirrolidin-1-il)piridazina-3-carboxamida

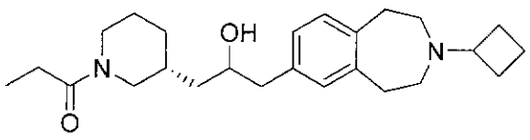


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.47 - 1.66 (m, 2 H) 1.69 - 1.85 (m, 2 H) 1.91 - 2.08 (m, 6 H) 2.22 - 2.42 (m, 4 H) 2.66 - 2.85 (m, 5 H) 3.42 - 3.62 (m, 4 H) 4.36 - 4.49 (m, 2 H) 6.91 - 6.98 (m, 1 H) 7.00 - 7.11 (m, 3 H) 7.77 - 7.88 (m, 1 H) 9.11 - 9.26 (m, 1 H)

MS ES$^+$: 406

2.250 Ejemplo 250 (diastereómero del Ejemplo 325)

1-((3R)-3-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)propan-1-ona

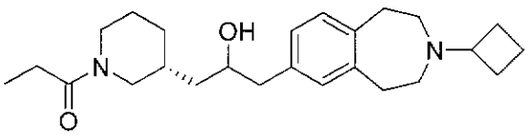


1H NMR (400 MHz, CD3OD) δ 6.89 - 7.06 (m, 3 H) 4.20 - 4.32 (m, 1 H) 3.69 - 3.97 (m, 2 H) 3.01 - 3.15 (m, 1 H) 2.77 - 2.97 (m, 5 H) 2.56 - 2.75 (m, 3 H) 2.21 - 2.56 (m, 6 H) 2.03 - 2.19 (m, 2 H) 1.88 - 2.03 (m, 2 H) 1.76 - 1.88 (m, 1 H) 1.56 - 1.76 (m, 4 H) 1.18 - 1.57 (m, 4 H) 1.02 - 1.16 (m, 3 H).

MS ES$^+$: 399

2.251 Ejemplo 251 (diastereómero del Ejemplo 325)

1-((3R)-3-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)propan-1-ona

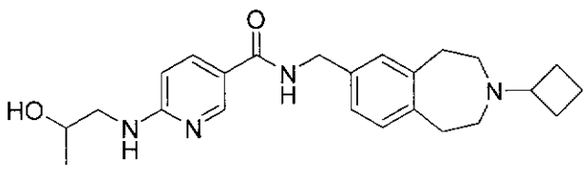


1H NMR (400 MHz, CD_3OD) δ 6.87 - 7.07 (m, 3 H) 4.20 - 4.35 (m, 1 H) 3.71 - 3.91 (m, 2 H) 2.98 - 3.11 (m, 1 H) 2.57 - 2.94 (m, 8 H) 2.28 - 2.54 (m, 6 H) 2.01 - 2.18 (m, 2 H) 1.81 - 2.01 (m, 3 H) 1.53 - 1.78 (m, 4 H) 1.25 - 1.53 (m, 3 H) 1.02 - 1.17 (m, 4 H).

MS ES$^+$: 399

2.252 Ejemplo 252

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(2-hidroxipropilamino)nicotinamida

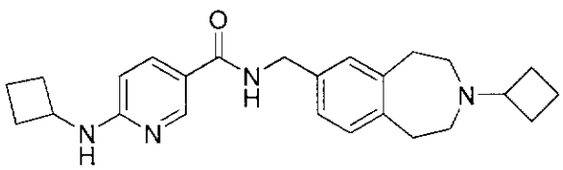


^{1}H NMR (400 MHz, DMSO-d_6) ppm 1.03 - 1.12 (m, 3 H) 1.48 - 1.67 (m, 2 H) 1.69 - 1.86 (m, 2 H) 1.91 - 2.08 (m, 2 H) 2.23 - 2.42 (m, 4 H) 2.67 - 2.85 (m, 5 H) 3.16 - 3.29 (m, 2 H) 3.71 - 3.86 (m, 1 H) 4.32 - 4.44 (m, 2 H) 4.70 - 4.79 (m, 1 H) 6.47 - 6.58 (m, 1 H) 6.97 - 7.08 (m, 4 H) 7.77 - 7.86 (m, 1 H) 8.49 - 8.55 (m, 1 H) 8.56 - 8.66 (m, 1 H)

MS ES$^+$: 409

2.253Ejemplo 253

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(ciclobutilamino)nicotinamida

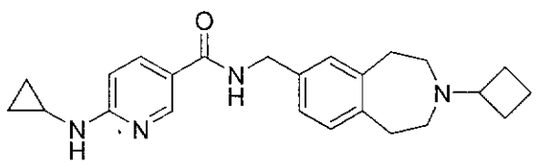


^{1}H NMR (400 MHz, MeOD-d_4) 8.44 - 8.52 (m, 1 H), 7.78 - 7.89 (m, 1 H), 6.99 - 7.14 (m, 3 H), 6.40 - 6.51 (m, 1 H), 4.42 - 4.53 (m, 2 H), 4.24 - 4.38 (m, 1 H), 2.71 - 2.99 (m, 5 H), 2.33 - 2.55 (m, 6 H), 2.04 - 2.17 (m, 2 H), 1.85 - 2.04 (m, 4 H), 1.54 - 1.85 (m, 4 H)

MS ES$^+$: ES$^+$

2.254 Ejemplo 254

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(ciclopropilamino)nicotinamida



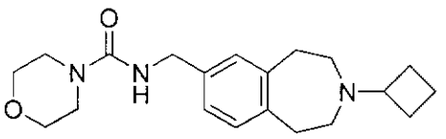
^{1}H NMR (400 MHz, MeOD-d_4) 8.48 - 8.60 (m, 1 H), 7.91 - 8.01 (m, 1 H), 7.03 - 7.15 (m, 3 H), 6.69 - 6.79 (m, 1 H), 4.51 (s, 2 H), 2.93 (br. s., 5 H), 2.30 - 2.67 (m, 4 H), 2.06 - 2.18

(m, 2 H), 1.86 - 2.07 (m, 2 H), 1.60 - 1.81 (m, 2 H), 0.76 - 0.91 (m, 2 H), 0.47 - 0.62 (m, 2 H)

MS ES^+: ES^-

2.255 Ejemplo 255

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)morfolina-4-carboxamida

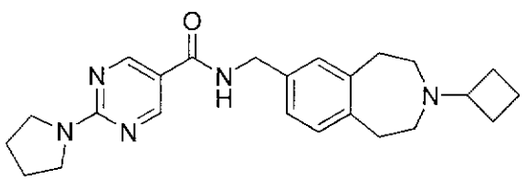


^{1}H NMR (400 MHz, CLOROFORMO-d) 6.85 (s, 3H), 4.33 - 4.67 (m, 1H), 4.05 - 4.31 (m, 2H), 3.37 - 3.62 (m, 4H), 3.03 - 3.28 (m, 4H), 1.66 - 3.01 (m, 16H).

MS ES^+: 345

2.256 Ejemplo 256

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-(pirrolidin-1-il)pirimidina-5-carboxamida

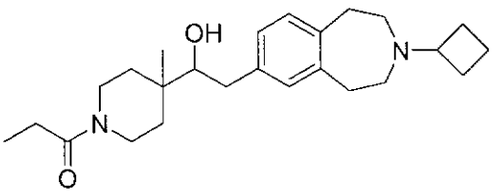


NMR: ^{1}H NMR (400 MHz, DMSO) 8.65 (t, 1H), 8.53 (s, 1H), 7.82 (s, 1H), 6.90-7.01 (m, 3H), 4.30 (d, 2H), 3.37-3.49 (m, 4H), 2.57-2.79 (m, 5H), 2.11-2.33 (m, 4H), 1.82-1.98 (m, 6H), 1.61-1.78 (m, 2H), 1.39-1.57 (m, 2H)

MS ES^+: 406

2.257 Ejemplo 257 (Enantiómero del Ejemplo 228)

1-{4-[2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1-hidroxietil]-4-metilpiperidin-1-il}propan-1-ona

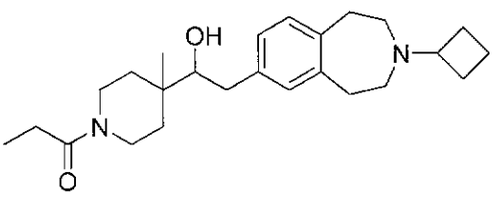


1H NMR (400 MHz, CLOROFORMO-d) d ppm 1.09 (s, 3 H) 1.12 - 1.21 (m, 3 H) 1.35 - 1.46 (m, 1 H) 1.46 - 1.52 (m, 1 H) 1.52 - 1.79 (m, 7 H) 1.83 - 2.01 (m, 1 H) 2.02 - 2.18 (m, 2 H) 2.29 - 2.56 (m, 6 H) 2.72 - 3.04 (m, 6 H) 3.18 - 3.33 (m, 1 H) 3.39 - 3.48 (m, 1 H) 3.63 - 3.76 (m, 1 H) 4.29 - 4.42 (m, 1 H) 6.95 (br. s., 2 H) 7.03 - 7.09 (m, 1 H)

MS ES$^+$: 399

2.258 Ejemplo 258 (enantiómero del Ejemplo 228)

1-{4-[2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1-hidroxietil]-4-metilpiperidin-1-il}propan-1-ona

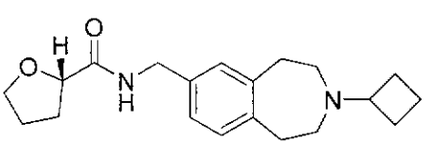


1H NMR (400 MHz, CLOROFORMO-d) d ppm 1.09 (s, 3 H) 1.12 - 1.21 (m, 3 H) 1.35 - 1.46 (m, 1 H) 1.46 - 1.52 (m, 1 H) 1.52 - 1.79 (m, 7 H) 1.83 - 2.01 (m, 1 H) 2.02 - 2.18 (m, 2 H) 2.29 - 2.56 (m, 6 H) 2.72 - 3.04 (m, 6 H) 3.18 - 3.33 (m, 1 H) 3.39 - 3.48 (m, 1 H) 3.63 - 3.76 (m, 1 H) 4.29 - 4.42 (m, 1 H) 6.95 (br. s., 2 H) 7.03 - 7.09 (m, 1 H)

MS ES$^+$: 399

2.259 Ejemplo 259

Hidrocloruro de (S)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)tetrahidrofuran-2-carboxamida

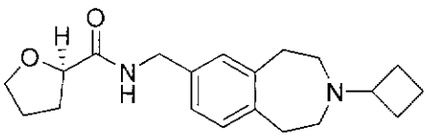


^{1}H NMR (400 MHz, DMSO-d_6) 10.60 - 10.88 (m, 1 H), 8.20 - 8.38 (m, 1 H), 7.07 (s, 3 H), 4.23 (m, 3 H), 3.84 - 3.99 (m, 1 H), 3.71 - 3.84 (m, 1 H), 3.55 - 3.72 (m, 1 H), 3.43 - 3.56 (m, 2 H), 3.19 - 3.30 (m, 2 H), 2.87 - 3.02 (m, 2 H), 2.64 - 2.83 (m, 2 H), 2.28 - 2.45 (m, 2 H), 2.04 - 2.26 (m, 3 H), 1.73 (m, 5 H)

MS ES$^-$:327

2.260 Ejemplo 260

Hidrocloruro de (R)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)tetrahidrofuran-2-carboxamida

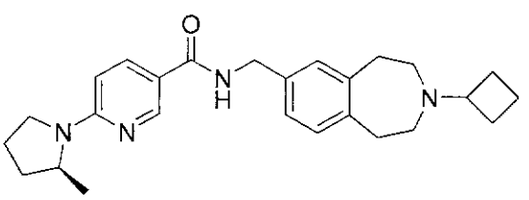


^{1}H NMR (400 MHz, DMSO-d_6) 10.59 - 10.90 (m, 1 H), 8.21 - 8.38 (m, 1 H), 7.07 (s, 3 H), 4.23 (s, 3 H), 3.83 - 3.98 (m, 1 H), 3.72 - 3.84 (m, 1 H), 3.55 - 3.72 (m, 1 H), 3.43 - 3.55 (m, 2 H), 3.20 - 3.29 (m, 2 H), 2.85 - 3.03 (m, 2 H), 2.62 - 2.84 (m, 2 H), 2.29 - 2.45 (m, 2 H), 2.03 - 2.27 (m, 3 H), 1.51 - 1.95 (m, 5 H)

MS ES$^+$:329

2.261 Ejemplo 261

(S)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(2-metilpirrolidin-1-il)nicotinamida

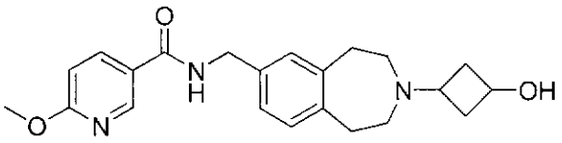


NMR: ^{1}H NMR (400 MHz, DMSO) δ 8.60-8.72 (m, 2H), 7.95 (d, 1H), 6.96-7.09 (m, 3H), 6.45 (d, 1H), 4.39 (d, 2H), 4.13-4.24 (m, 1H), 3.45-3.56 (m, 1H), 3.25-3.35 (m, 1H), 2.61-2.87 (m, 5H), 2.20-2.40 (m, 4H), 1.86-2.11 (m, 5H), 1.39-1.85 (m, 5H), 1.15 (d, 3H)

MS ES$^+$: 419

2.262 Ejemplo 262

N-((3-(3-hidroxiciclobutil)-2,3,4,5-tetrahidro-1*H*-benzo[*d*]azepin-7-il)metil)-6-metoxinicotinamida

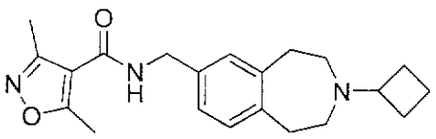


1H NMR (400 MHz, CD_3OD) δ 8.60 - 8.69 (m, 1 H) 8.04 - 8.14 (m, 1 H) 7.02 - 7.19 (m, 3 H) 6.78 - 6.89 (m, 1 H) 4.50 (s, 2 H) 3.94 (s, 3 H) 3.86 - 3.95 (m, 1 H) 2.94 (br. s., 4 H) 2.41 - 2.73 (m, 7 H) 1.76 - 1.92 (m, 2 H).

MS ES$^+$: 382.

2.263 Ejemplo 263

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-3,5-dimetil-1,2-oxazol-4-carboxamida



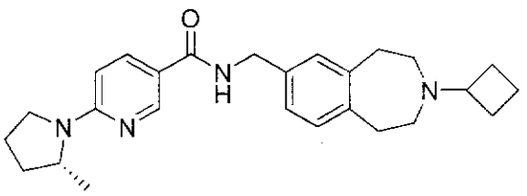
NMR: ^{1}H NMR (400 MHz, CLOROFORMO-d) δ 7.03 - 7.18 (m, 3H), 5.69 - 5.89 (m, 1H), 4.48 - 4.65 (m, 2H), 2.86 - 3.02 (m, 4H), 2.71 - 2.86 (m, 1H), 2.55 - 2.68 (m, 4H), 2.33 - 2.55 (m, 6H), 2.02 - 2.17 (m, 2H), 1.83 - 2.00 (m, 2H), 1.59 - 1.79 (m, 2H)

MS ES$^+$: 353

2.264 Ejemplo 264

(R)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(2-metilpirrolidin-1-il)nicotinamida

000379

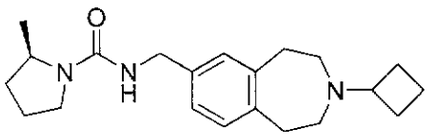


NMR: ^{1}H NMR (400 MHz, DMSO) 8.57-8.69 (m, 2H), 7.94 (dd, 1H), 6.98-7.07 (m, 3H), 6.46 (d, 1H), 4.38 (d, 2H), 4.15-4.24 (m, 1H), 3.47-3.55 (m, 1H), 3.25-3.35 (m, 1H), 2.63-2.85 (m, 5H), 2.24-2.40 (m, 4H), 1.89-2.11 (m, 5H), 1.48-1.84 (m, 5H), 1.16 (d, 3H)

MS ES$^+$: 419

2.265 Ejemplo 265

(*R*)-*N*-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-metilpirrolidina-1-carboxamida

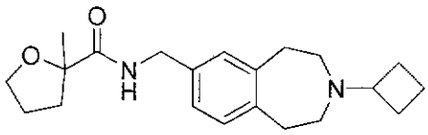


^{1}H NMR (400 MHz, METANOL-d_4) 6.97 - 7.22 (m, 3H), 6.34 - 6.72 (m, 1H), 4.11 - 4.44 (m, 2H), 3.85 - 4.04 (m, 1H), 3.47 - 3.78 (m, 1H), 3.31 - 3.45 (m, 1H), 3.25 (1H, bajo solvente punta) 2.84 - 3.19 (m, 4H), 2.09 - 2.42 (m, 5H), 1.45 - 2.09 (m, 8H), 1.14 (nuno, 4H)

MS ES$^+$: 342

2.266 Ejemplo 266

Hidrocloruro de N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-metiltetrahidrofuran-2-carboxamida



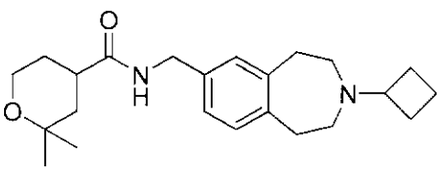
^{1}H NMR (400 MHz, DMSO-d_6) 10.69 - 10.97 (m, 1 H), 8.06 - 8.26 (m, 1 H), 7.07 (s, 3 H), 4.23 (m, 2 H), 3.80 - 3.97 (m, 2 H), 3.58 - 3.79 (m, 1 H), 3.42 - 3.58 (m, 2 H), 3.27 - 3.42

(m, 2 H), 2.87 - 3.03 (m, 2 H), 2.63 - 2.85 (m, 2 H), 2.30 - 2.46 (m, 2 H), 2.08 - 2.30 (m, 3 H), 1.83 - 1.97 (m, 1 H), 1.56 - 1.83 (m, 4 H), 1.33 (s, 3 H)

MS ES^-: ES^+

2.267 Ejemplo 267

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2,2-dimetiltetrahidro-2H-piran-4-carboxamida

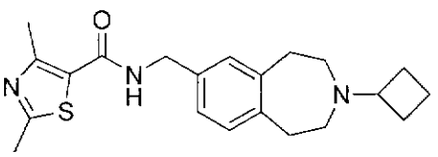


^1H NMR (400 MHz, MeOD-d_4) δ 6.80 - 6.94 (m, 3 H), 4.13 (s, 2 H), 3.49 - 3.62 (m, 2 H), 2.60 - 2.80 (m, 5 H), 2.43 - 2.59 (m, 1 H), 2.31 (br. s., 4 H), 1.94 (m, 2 H), 1.78 (br. s., 2 H), 1.48 (m, 6 H), 1.07 (m, 6 H)

MS ES^+: 371

2.268 Ejemplo 268

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2,4-dimetiltiazol-5-carboxamida

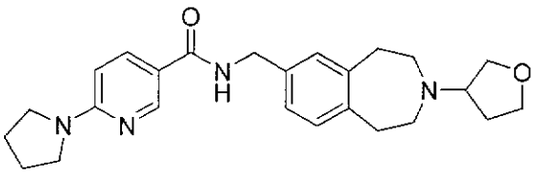


^1H NMR (400 MHz, MeOD-d_4) δ 6.87 - 6.99 (m, 3 H), 4.30 (s, 2 H), 2.62 - 2.83 (m, 5 H), 2.51 (s, 3 H), 2.41 (s, 3 H), 2.21 - 2.39 (m, 4 H), 1.90 - 2.01 (m, 2 H), 1.71 - 1.85 (m, 2 H), 1.54 (m, 2 H)

MS ES^+: 370

2.269 Ejemplo 269

6-(pirrolidin-1-il)-N-((3-(tetrahidrofuran-3-il)-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)nicotinamida

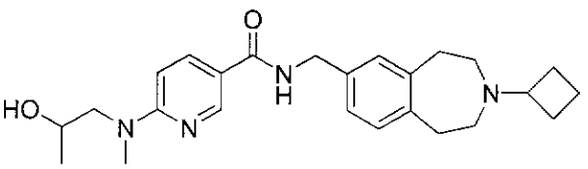


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.66 - 1.82 (m, 1 H) 1.86 - 2.03 (m, 5 H) 2.53 - 2.64 (m, 2 H) 2.75 - 2.89 (m, 4 H) 3.13 - 3.25 (m, 1 H) 3.38 - 3.47 (m, 4 H) 3.47 - 3.55 (m, 1 H) 3.56 - 3.66 (m, 1 H) 3.69 - 3.86 (m, 2 H) 4.31 - 4.45 (m, 2 H) 6.41 - 6.50 (m, 1 H) 6.97 - 7.09 (m, 3 H) 7.90 - 8.02 (m, 1 H) 8.58 - 8.72 (m, 2 H) 2H solapados con DMSO residual

MS ES$^+$: 421

2.270 Ejemplo 270

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-((2-hidroxipropil)(metil)amino)nicotinamida

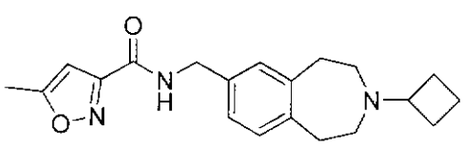


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.05 - 1.10 (m, 3 H) 1.50 - 1.68 (m, 2 H) 1.71 - 1.85 (m, 2 H) 1.94 - 2.09 (m, 2 H) 2.24 - 2.43 (m, 4 H) 2.68 - 2.86 (m, 5 H) 3.11 (s, 3 H) 3.37 - 3.48 (m, 1 H) 3.51 - 3.62 (m, 1 H) 3.85 - 4.00 (m, 1 H) 4.34 - 4.45 (m, 2 H) 4.69 - 4.76 (m, 1 H) 6.60 - 6.70 (m, 1 H) 6.97 - 7.11 (m, 3 H) 7.91 - 8.00 (m, 1 H) 8.59 - 8.63 (m, 1 H) 8.64 - 8.73 (m, 1 H)

MS ES$^+$: 423

2.271 Ejemplo 271

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-5-metilisoxazol-3-carboxamida

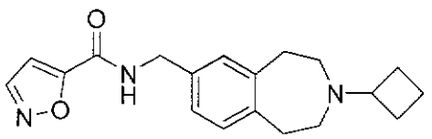


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.49 - 1.66 (m, 2 H) 1.69 - 1.84 (m, 2 H) 1.93 - 2.07 (m, 2 H) 2.21 - 2.41 (m, 4 H) 2.43 - 2.48 (m, 3 H) 2.69 - 2.85 (m, 5 H) 4.27 - 4.43 (m, 2 H) 6.50 - 6.58 (m, 1 H) 6.96 - 7.10 (m, 3 H) 9.08 - 9.22 (m, 1 H)

MS ES$^+$: 340

2.272 Ejemplo 272

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)isoxazol-5-carboxamida

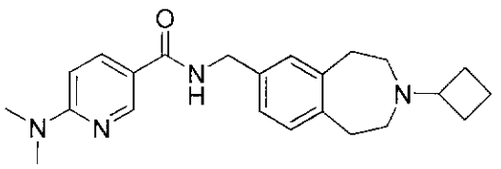


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.40 - 1.61 (m, 2 H) 1.62 - 1.79 (m, 2 H) 1.85 - 2.01 (m, 2 H) 2.26 (br. s., 4 H) 2.62 - 2.80 (m, 5 H) 4.24 - 4.39 (m, 2 H) 6.91 - 7.08 (m, 4 H) 8.61 - 8.74 (m, 1 H) 9.24 - 9.46 (m, 1 H)

MS ES$^+$: 326

2.273 Ejemplo 273

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-(dimetilamino)piridina-3-carboxamida

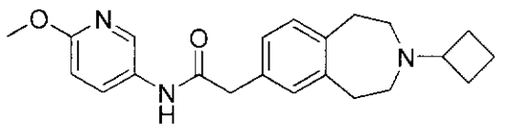


NMR: ^{1}H NMR (400 MHz, CLOROFORMO-d) □ 8.40 - 8.54 (m, 1H), 7.72 - 7.86 (m, 1H), 6.92 - 7.02 (m, 3H), 6.34 - 6.44 (m, 1H), 5.95 - 6.11 (m, 1H), 4.47 (d, 2H), 2.97 - 3.11 (m, 6H), 2.74 - 2.87 (m, 4H), 2.61 - 2.73 (m, 1H), 2.23 - 2.45 (m, 4H), 1.89 - 2.03 (m, 2H), 1.73 - 1.86 (m, 2H), 1.50 - 1.65 (m, 2H)

MS ES$^+$: 379, ES$^-$:377

2.274 Ejemplo 274

2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-N-(6-metoxipiridin-3-il)acet amida

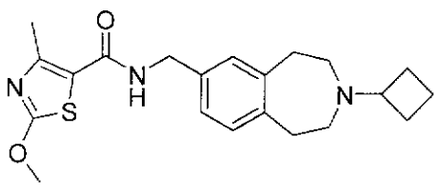


^{1}H NMR (400 MHz, DMSO-d_6) □ 10.14 (s, 1H), 8.31 - 8.39 (m, 1H), 7.84 - 7.95 (m, 1H), 7.05 (br. s., 3H), 6.74 - 6.82 (m, 1H), 3.81 (s, 3H), 3.55 (s, 2H), 2.82 (br. s., 5H), 2.34 (br. s., 4H), 2.00 (d, *J* = 5.81 Hz, 2H), 1.79 (br. s., 2H), 1.48 - 1.69 (m, 2H)

MS ES$^+$: 366

2.275 Ejemplo 275

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-metoxi-4-metiltiazol-5-carboxamida

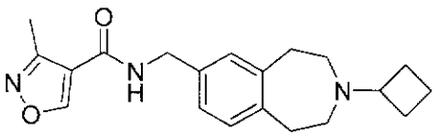


^{1}H NMR (400 MHz, MeOD) □ 6.94 (s, 3 H), 4.30 (s, 2 H), 3.94 (s, 3 H), 2.79 (br. s., 5 H), 2.35 (s, 7 H), 1.91 - 2.06 (m, 2 H), 1.71 - 1.91 (m, 2 H), 1.44 - 1.66 (m, 2 H)

MS ES$^+$: 386

2.276 Ejemplo 276

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3-metilisoxazol-4-carboxamida

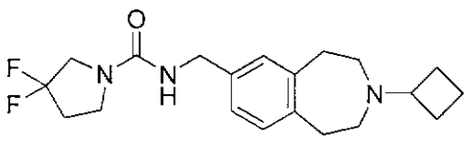


^{1}H NMR (400 MHz, MeOD) □ 9.14 (s, 1 H), 7.23 (s, 3 H), 4.59 (s, 2 H), 2.90 - 3.14 (m, 5 H), 2.60 (s, 7 H), 2.25 (m, 2 H), 2.09 (br. s., 2 H), 1.70 - 1.96 (m, 2 H)

MS ES$^+$: 340

2.277Ejemplo 277

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3,3-difluoropirrolidina-1-carboxamida

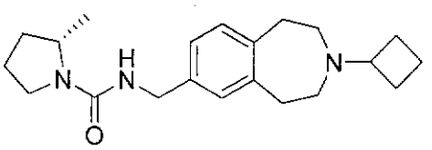


^{1}H NMR (400 MHz, METANOL-d_4) □ 7.07 (s, 3H), 4.21 (s, 2H), 3.42 - 3.67 (m, 7H), 3.06 - 3.17 (m, 2H), 2.90 - 3.04 (m, 2H), 2.61 - 2.76 (m, 2H), 2.12 - 2.39 (m, 6H), 1.60 - 1.91 (m, 2H)

MS ES$^+$: 364

2.278 Ejemplo 278

(*S*)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-metilpirrolidina-1-carboxamida

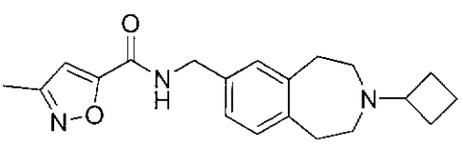


^{1}H NMR (400 MHz, METANOL-d_4) □ 6.97 - 7.22 (m, 3H), 6.34 - 6.72 (m, 1H), 4.11 - 4.44 (m, 2H), 3.85 - 4.04 (m, 1H), 3.47 - 3.78 (m, 1H), 3.31 - 3.45 (m, 1H), 3.25 (1H, bajo solvente punta) 2.84 - 3.19 (m, 4H), 2.09 - 2.42 (m, 5H), 1.45 - 2.09 (m, 8H), 1.14 (nuno, 4H)

MS ES$^+$: 342

2.279 Ejemplo 279

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3-metilisoxazol-5-carboxamida

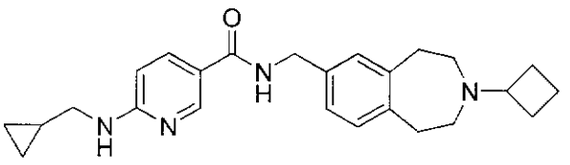


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1.43 - 1.61 (m, 2 H) 1.64 - 1.79 (m, 2 H) 1.89 - 2.01 (m, 2 H) 2.19 - 2.34 (m, 7 H) 2.62 - 2.81 (m, 5 H) 4.27 - 4.36 (m, 2 H) 6.86 - 6.91 (m, 1 H) 6.93 - 7.05 (m, 3 H) 9.24 - 9.37 (m, 1 H)

MS ES$^+$: 340

2.280 Ejemplo 280

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-[(ciclopropilmetil)amino]piridina-3-carboxamida

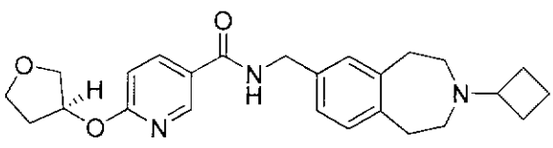


NMR: ^{1}H NMR (400 MHz, CLOROFORMO-d) □ 8.25 - 8.31 (m, 1H), 7.61 - 7.69 (m, 1H), 6.82 - 6.91 (m, 3H), 6.10 - 6.19 (m, 1H), 5.83 - 5.94 (m, 1H), 4.70 - 4.80 (m, 1H), 4.30 - 4.38 (m, 2H), 2.91 - 2.99 (m, 2H), 2.61 - 2.75 (m, 4H), 2.48 - 2.62 (m, 1H), 2.11 - 2.30 (m, 4H), 1.79 - 1.90 (m, 2H), 1.59 - 1.77 (m, 2H), 1.37 - 1.52 (m, 2H), 0.81 - 0.93 (m, 1H), 0.29 - 0.38 (m, 2H), -0.01 - 0.10 (m, 2H)

MS ES$^+$: 405, ES$^-$: 403

2.281 Ejemplo 281

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-[(3S)-tetrahidrofuran-3-iloxi]piridina-3-carboxamida

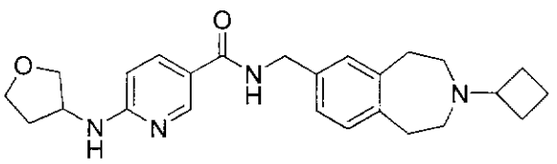


NMR: ^{1}H NMR (400 MHz, CLOROFORMO-d) δ 8.55 - 8.61 (m, 1H), 7.95 - 8.06 (m, 1H), 7.08 - 7.15 (m, 3H), 6.74 - 6.83 (m, 1H), 6.16 - 6.26 (m, 1H), 5.58 - 5.66 (m, 1H), 4.55 - 4.64 (m, 2H), 3.97 - 4.10 (m, 2H), 3.86 - 3.97 (m, 2H), 2.88 - 3.01 (m, 4H), 2.73 - 2.85 (m, 1H), 2.37 - 2.55 (m, 4H), 2.21 - 2.36 (m, 1H), 2.04 - 2.20 (m, 3H), 1.85 - 2.00 (m, 2H), 1.62 - 1.79 (m, 2H)

MS ES$^+$: 422, ES$^-$: 420

2.282 Ejemplo 282

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-(tetrahidrofuran-3-ilamino)piridina-3-carboxamida

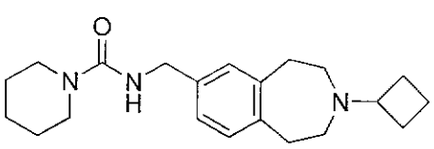


NMR: ^{1}H NMR (400 MHz, CLOROFORMO-d) δ 8.39 - 8.49 (m, 1H), 7.74 - 7.86 (m, 1H), 6.94 - 7.09 (m, 3H), 6.24 - 6.36 (m, 1H), 5.96 - 6.12 (m, 1H), 4.76 - 4.88 (m, 1H), 4.44 - 4.56 (m, 2H), 4.33 - 4.44 (m, 1H), 3.84 - 3.94 (m, 2H), 3.70 - 3.82 (m, 1H), 3.58 - 3.68 (m, 1H), 2.76 - 2.87 (m, 4H), 2.59 - 2.76 (m, 1H), 2.18 - 2.46 (m, 5H), 1.90 - 2.06 (m, 2H), 1.70 - 1.91 (m, 3H), 1.52 - 1.68 (m, 2H)

MS ES$^+$: 421, ES$^-$: 419

2.283 Ejemplo 283

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)piperidina-1-carboxamida

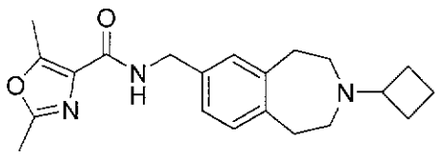


^{1}H NMR (400 MHz, METANOL-d$_4$) δ 7.11 - 7.24 (m, 3H), 4.32 (s, 2H), 3.59 - 3.81 (m, 3H), 3.37 - 3.46 (m, 4H), 3.18 - 3.30 (m, 2H), 3.02 - 3.13 (m, 2H), 2.73 - 2.86 (m, 2H), 2.27 - 2.47 (m, 4H), 1.75 - 2.00 (m, 2H), 1.62 - 1.72 (m, 2H), 1.51 - 1.60 (m, 4H)

MS ES$^+$: 342

2.284 Ejemplo 284

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2,5-dimetiloxazol-4-carboxamida

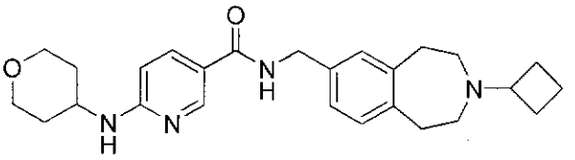


^{1}H NMR (400 MHz, MeOD) 7.09 (m 3 H), 4.47 (s, 2 H), 2.93 (br. s., 5 H), 2.34 - 2.64 (m, 10 H), 2.05 - 2.20 (m, 2 H), 1.86 - 2.04 (m, 2 H), 1.58 - 1.84 (m, 2 H)

MS ES$^+$: 354

2.285 Ejemplo 285

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-(tetrahidro-2H-piran-4-ilamino)piridina-3-carboxamida

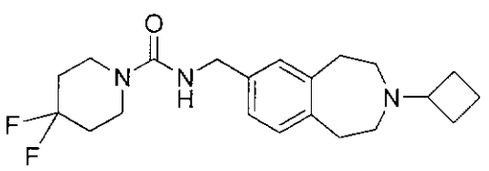


NMR: ^{1}H NMR (400 MHz, METANOL-d_4) 8.36 - 8.44 (m, 1H), 7.70 - 7.78 (m, 1H), 6.94 - 7.04 (m, 3H), 6.38 - 6.47 (m, 1H), 4.38 (s, 2H), 3.81 - 3.95 (m, 3H), 3.40 - 3.50 (m, 2H), 2.75 - 2.92 (m, 5H), 2.31 - 2.59 (m, 4H), 1.97 - 2.09 (m, 2H), 1.78 - 1.93 (m, 4H), 1.52 - 1.71 (m, 2H), 1.37 - 1.52 (m, 2H)

MS ES$^+$: 435

2.286 Ejemplo 286

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-4,4-difluoropiperidina-1-carboxamida



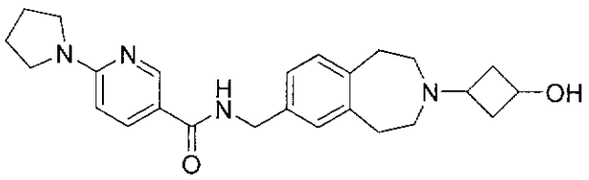
000383

NMR: ^{1}H NMR (400 MHz, METANOL-d_4) δ 7.17 - 7.30 (m, 3H), 4.41 - 4.50 (m, 2H), 3.65 - 3.76 (m, 4H), 3.05 - 3.33 (m, 5H), 2.67 - 2.97 (m, 4H), 2.28 - 2.41 (m, 2H), 2.03 - 2.26 (m, 6H), 1.81 - 1.99 (m, 2H)

MS ES$^+$: 378

2.287 Ejemplo 287

N-((3-(3-hidroxiciclobutil)-2,3,4,5-tetrahidro-1*H*-benzo[d]azepin-7-il)metil)-6-(pirrolidin-1-il)nicotinamida

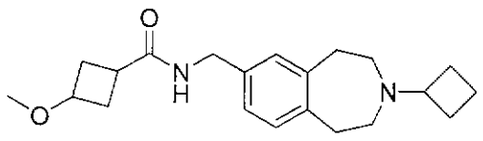


H NMR (400 MHz, CD_3OD) δ 8.55 - 8.59 (m, 1 H) 7.91 - 7.98 (m, 1 H) 7.03 - 7.12 (m, 3 H) 6.48 - 6.53 (m, 1 H) 4.49 (s, 2 H) 3.85 - 3.96 (m, 1 H) 3.44 - 3.55 (m, 4 H) 2.87 - 2.97 (m, 4 H) 2.30 - 2.60 (m, 7 H) 2.01 - 2.08 (m, 4 H) 1.75 - 1.87 (m, 2 H).

MS ES$^+$: 421.

2.288 Ejemplo 288

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3-metoxiciclobutanocarboxamida

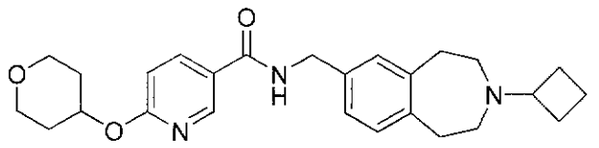


^{1}H NMR (400 MHz, MeOD) δ 6.96 - 7.15 (m, 3 H), 4.31 (m, 2 H), 4.05 - 4.19 (m, 0.3 H), 3.73 - 3.89 (m, 0.7 H), 3.25 (s, 3 H), 2.97 - 3.10 (m, 0.3 H), 2.92 (m, 5 H), 2.56 - 2.70 (m, 0.7 H), 2.33 - 2.56 (m, 6 H), 2.04 - 2.25 (m, 4 H), 1.84 - 2.05 (m, 2 H), 1.55 - 1.82 (m, 2 H)

MS ES$^+$: 343 (dos picos cis y trans isómeros)

2.289 Ejemplo 289

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(tetrahidro-2H-piran-4-iloxi)nicotinamida

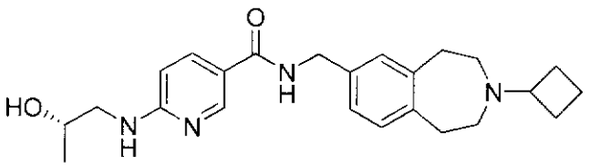


^{1}H NMR (400 MHz, DMSO-d_6) ¯ 8.95 (s, 1 H), 8.62 - 8.72 (m, 1 H), 8.08 - 8.21 (m, 1 H), 7.05 (br. s., 3 H), 6.80 - 6.93 (m, 1 H), 5.18 - 5.32 (m, 1 H), 4.41 (m, 2 H), 3.79 - 3.88 (m, 2 H), 3.45 - 3.61 (m, 2 H), 2.81 (br. s., 5 H), 2.34 (m, 4 H), 1.92 - 2.09 (m, 4 H), 1.71 - 1.91 (m, 2 H), 1.46 - 1.71 (m, 4 H)

MS ES$^+$: 436

2.290 Ejemplo 290

(S)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(2-hidroxipropilamino)nicotinamida

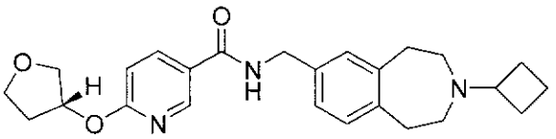


^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 0.81 - 0.92 (m, 3 H) 1.25 - 1.47 (m, 2 H) 1.47 - 1.67 (m, 2 H) 1.70 - 1.89 (m, 2 H) 1.99 - 2.23 (m, 4 H) 2.45 - 2.75 (m, 5 H) 2.95 - 3.09 (m, 2 H) 3.50 - 3.65 (m, 1 H) 4.11 - 4.22 (m, 2 H) 4.49 - 4.59 (m, 1 H) 6.27 - 6.36 (m, 1 H) 6.71 - 6.97 (m, 4 H) 7.54 - 7.68 (m, 1 H) 8.28 - 8.34 (m, 1 H) 8.35 - 8.49 (m, 1 H)

MS ES$^+$: 409

2.291 Ejemplo 291

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-[(3R)-tetrahidrofuran-3-iloxi]piridina-3-carboxamida

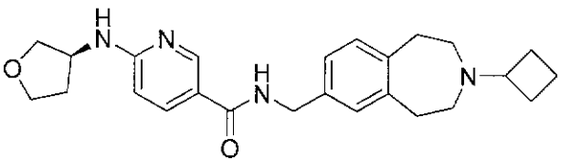


NMR: NMR: ^{1}H NMR (400 MHz, METANOL-d_4) □ 8.80 - 8.87 (m, 1H), 8.27 - 8.33 (m, 1H), 7.24 - 7.34 (m, 3H), 6.99 - 7.08 (m, 1H), 5.77 - 5.84 (m, 1H), 4.66 - 4.75 (m, 2H), 4.03 - 4.25 (m, 4H), 2.97 - 3.16 (m, 5H), 2.57 - 2.74 (m, 4H), 2.43 - 2.57 (m, 1H), 2.24 - 2.37 (m, 3H), 2.06 - 2.22 (m, 2H), 1.81 - 1.97 (m, 2H)

MS ES$^+$: 422, ES$^-$: 420

2.292 Ejemplo 292

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-[(3S)-tetrahidrofuran-3-ilamino]piridina-3-carboxamida

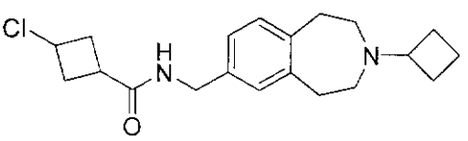


1H NMR (400 MHz, METANOL-d4) d 8.51 - 8.60 (m, 1H), 7.84 - 7.92 (m, 1H), 7.05 - 7.18 (m, 3H), 6.53 - 6.60 (m, 1H), 4.45 - 4.56 (m, 3H), 3.94 - 4.03 (m, 2H), 3.79 - 3.91 (m, 1H), 3.64 - 3.72 (m, 1H), 2.86 - 3.04 (m, 5H), 2.44 - 2.72 (m, 4H), 2.25 - 2.37 (m, 1H), 2.10 - 2.21 (m, 2H), 1.88 - 2.07 (m, 3H), 1.64 - 1.81 (m, 2H)

MS ES$^+$: 421

2.293 Ejemplo 293

3-cloro-N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]ciclobutanocarboxamida

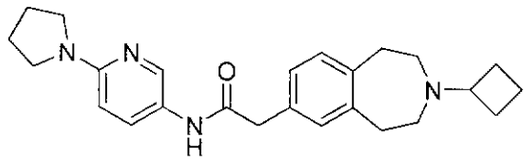


1H NMR (400 MHz, MeOD) d 6.97 - 7.11 (m, 3 H), 4.57 - 4.69 (m, 0.3 H), 4.34 - 4.46 (m, 0.7 H), 4.31 (m, 2 H), 3.23 - 3.30 (m, 0.3 H), 2.62 - 3.00 (m, 7.7 H), 2.31 - 2.65 (m, 6 H), 2.05 - 2.19 (m, 2 H), 1.86 - 2.04 (m, 2 H), 1.57 - 1.83 (m, 2 H)

MS ES$^+$: 347

2.294Ejemplo 294

2-(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-N-[6-(pirrolidin-1-il)piridin-3-il]acetamida

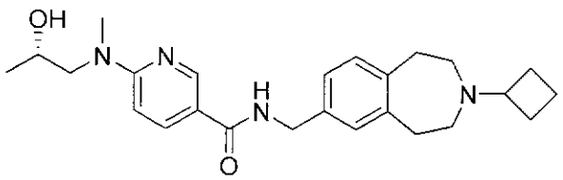


1H NMR (400 MHz, MeOD) d 8.11 - 8.20 (m, 1 H), 7.65 - 7.76 (m, 1 H), 7.05 - 7.18 (m, 3 H), 6.42 - 6.53 (m, 1 H), 3.61 (s, 2 H), 3.42 (m, 4 H), 2.96 (m, 5 H), 2.57 (br. s., 4 H), 2.15 (m, 2 H), 1.90 - 2.10 (m, 6 H), 1.75 (br. s., 2 H)

MS ES$^+$: 405

2.295 Ejemplo 295

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-{[(2S)-2-hidroxipropil](metil)amino}piridina-3-carboxamida

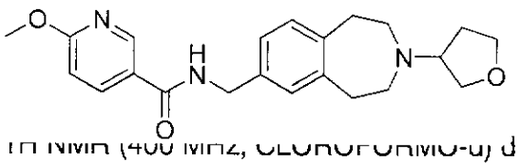


1H NMR (400 MHz, DMSO-d6) d ppm 1.03 - 1.17 (m, 3 H) 1.52 - 1.70 (m, 2 H) 1.73 - 1.90 (m, 2 H) 1.96 - 2.13 (m, 2 H) 2.21 - 2.48 (m, 4 H) 2.71 - 2.89 (m, 5 H) 3.15 (s, 3 H) 3.41 - 3.50 (m, 1 H) 3.54 - 3.66 (m, 1 H) 3.89 - 4.05 (m, 1 H) 4.36 - 4.50 (m, 2 H) 4.71 - 4.81 (m, 1 H) 6.64 - 6.74 (m, 1 H) 6.98 - 7.15 (m, 3 H) 7.93 - 8.06 (m, 1 H) 8.62 - 8.67 (m, 1 H) 8.67 - 8.76 (m, 1 H)

MS ES$^+$: 423

2.296 Ejemplo 296

6-metoxi-N-{[3-(tetrahidrofuran-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il]metil}piridina-3-carboxamida

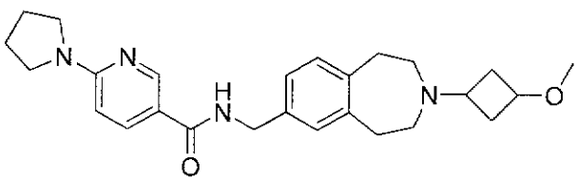


RMN ^{1}H (400 MHz, CLOROFORMO-d) d 8.56 - 8.63 (m, 1H), 7.97 - 8.05 (m, 1H), 7.06 - 7.15 (m, 3H), 6.74 - 6.82 (m, 1H), 6.14 - 6.28 (m, 1H), 4.55 - 4.65 (m, 2H), 3.91 - 4.04 (m, 4H), 3.83 - 3.91 (m, 1H), 3.67 - 3.81 (m, 2H), 3.23 - 3.33 (m, 1H), 2.86 - 2.99 (m, 4H), 2.66 - 2.78 (m, 2H), 2.50 - 2.65 (m, 2H), 1.99 - 2.11 (m, 1H), 1.82 - 1.96 (m, 1H)

MS ES$^+$: 382

2.297 Ejemplo 297

N-{[3-(3-metoxiciclobutil)-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il]metil}-6-(pirrolidin-1-il)piridina-3-carboxamida

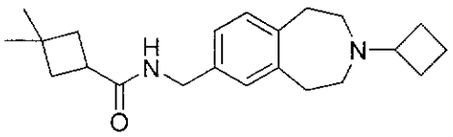


1H NMR (400 MHz, CD3OD) δ 1H NMR (400 MHz, METANOL-d4) d ppm 8.52 - 8.63 (m, 1 H) 7.88 - 8.00 (m, 1 H) 6.99 - 7.13 (m, 3 H) 6.48 - 6.55 (m, 1 H) 4.49 (s, 2 H) 3.54 - 3.67 (m, 1 H) 3.45 - 3.54 (m, 4 H) 3.24 (s, 3 H) 2.85 - 2.96 (m, 4 H) 2.37 - 2.58 (m, 7 H) 1.97 - 2.10 (m, 4 H) 1.70 - 1.86 (m, 2 H)

MS ES$^+$: 435

2.298 Ejemplo 298

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-3,3-dimetilciclobutanocarboxamida

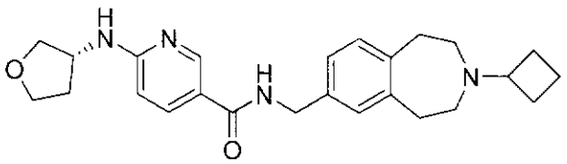


1H NMR (400 MHz, MeOD) d 6.96 - 7.13 (m, 3 H), 4.30 (s, 2 H), 2.99 - 3.14 (m, 1 H), 2.92 (m, 5 H), 2.23 - 2.66 (m, 4 H), 1.84 - 2.21 (m, 8 H), 1.58 - 1.81 (m, 2 H), 1.20 (s, 3 H), 1.10 (s, 3 H)

MS ES$^+$: 341

2.299 Ejemplo 299

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-[(3R)-tetrahidrofuran-3-ilamino]piridina-3-carboxamida

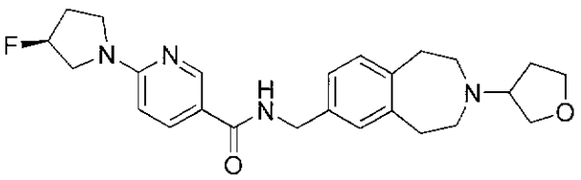


1H NMR (400 MHz, METANOL-d4) d 8.49 - 8.59 (m, 1H), 7.81 - 7.92 (m, 1H), 7.05 - 7.15 (m, 3H), 6.51 - 6.61 (m, 1H), 4.44 - 4.56 (m, 3H), 3.94 - 4.03 (m, 2H), 3.81 - 3.91 (m, 1H), 3.65 - 3.74 (m, 1H), 2.80 - 2.99 (m, 5H), 2.40 - 2.60 (m, 4H), 2.26 - 2.37 (m, 1H), 2.06 - 2.17 (m, 2H), 1.88 - 2.03 (m, 3H), 1.63 - 1.79 (m, 2H)

MS ES$^+$: 421

2.300 Ejemplo 300

6-((S)-3-fluoropirrolidin-1-il)-N-((3-(tetrahidrofuran-3-il)-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)nicotinamida



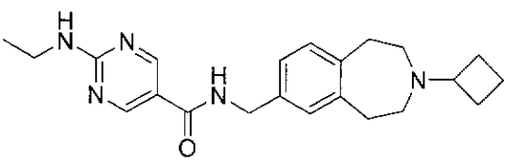
1H NMR (400 MHz, CD3OD-d4) δ 8.49 - 8.59 (m, 1H), 7.81 - 7.92 (m, 1H), 7.05 - 7.15 (m, 3H), 6.51 - 6.61 (m, 1H), 4.44 - 4.56 (m, 3H), 3.94 - 4.03 (m, 2H), 3.81 - 3.91 (m, 1H), 3.65

- 3.74 (m, 1H), 2.80 - 2.99 (m, 5H), 2.40 - 2.60 (m, 4H), 2.26 - 2.37 (m, 1H), 2.06 - 2.17 (m, 2H), 1.88 - 2.03 (m, 3H), 1.63 - 1.79 (m, 2H)

MS ES$^+$: 439

2.301Ejemplo 301

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-(etilamino)pirimidina-5-carboxamida

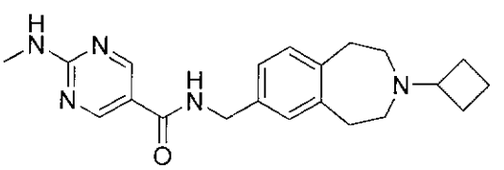


1H NMR (400 MHz, CD3OD) δ 8.34 - 8.94 (m, 2H), 6.73 - 7.32 (m, 3H), 4.12 - 4.45 (m, 2H), 3.23 - 3.48 (m, 2H), 2.53 - 2.88 (m, 5H), 1.34 - 2.49 (m, 10H), 1.12 (m, 3H)

MS ES$^-$: 380

2.302 Ejemplo 302

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-(metilamino)pirimidina-5-carboxamida

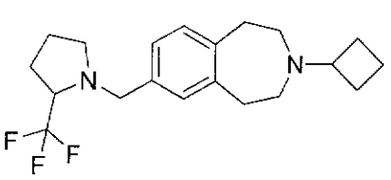


1H NMR (400 MHz, CD3OD) δ 8.28 - 8.88 (m, 2H), 6.73 - 7.26 (m, 3H), 4.10 - 4.45 (m, 2H), 2.52 - 2.93 (m, 8H), 1.88 (m, 10H)

MS ES$^+$: 365

2.303 Ejemplo 303

3-ciclobutil-7-((2-(trifluorometil)pirrolidin-1-il)metil)-2,3,4,5-tetrahidro-1H-benzo[d]azepina

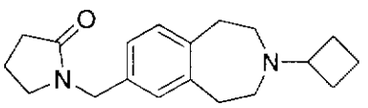


1H NMR (400 MHz, CDCl3-d) δ 7.07 (s, 3H), 4.01 - 4.28 (m, 1H), 3.49 - 3.71 (m, 1H), 3.17 - 3.41 (m, 1H), 2.69 - 3.11 (m, 6H), 2.25 - 2.66 (m, 5H), 1.88 (ninguno, 10H)

MS ES^+: 354

2.304 Ejemplo 304

1-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)pirrolidin-2-ona

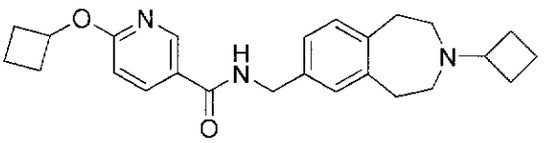


1H NMR (400 MHz, CDCl3-d) δ 6.94 - 7.15 (m, 3H), 4.31 - 4.52 (m, 2H), 3.19 - 3.40 (m, 2H), 2.84 - 3.00 (m, 4H), 2.69 - 2.84 (m, 1H), 2.33 - 2.58 (m, 5H), 1.81 - 2.19 (m, 6H), 1.68 (ninguno, 3H)

MS ES^+: 299

2.305 Ejemplo 305

6-ciclobutoxi-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)nicotinamida

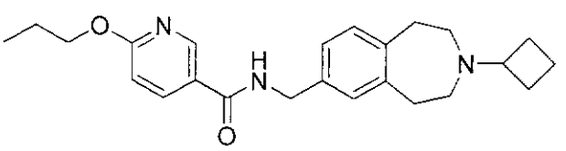


NMR: 1H NMR (400 MHz, DMSO) d 8.94 (t, 1H), 8.66 (d, 1H), 8.14 (dd, 1H), 7.00-7.07 (m, 3H), 6.84 (dd, 1H), 5.18 (quint, 1H), 4.41 (d, 2H), 2.68-2.84 (m, 5H), 2.23-2.46 (m, 6H), 1.94-2.13 (m, 4H), 1.70-1.84 (m, 3H), 1.48-1.70 (m, 3H)

MS ES^-: 406

2.306 Ejemplo 306

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-propoxynicotinamida

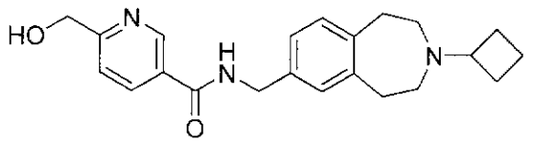


NMR: 1H NMR (400 MHz, DMSO) d 8.84 (s, 1H), 8.69 (s, 1H), 8.15 (dd, 1H), 7.05 (s, 3H), 6.85 (dd, 1H), 4.35-4.51 (m, 2H), 4.16-4.35 (m, 2H), 2.70-2.92 (m, 5H), 2.25-2.45 (m, 4H), 1.91-2.10 (m, 2H), 1.68-1.90 (m, 4H), 1.48-1.68 (m, 2H), 0.78-1.16 (m, 3H)

MS ES$^+$: 394

2.307 Ejemplo 307

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(hidroximetil)nicotinamida

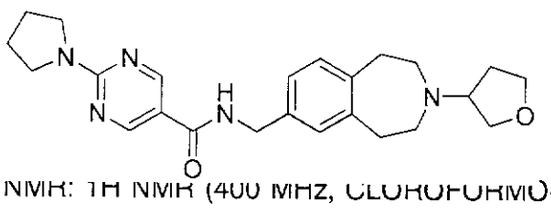


1H NMR (400 MHz, CLOROFORMO-d) d 8.72 - 9.13 (m, 1H), 7.90 - 8.28 (m, 1H), 7.31 - 7.48 (m, 1H), 7.01 - 7.20 (m, 3H), 6.19 - 6.51 (m, 1H), 4.73 - 5.03 (m, 2H), 4.46 - 4.73 (m, 2H), 3.41 - 3.65 (m, 1H), 2.69 - 3.07 (m, 5H), 2.25 - 2.68 (m, 3H), 1.87 (ninguno, 6H)

MS ES$^+$: 366

2.308 Ejemplo 308

2-(pirrolidin-1-il)-N-((3-(tetrahidrofuran-3-il)-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)pirimidina-5-carboxamida

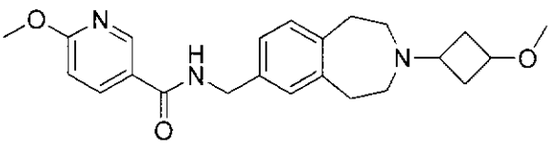


NMR: 1H NMR (400 MHz, CLOROFORMO-d) d 8.64 - 8.82 (m, 2H), 7.03 - 7.17 (m, 3H), 6.05 - 6.19 (m, 1H), 4.51 - 4.67 (m, 2H), 3.93 - 4.03 (m, 1H), 3.84 - 3.92 (m, 1H), 3.69 - 3.82 (m, 2H), 3.56 - 3.69 (m, 4H), 3.22 - 3.35 (m, 1H), 2.85 - 3.02 (m, 4H), 2.66 - 2.79 (m, 2H), 2.51 - 2.65 (m, 2H), 1.97 - 2.12 (m, 5H), 1.83 - 1.97 (m, 1H)

MS ES$^+$: 422

2.309 Ejemplo 309

6-metoxi-N-((3-(3-metoxiciclobutil)-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)nicotinamida

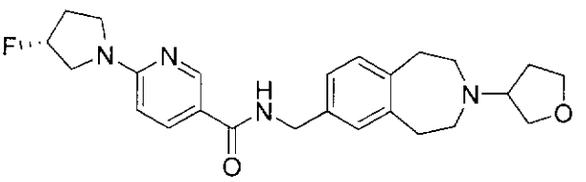


1H NMR (400 MHz, CD3OD) δ 8.61 - 8.70 (m, 1 H) 8.05 - 8.13 (m, 1 H) 7.02 - 7.12 (m, 3 H) 6.79 - 6.87 (m, 1 H) 4.50 (s, 2 H) 3.96 (s, 3 H) 3.62 (m, 1 H) 3.24 (s, 3 H) 2.87 - 2.96 (m, 4 H) 2.34 - 2.62 (m, 7 H) 1.72 - 1.86 (m, 2 H).

MS ES$^+$: 396

2.310 Ejemplo 310

6-((R)-3-fluoropirrolidin-1-il)-N-((3-(tetrahidrofuran-3-il)-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)nicotinamida

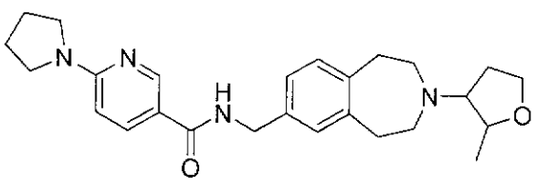


1H NMR (400 MHz, METANOL-d4) □ 8.57 - 8.69 (m, 1H), 7.94 - 8.05 (m, 1H), 7.03 - 7.16 (m, 3H), 6.54 - 6.62 (m, 1H), 5.31 - 5.52 (m, 1H), 4.45 - 4.56 (m, 2H), 3.92 - 4.00 (m, 1H), 3.82 - 3.91 (m, 2H), 3.65 - 3.80 (m, 5H), 3.52 - 3.63 (m, 1H), 2.87 - 3.00 (m, 4H), 2.54 - 2.79 (m, 4H), 2.06 - 2.45 (m, 3H), 1.83 - 1.96 (m, 1H)

MS ES$^+$: 439

2.311 Ejemplo 311

N-((3-(2-metiltetrahidrofuran-3-il)-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(pirrolidin-1-il)nicotinamida

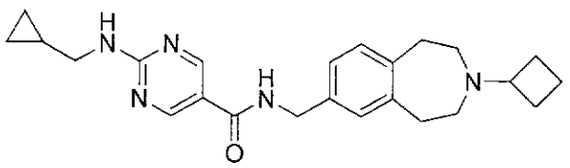


1H NMR (400 MHz, DMSO-d6) □ ppm 1.06 - 1.19 (m, 3 H) 1.79 - 2.03 (m, 6 H) 2.54 - 2.67 (m, 2 H) 2.77 - 2.89 (m, 4 H) 2.93 - 3.03 (m, 1 H) 3.37 - 3.49 (m, 4 H) 3.54 - 3.69 (m, 1 H) 3.79 - 3.89 (m, 1 H) 3.93 - 4.05 (m, 1 H) 4.34 - 4.44 (m, 2 H) 6.40 - 6.52 (m, 1 H) 6.97 - 7.10 (m, 3 H) 7.89 - 8.01 (m, 1 H) 8.57 - 8.73 (m, 2 H), 2H was hidden with the residure of DMSO.

MS ES$^+$: 435

2.312 Ejemplo 312

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-2-[(ciclopropilmetil)amino]pirimidina-5-carboxamida

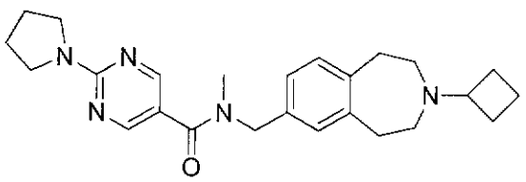


1H NMR (400 MHz, CLOROFORMO-d) □ 8.70 (br. s., 2H), 7.02 - 7.17 (m, 3H), 6.12 (br. s., 1H), 5.58 (br. s., 1H), 4.57 (d, J = 5.31 Hz, 2H), 3.33 (t, J = 6.32 Hz, 2H), 1.43 - 3.11 (m, 15H), 0.98 - 1.19 (m, 1H), 0.49 - 0.67 (m, 2H), 0.27 (q, J = 4.88 Hz, 2H)

MS ES$^+$: 406

2.313 Ejemplo 313

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-N-metil-2-(pirrolidin-1-il)pirimidina-5-carboxamida

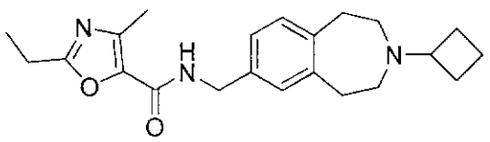


1H NMR (400 MHz, DICLOROMETANO-d2) □ 8.38 (s, 2H), 6.83 - 7.11 (m, 3H), 4.51 (s, 2H), 3.30 - 3.59 (m, 5H), 2.90 (s, 8H), 2.34 (br. s., 3H), 1.36 - 2.14 (m, 10H)

MS ES$^+$: 421

2.314 Ejemplo 314

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-2-etil-4-metil-1,3-oxazol-5-carboxamida

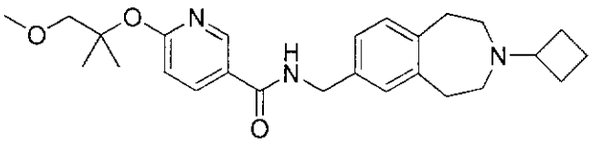


1H NMR (400 MHz, METANOL-d4) □ 6.98 - 7.16 (m, 3H), 4.45 (s, 2H), 2.74 - 3.00 (m, 7H), 2.30 - 2.59 (m, 7H), 2.03 - 2.15 (m, 2H), 1.85 - 2.01 (m, 2H), 1.58 - 1.84 (m, 2H), 1.25 - 1.48 (m, 3H)

MS ES$^+$: 368

2.315 Ejemplo 315

N-[(3-ciclobutil-2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)metil]-6-[(1-metoxi-2-metilpropan-2-il)oxy]piridina-3-carboxamida

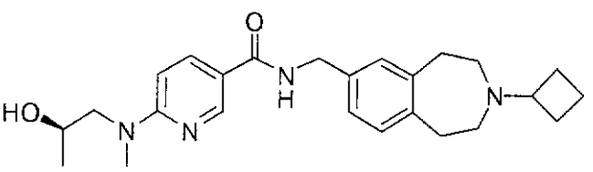


1H NMR (400 MHz, CD3OD) δ 8.55 - 8.67 (m, 1 H) 7.98 - 8.07 (m, 1 H) 7.00 - 7.13 (m, 3 H) 6.69 - 6.78 (m, 1 H) 4.50 (s, 2 H) 3.72 (s, 2 H) 3.36 (s, 3 H) 2.88 - 2.95 (m, 4 H) 2.76 - 2.87 (m, 1 H) 2.46 (br. s., 4 H) 2.04 - 2.15 (m, 2 H) 1.86 - 2.00 (m, 2 H) 1.61 - 1.77 (m, 2 H) 1.57 (s, 6 H).

MS ES$^-$: 438

2.316 Ejemplo 316

(R)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-((2-hidroxipropil)(metil)amino)nicotinamida

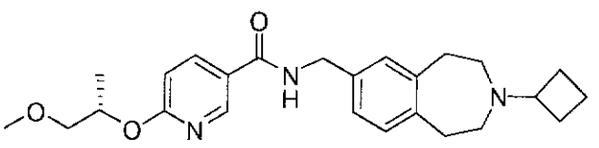


1H NMR (400 MHz, DMSO-d6) ppm 0.98 - 1.12 (m, 3 H) 1.47 - 1.66 (m, 2 H) 1.69 - 1.85 (m, 2 H) 1.93 - 2.08 (m, 2 H) 2.21 - 2.42 (m, 4 H) 2.66 - 2.86 (m, 5 H) 3.10 (s, 3 H) 3.36 - 3.46 (m, 1 H) 3.49 - 3.61 (m, 1 H) 3.85 - 3.98 (m, 1 H) 4.32 - 4.45 (m, 2 H) 4.67 - 4.76 (m, 1 H) 6.58 - 6.70 (m, 1 H) 6.96 - 7.09 (m, 3 H) 7.90 - 7.99 (m, 1 H) 8.58 - 8.62 (m, 1 H) 8.62 - 8.72 (m, 1 H)

MS ES$^+$: 423

2.317 Ejemplo 317

(S)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(1-metoxipropan-2-iloxi)nicotinamida

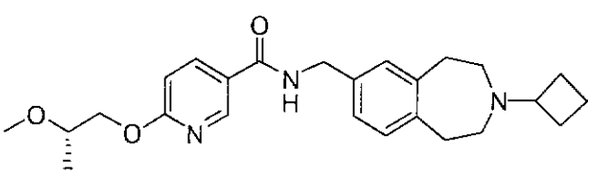


1H NMR (400 MHz, CD3OD) δ 8.61 - 8.64 (m, 1 H) 8.06 - 8.10 (m, 1 H) 7.04 - 7.12 (m, 3 H) 6.77 - 6.82 (m, 1 H) 5.38 - 5.48 (m, 1 H) 4.50 (s, 2 H) 3.50 - 3.64 (m, 2 H) 3.37 (s, 3 H) 2.87 - 2.95 (m, 4 H) 2.77 - 2.87 (m, 1 H) 2.46 (br. s., 4 H) 2.04 - 2.15 (m, 2 H) 1.87 - 1.99 (m, 2 H) 1.60 - 1.77 (m, 2 H) 1.29 - 1.34 (m, 3 H).

MS ES$^+$: 424

2.318 Ejemplo 318

(S)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-6-(2-metoxipropoxi)nicotinamida



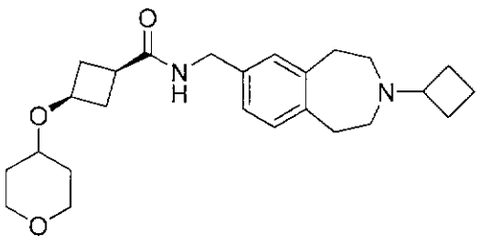
1H NMR (400 MHz, CD3OD) δ 8.61 - 8.67 (m, 1 H) 8.07 - 8.14 (m, 1 H) 7.02 - 7.13 (m, 3 H) 6.83 - 6.89 (m, 1 H) 4.50 (s, 2 H) 4.27 - 4.39 (m, 2 H) 3.71 - 3.80 (m, 1 H) 3.41 (s, 3 H)

2.88 - 2.96 (m, 4 H) 2.78 - 2.88 (m, 1 H) 2.46 (br. s., 4 H) 2.05 - 2.15 (m, 2 H) 1.87 - 2.00 (m, 2 H) 1.60 - 1.77 (m, 2 H) 1.20 - 1.27 (m, 3 H).

MS ES$^+$: 424

2.319 Ejemplo 319

cis-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3-(tetrahidro-2H-piran-4-iloxi)ciclobutanocarboxamida

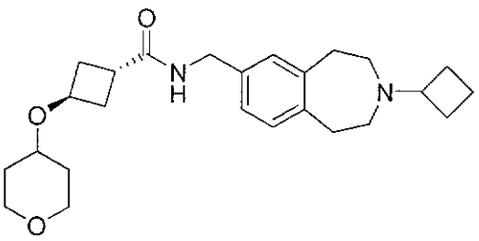


1H NMR (400 MHz, DICLOROMETANO-d2) Shift 6.84 - 7.06 (m, 3H), 5.68 (br. s., 1H), 4.19 - 4.31 (m, 2H), 3.72 - 3.94 (m, 3H), 3.39 (tt, J = 4.23, 8.91 Hz, 1H), 3.22 - 3.34 (m, 2H), 2.79 (br. s., 4H), 1.32 - 2.52 (m, 20H)

MS ES$^+$: 413

2.320 Ejemplo 320

trans-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-3-(tetrahidro-2H-piran-4-iloxi)ciclobutanocarboxamida

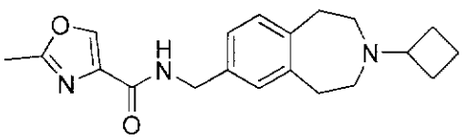


1H NMR (400 MHz, DICLOROMETANO-d2) conversión 6.94 - 7.18 (m, 3H), 5.77 (br. s., 1H), 4.28 - 4.49 (m, 3H), 3.81 - 3.99 (m, 2H), 3.44 - 3.61 (m, 1H), 3.32 - 3.46 (m, 2H), 2.65 - 3.11 (m, 5H), 2.28 - 2.59 (m, 5H), 2.15 - 2.28 (m, 2H), 2.01 - 2.15 (m, 2H), 1.31 - 2.01 (m, 10H)

MS ES$^+$: 413

3.321 Ejemplo 321

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-metiloxazol-4-carboxamida

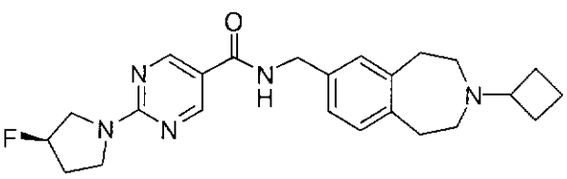


1H NMR (400 MHz, MeOD) d 8.21 - 8.31 (m, 1 H), 7.04 - 7.13 (m, 3 H), 4.49 (s, 2 H), 2.76 - 2.99 (m, 5 H), 2.48 (s, 7 H), 2.05 - 2.19 (m, 2 H), 1.87 - 2.03 (m, 2 H), 1.58 - 1.82 (m, 2 H)

MS ES^+: 340

3.322 Ejemplo 322

(R)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-(3-fluoropirrolidin-1-il)pirimidina-5-carboxamida

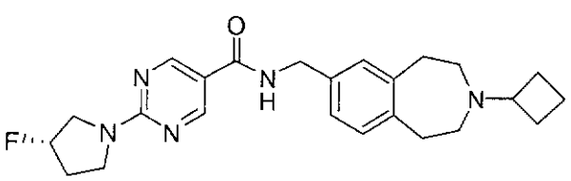


1H NMR (400 MHz, CD3OD / CD2Cl2) δ 8.79 (s, 2 H) 7.00 - 7.14 (m, 3 H) 5.26 - 5.48 (m, 1 H) 4.49 (s, 2 H) 3.58 - 4.05 (m, 4 H) 2.75 - 2.98 (m, 5 H) 2.17 - 2.60 (m, 6 H) 2.03 - 2.17 (m, 2 H) 1.84 - 2.01 (m, 2 H) 1.57 - 1.77 (m, 2 H).

MS ES^+: 424

3.323 Ejemplo 323

(S)-N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-(3-fluoropirrolidin-1-il)pirimidina-5-carboxamida

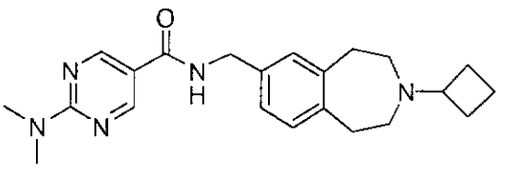


1H NMR (400 MHz, CD3OD / CD2Cl2) δ 8.79 (s, 2 H) 7.01 - 7.13 (m, 3 H) 5.29 - 5.48 (m, 1 H) 4.49 (s, 2 H) 3.58 - 4.03 (m, 4 H) 2.75 - 3.01 (m, 5 H) 2.16 - 2.67 (m, 6 H) 2.03 - 2.14 (m, 2 H) 1.86 - 2.03 (m, 2 H) 1.58 - 1.78 (m, 2 H).

MS ES^+: 424

3.324 Ejemplo 324

N-((3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)metil)-2-(dimetilamino)pirimidina-5-carboxamida

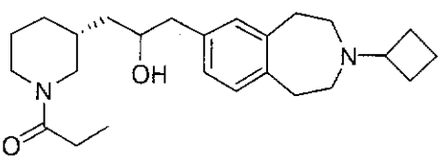


1H NMR (400 MHz, CD3OD) δ 8.76 (s, 2 H) 7.02 - 7.15 (m, 3 H) 4.48 (s, 2 H) 3.23 (s, 6 H) 2.76 - 2.98 (m, 5 H) 2.48 (br. s., 4 H) 2.03 - 2.18 (m, 2 H) 1.85 - 2.01 (m, 2 H) 1.56 - 1.80 (m, 2 H).

MS ES^+: 380

3.325 Ejemplo 325

1-((3R)-3-(3-(3-ciclobutil-2,3,4,5-tetrahidro-1H-benzo[d]azepin-7-il)-2-hidroxipropil)piperidin-1-il)propan-1-ona



1H NMR (400 MHz, CD3OD) δ 6.85 - 7.11 (m, 3 H) 4.19 - 4.43 (m, 1 H) 3.68 - 3.98 (m, 2 H) 2.58 - 3.19 (m, 9 H) 2.28 - 2.57 (m, 5 H) 1.55 - 2.18 (m, 9 H) 1.01 - 1.55 (m, 8 H)

MS ES^+: 399

3. Eficacia biológica de los compuestos de la invención

3.1 Análisis de Unión a H3 In Vitro

La capacidad de los compuestos para unirse al receptor H3 fue determinada al medir la reducción en el enlace tritiado N-α-metil-histamina (^{3}H-NαMH) en un ensayo de unión competitiva. Se monitorearon cambios en los niveles del radio-marcador unido por conteo de centelleo con un Microbeta Trilux (Perkin Elmer).

Las membranas fueron preparadas a partir de células CHO-K1 expresando establemente el receptor H3 humano, cultivadas rutinariamente como monocapas en el medio Ham's F12 (Invitrogen) suplementado con 10% Foetal Clone III (Hyclone), 500μg/ml de G418 (Invitrogen), 5 μg/ml de blasticidina S (Invivogen) y 50 μg/ml de Gentamicina (Sigma) en CO_2 al 5% a 37°C. Las células fueron cultivadas hasta un 80-95% de confluencia, enjuagadas una vez con 1x PBS (Invitrogen) y separadas por incubación con 1x PBS conteniendo 0.02% de EDTA (Sigma) durante 10 minutos a temperatura ambiente. Las células fueron recolectadas por centrifugación a 900 xg, 4°C por 10 minutos. Las células fueron enjuagadas una vez con 1x PBS y re-suspendidas en un buffer de homogenización a temperatura de hielo (50mM de Tris-HCl (pH 7.4), 2.5mM de EDTA, 5mM de $MgCl_2$, 200mM de Sucrosa) a $1x10^7$ células/ml y mantenidas en hielo. Las células fueron homogenizadas sobre hielo y el debris fue removido por centrifugación a 500 x g, 4°C durante 5 minutos. El sobrenadante resultante fue centrifugado a 75,600 xg, 4°C por 60 minutos. Las membranas fueron suspendidas en un buffer de homogenización, se determinó la concentración de proteína (BCA Protein Assay kit (Pierce)), fueron diluídas a 2.2 mg/ml, dispensadas en alícuotas de 1 ml y almacenadas a -80 °C.

Las membranas fueron descongeladas sobre hielo, sonicadas con 4 ciclos de 20 pulsos (50% amplitud, 0.5 pulso) (UP200S Hielscher) sobre hielo, diluídas en un bufer de ensayo (50mM de Tris-HCl (pH7.4), 5mM de $MgCl_2$) para 62.5 μg/ml. El compuesto fue diluído serialmente en DMSO antes de ser diluído 1:10 en buffer de ensayo. Se agregaron 5μg de membrana en 80 μl de buffer de ensayo por cadapocillo de una placa de 96 pocillos de poliestireno (Corning). Se agregó 10 μl de compuesto por pocillo. El ensayo fue iniciado

por la adición de 10 µl de 20nM ^{3}H-NαMH por pocillo e incubado durante una hora a temperatura ambiente con agitación. La unión total se determinó en la presencia de 1% DMSO y la unión no específica fue determinada por la inclusión de 1 µM de R-α-metilo-histamina (RαMH). Las incubaciones fueron luego filtradas a través de un filtro tipo filtermat A (Perkin Elmer) y lavadas tres veces con buffer de ensayo. Los filtros tipo filtermats fueron secados a 42° C por dos horas, se agregó centelleante y se determinó el nivel de radioactividad fijada.

Los valores IC50 para los compuestos fueron determinados a partir de estudios de dosis-respuesta en escala logaritmica de siete puntos y representan la concentración de compuesto requerida para inhibir el 50% de la unión específica de ^{3}H-NαMH 2nM (diferencia entre la unión total y la unión no específica). Las curvas fueron generadas usando el promedio de pocillos duplicados para cada punto de información y fueron analizadas utilizando regresión no lineal de una curva de dosis respuesta sigmoidea. (pendiente variable).

3.2 Ensayo Funcional H3 In Vitro

La actividad funcional de los compuestos en el receptor H3 fue determinada midiendo los cambios en el nivel de cAMP intracelular, utilizando un ensayo del reportero luciferasa llevando un elemento de respuesta a cAMP. Los cambios en la expresión de luciferasa fueron monitoreados por un lector de placa de luminiscencia, Analyst HT (MDS Analítica). Los aumentos en cAMP intracelular fueron detectados fácilmente al activar la proteína quinasa A por forskolina (Sigma) y la supresión de esta respuesta fue observada con la aplicación del agonista RαMH (Sigma) del receptor H3 .

Células CHO(dhfr^{-})-cre-luc expresando establemente los receptores H3 humanos fueron cultivadas rutinariamente como monocapas en *Minimal Essential Medium α (MEMα) (Invitrogen)* suplementadas con 10% FBS dializado (Hyclone), en 5% CO_2 a 37°C. 48 horas previas al ensayo, las células fueron sembradas en placas de 384 pocillos de pared

blanca y base clara (Corning) a una densidad de 5000 células/pocillo. En el día del ensayo, el medio de cultivo fue removido y reemplazado por 15 µl de buffer de ensayo (MEMα, 5 mg/ml de BSA libre de ácido graso (Sigma)) por pocillo. Luego, las células fueron incubadas durante 30 minutos a 37°C, 5% CO_2. El compuesto fue diluído serialmente en DMSO antes de ser diluído 1:10 con buffer del ensayo. Se agregaron 2.5 µl de compuesto diluído en buffer de ensayo y las células fueron incubadas por 5 minutos a 37°C, 5% CO_2. Luego, 2.5 µl de cada reactivo fueron agregados en el siguiente orden: RαMH (10 nM), isobutilmetilxantina (1-metil-3-(2-metilpropil)-7H-purina-2,6-diona; IBMX) (500 µM) (Sigma) y forskolina (1 µM). Las células luego fueron incubadas durante 90 minutos a 37°C, 5% CO_2, seguido por 30 minutos a temperatura ambiente. Al final de la incubación, se agregaron 25 µl de reactivo *Steadylite* (Perkin Elmer), las placas fueron selladas y colocadas en un agitador por 5 minutos. Luego fue medido el nivel de la salida de luz para determinar el nivel de expresión de luciferasa.

Los valores IC50 de los compuestos fueron determinados a partir de estudios de dosis-respuesta en escala semi-logarítmica de diez puntos y representan la concentración del compuesto requerido para prevenir el 50% de inhibición de células estimuladas por forskolina, en la presencia de RαMH solo. Las curvas se generaron usando el promedio de pocillos duplicados para cada punto de información y fueron analizadas usando regresión no lineal de una curva de dosis respuesta de cuatro parámetros.

3.3 Resultados

Los resultados de los ensayos biológicos llevados a cabo en 3.1 y 3.2 anteriores, fueron los siguientes:

Compuesto Ejemplo	Unión de hH3 IC_{50}/nM	hH3 funcional IC_{50}/nM
Ejemplo 1	1	0.7
Ejemplo 5	22	31

000407

Ejemplo 11	30	
Ejemplo 19	20	
Ejemplo 20	11	3
Ejemplo 21	13	
Ejemplo 23	11	2
Ejemplo 24	44	16
Ejemplo 25	37	
Ejemplo 26	36	
Ejemplo 27	21	
Ejemplo 29	13	8
Ejemplo 30	5	
Ejemplo 34	26	5
Ejemplo 35	11	1
Ejemplo 36	12	2
Ejemplo 38	9	
Ejemplo 40	3	2
Ejemplo 42	9	30
Ejemplo 44	14	3
Ejemplo 45	13	
Ejemplo 49	34	
Ejemplo 50	24	
Ejemplo 53	51	6
Ejemplo 54	10	
Ejemplo 55	12	
Ejemplo 57	12	

000408

Ejemplo 59	6	3
Ejemplo 63	6	
Ejemplo 65	4	
Ejemplo 67	11	
Ejemplo 68	1	3
Ejemplo 69	2	0.5
Ejemplo 70	5	3
Ejemplo 72	1	2
Ejemplo 73	12	1
Ejemplo 74	3	1
Ejemplo 75	15	
Ejemplo 77	3	1
Ejemplo 78	4	2
Ejemplo 79	6	3
Ejemplo 81	0.4	0.8
Ejemplo 84	10	
Ejemplo 85	14	
Ejemplo 86	3	1
Ejemplo 87	4	
Ejemplo 88	5	2
Ejemplo 89	18	
Ejemplo 90	10	
Ejemplo 91	6	
Ejemplo 92	4	1
Ejemplo 93	29	

000409

Ejemplo 95	18	
Ejemplo 96	18	
Ejemplo 97	9	2
Ejemplo 98	15	
Ejemplo 99	18	
Ejemplo 100	2	0.5
Ejemplo 102	18	
Ejemplo 103	11	1
Ejemplo 106	13	
Ejemplo 107	9	4
Ejemplo 108	1	4
Ejemplo 109	2	
Ejemplo 110	17	
Ejemplo 111	7	7
Ejemplo 113	13	
Ejemplo 114	12	19
Ejemplo 120	1	
Ejemplo 131	30	
Ejemplo 132	6	
Ejemplo 134	13	1
Ejemplo 137	26	
Ejemplo 143	24	7
Ejemplo 146	10	10
Ejemplo 155	24	
Ejemplo 164	10	5

000120

Ejemplo 167	22	71
Ejemplo 171	14	4
Ejemplo 181	21	4
Ejemplo 191	13	2
Ejemplo 194	26	7
Ejemplo 211	6	9
Ejemplo 216	41	20
Ejemplo 221	11	3
Ejemplo 224	2	4
Ejemplo 231	23	15
Ejemplo 233	2	16
Ejemplo 239	16	1
Ejemplo 242	0.6	3
Ejemplo 244	10	6
Ejemplo 251	11	6
Ejemplo 253	1	4
Ejemplo 256	0.3	3
Ejemplo 257	25	7
Ejemplo 262	25	10
Ejemplo 263	18	6
Ejemplo 265	6	4
Ejemplo 268	4	
Ejemplo 269	2.5	
Ejemplo 274	9	
Ejemplo 275	7	

Ejemplo 276	19	
Ejemplo 280	0.3	
Ejemplo 281	0.8	
Ejemplo 282	1	
Ejemplo 287	1	
Ejemplo 290	3	
Ejemplo 294	8	
Ejemplo 300	5	
Ejemplo 302	3	
Ejemplo 304	61	34
Ejemplo 306	18	2
Ejemplo 313	1	
Ejemplo 315	2	
Ejemplo 316	0.9	
Ejemplo 319	62	

Estos resultados indican que los compuestos de la invención tienen una potente actividad antagonista o agonista inverso en el receptor H3, ambos, en términos de unión y en términos de inhibición de la respuesta funcional causada por la activación del receptor. Los compuestos probados anteriormente muestran valores IC_{50} de menos de 1 μM, y varios compuestos muestran afinidad nanomolar baja en el receptor de H3. En consecuencia, se espera que los compuestos de la invención tengan utilidad en la prevención o tratamiento de las condiciones, tales como las mencionadas anteriormente, en las cuales la actividad del receptor H3 está implicada.

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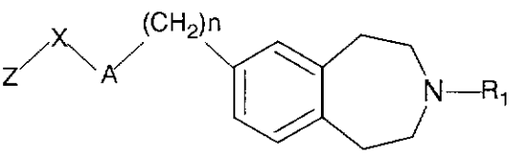
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REIVINDICACIONES

1. Un compuesto que tiene la fórmula:



en donde:

R1 es un grupo seleccionado de C_{3-8} cicloalquilo, C_{1-6} alquilo, C_{1-6} alquileno-C_{3-8} cicloalquilo, cada uno de los grupos pueden ser opcionalmente sustituidos con C_{1-6} alquilo, halógeno, haloC_{1-6} alquilo o OR15, o R1 es heterociclilo, opcionalmente sustituido con C_{1-6} alquilo, haloC_{1-6} alquilo o OR15;

n es 0, 1, 2, 3 o 4, el grupo alquileno -$(CH_2)_n$- formado de este modo siendo opcionalmente sustituido con un grupo seleccionado de C_{1-4} alquilo, C_{3-8} cicloalquilo y arilsulfonilo;

A es un grupo seleccionado de -N(R2)CO-, -CON(R2)-, -OC(O)-, -C(O)O-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cicloalquileno-, -C(R2)(haloC_{1-6} alquilo)-, C_{1-4} alquileno y -C(OR3)(haloC_{1-6} alquilo)-;

R2 y R3 cada uno son independientemente seleccionados de H, C_{1-6} alquilo y C_{3-8} cicloalquilo, o cuando A es -N(R2)CO- y X está ausente, R2 puede formar, junto con el átomo de nitrógeno adyacente y Z, un grupo heterociclilo que contiene N, el cual puede ser sustituido opcionalmente;

X está ausente o es C_{1-4} alquileno o C_{2-4} alquenileno, cada uno de los cuales puede ser opcionalmente sustituido con uno o más grupos C_{1-4} alquilo, OR16, halógeno o haloC_{1-6} alquilo;

Z es seleccionado de arilo, heteroarilo, C_{3-8} cicloalquilo, y heterociclilo, cada uno de los cuales puede ser opcionalmente sustituido por un grupo seleccionado de -Y-arilo, -Y-

heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo, o cuando X está presente, Z puede ser H, o cuando X está ausente y A es -C(R2)(OR3)- o -N(R2)CO-, Z puede ser H, o cuando A es -N(R2)CO- y X está ausente, Z puede formar, junto con el átomo de nitrógeno adyacente y R2, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido, en donde, cuando A es -CO-, Z está ligado a X o A via un átomo de carbono y en donde, cuando A es –N(R2)CO- y Z es H, R1 es C_{3-8} cicloalquilo; y

Y representa un enlace, C_{1-6} alquileno, CO, NR14, COC_{2-6} alquenileno, O, SO_2 o $NHCOC_{1-6}$ alquileno;

en donde dichos grupos Z cicloalquilo, arilo, heteroarilo y heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes, y los cuales son seleccionados de halógeno, haloC_{1-6} alquilo, hidroxi, ciano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alquil-NR5R6, -C_{3-8} cicloalquil-NR5R6, -CONR12R13, -NR12COR13, -NR5SO_2R6, -OCONR5R6, -NR5CO_2R6, -NR4CONR5R6 o -SO_2NR5R6-SHR8, -alquil-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, -alquil-SO_2R9, -alquil-CONHR9, -alquil-SONHR9, -alquil-COR10, -CO-alquil-R10, -O-alquilo-R11 (en donde R4, R5 y R6 independientemente representan hidrógeno, C_{1-6} alquilo, -C_{3-8} cicloalquilo, -C_{1-6} alquileno-C_{3-8} cicloalquilo, arilo, heterociclilo o heteroarilo, en donde R8 representa C_{1-6} alquilo, en donde R9 representa C_{1-6} alquilo o arilo, en donde R10 representa arilo, en donde R11 representa C_{3-8} cicloalquilo o arilo, R12, R13, R14, R15 y R16, cada uno representa independientemente H o C_{1-6} alquilo, y en donde -NR5R6 y -NR12R13 pueden representar un grupo heterociclilo que contiene nitrógeno); en donde dichos grupos R4, R5, R6 R8, R9, R10 y R11 pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes, y los cuales están seleccionados del grupo que consiste de halógeno, hidroxi, C_{1-6} alquilo, C_{1-6} alcoxi, ciano, amino, =O o trifluorometilo;

y en donde los sustituyentes de Z seleccionados de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes seleccionados de =O, hidroxi, ciano, nitro, halógeno, haloC_{1-6} alquilo y C_{1-6} alquilo;

y en donde, cuando A es C_{1-4} alquileno, dicho grupo Z cicloalquilo, arilo, heteroarilo o heterociclilo (como un grupo heterociclilo Z) es sustituido al menos con hidroxi, CF_3, o =O;

y en donde, cuando A es CON(R2) n es 1;

o una sal aceptable para uso farmacéutico, o un éster de la misma,

siempre que: cuando A es -CO-, R1 es CH_3, C_{3-8} cicloalquilo-sustituido C_{1-6} alquileno o n-butilo, n es 0 y X es -CH_2CH_2-, Z no sea N-benzil sustituido 4-piperidinil, N-(3-fluorobenzil)-sustituido 4-piperidinil o N-acetil sustituido 4-piperidinil;

cuando A es -OC(O)-, R1 es ciclobutilo, n es 0 y X es -CH_2CH_2-, Z no sea H;

cuando A es -OC(O)-, R1 es n-propilo, n es 0 y X es -CH_2-, Z no sea H; y

cuando A es –CO-, R1 es CH_3, n es 0 y X es CH_2, Z no sea H.

2. Un compuesto de acuerdo a la reivindicación 1, en donde: R1 es C_{1-6} alquilo, C_{3-8} cicloalquil-C_{1-6} alquileno, o C_{3-8} cicloalquilo, cada uno de los cuales puede ser opcionalmente sustituido por uno o dos halógenos, hidroxi o C_{1-6} alcoxi (tal como metoxi), o R1 es heterociclilo, opcionalmente sustituido por hidroxi, C_{1-6} alcoxi o C_{1-6} alquilo;

n es 0, 1 o 2;

A es -N(R2)CO-, -OC(O)-, -CON(R2)-, -CO-, -C(R2)(OR3)-, C_{1-4}alquileno, -C(=N-O-R3)- o -C(=CHR3)-;

R2 y R3 son cada uno independientemente H o C_{1-6} alquilo;

o, cuando A es -N(R2)CO- y X está ausente, R2 puede formar, junto con el átomo de nitrógeno adyacente y Z, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido por uno a tres átomos de halógeno o grupos carbamoilo;

X está ausente o es C_{1-4} alquileno o C_{2-4} alquenileno, cada uno de los cuales puede ser opcionalmente sustituido con un grupo C_{1-4} alquilo; y

Z es arilo, heteroarilo, C_{3-8} cicloalquilo o heterociclilo,

cada uno de los cuales puede ser opcionalmente sustituido por

(1) un grupo seleccionado de -Y-arilo, -Y-heteroarilo, -Y-heterociclilo, y -Y-C_{3-8} cicloalquilo, en donde Y representa un enlace, O, NR14, o C_{1-6} alquileno, y dicho arilo es seleccionado de feniol, dicho heteroarilo es seleccionado de triazolilo, tiazolilo, tienilo y pirazolilo, dicho heterociclilo es seleccionado de morfolinilo, tetrahidrofuranilo, tetrahidropiranilo y pirrolidinilo, y dicho C_{3-8} cicloalquilo es seleccionado de ciclobutilo o ciclopropilo; o

(2) uno a tres sustituyentes seleccionados de

C_{1-6} alquilo, halógeno, haloC_{1-6} alquilo, ciano, amino, C_{1-6} alcoxi, C_{1-6} alquil-carbonilo, hidroxi-sustituido C_{1-6} alquil-carbonilo, C_{3-8} cicloalquil-carbonilo, carboxilo, C_{1-6} alcoxi-carbonilo, carbamoilo, C_{1-6} alquil-carbamoilo; C_{1-6} alquiloamino, y =O; o

Z puede ser H cuando X está presente, o Z puede ser H cuando X está ausente y A es -C(R2)(OR3)- o -N(R2)CO-,

en donde los sustituyentes de Z son seleccionados de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8}cicloalquilo y -Y-heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes seleccionados de =O, hidroxi, ciano, nitro, halógeno, haloC_{1-6} alquilo y C_{1-6} alquilo;

en donde, cuando A es C_{1-4} alquileno, dicho grupo Z cicloalquilo, arilo, heteroarilo o heterociclilo (como un grupo Z heterociclilo) es sustituido al menos con hidroxi, CF_3 o =O; y en donde, cuando A es CON(R2), n es 1.

3. Un compuesto de acuerdo a la reivindicación 1, en donde: R1 es C_{1-6} alquilo o C_{3-8} cicloalquilo, opcionalmente sustituido con halógeno o C_{1-6} alcoxi, o R1 es heterociclilo, opcionalmente sustituido con C_{1-6} alquilo;

n es 1;

A es –CON(R2)- o -N(R2)CO-;

R2 es seleccionado de H y C_{1-6} alquilo;

X está ausente o es C_{1-4} alquileno, el cual puede ser opcionalmente sustituido con uno o más grupos C_{1-4} alquilo o hidroxi;

Z es arilo, heteroarilo, C_{3-8} cicloalquilo o heterociclilo,

cada uno de los cuales puede ser opcionalmente sustituido por

(1) un grupo seleccionado de -Y-arilo, -Y-heteroarilo, Y-heterociclilo, y -Y-C_{3-8} cicloalquilo, en donde Y representa un enlace, O, NR14, o C_{1-6} alquileno, y dicho arilo es seleccionado de fenilo, dicho heteroarilo es seleccionado de triazolilo, tiazolilo, tienilo y pirazolilo, dicho heterociclilo es seleccionado de morfolinilo, tetrahidrofuranilo, tetrahidropiranilo, y pirrolidinilo, y dicho C_{3-8} cicloalquilo es seleccionado de ciclopropilo y ciclobutilo; o

(2) uno a tres sustituyentes seleccionados de

C_{1-6} alquilo, halógeno, haloC_{1-6} alquilo), ciano, amino, C_{1-6} alquilamino, N,N-C_{1-6} dialquilamino, C_{1-6} alcoxi, C_{1-6} alquil-carbonilo, carboxilo, C_{1-6} alcoxi-carbonilo, carbamoilo, C_{1-6} alquil-carbamoilo, hidroxi C_{1-6} alquilo y =O; o

Z puede ser H cuando X está presente,

en donde los sustituyentes de Z seleccionados de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8}cicloalquilo y -Y-heterociclilo pueden ser opcionamente sustituidos por uno o más sustituyentes seleccionados de =O. hidroxi, ciano, nitro, halógeno, haloC_{1-6} alquilo y C_{1-6} alquilo.

4. Un compuesto de acuerdo a la reivindicación 1, en donde: R1 es C_{1-6} alquilo o C_{3-8} cicloalquilo;

n es 1;

A es -C(R2)(OR3)-;

R2 y R3 son cada uno independientemente H o C_{1-6} alquilo;

X está ausente o es C_{1-4} alquileno;

Z es heteroarilo, o heterociclilo,

cada uno de los cuales puede ser opcionalmente sustituido por uno a tres sustituyentes seleccionados de C_{1-6} alquilo, halógeno, haloC_{1-6} alquilo, ciano, hidroxi, amino, C_{1-6} alcoxi, C_{1-6} alquil-carbonilo, hidroxi-sustituido C_{1-6} alquil-carbonilo, carboxilo, C_{1-6} alcoxi-carbonilo, C_{3-8} cicloalquil-carbonilo, carbamoilo, C_{1-6} alquil-carbamoilo.

5. Un compuesto de acuerdo a la reivindicación 1, en donde: R1 es C_{1-6} alquilo o C_{3-8} cicloalquilo;

n es 0;

A es C_{1-4} alquileno;

R2 y R3 son cada uno independientemente H o C_{1-6} alquilo;

X está ausente o es C_{1-4} alquileno;

Z es heteroarilo, o heterociclilo,

cada uno de los cuales puede ser opcionalmente sustituido por uno a tres sustituyentes seleccionados de

C_{1-6} alquilo, halógeno), haloC_{1-6} alquilo, ciano, hidroxi, amino, C_{1-6} alcoxi, C_{1-6} alquil-carbonilo, hidroxi-sustituido C_{1-6} alquil-carbonilo, carboxilo, C_{1-6} alcoxi-carbonilo, C_{3-8} cicloalquil-carbonilo, carbamoilo, C_{1-6} alquil-carbamoilo,

en donde dicho grupo Z heteroarilo o heterociclilo es sustituido al menos con hidroxi, CF_3 o =O.

6. Un compuesto de acuerdo a la reivindicación 1 o a la reivindicación 2, en donde R1 es C_{1-3} alquilo, heterociclilo o C_{3-8} cicloalquilo.

7. Un compuesto de acuerdo a la reivindicación 1 o a la reivindicación 2, en donde R1 es C_{1-3} alquilo sustituido con C_{3-8} cicloalquilo.

8. Un compuesto de acuerdo a la reivindicación 1 o a la reivindicación 2, en donde R1 is ciclopropiletilo o ciclopropilmetilo.

9. Un compuesto de acuerdo a la reivindicación 1 o a la reivindicación 2, en donde R1 es seleccionado de metilo, etilo, isopropilo, ciclopropilo, ciclobutilo, tetrahidrofuranilo y ciclopentilo.

10. Un compuesto de acuerdo a la reivindicación 1, en donde R1 es además sustituido con un grupo seleccionado de F, metilo, hidroxi, C_{1-6} alcoxi y CH_2F.

11. Un compuesto de acuerdo a cualquiera de las reivindicaciones precedentes, en donde R2 es H.

12. Un compuesto de acuerdo a cualquiera de las reivindicaciones precedentes, en donde R3 es H.

13. Un compuesto de acuerdo a cualquiera de las reivindicaciones precedentes, en donde X es un grupo C_{1-4} alquileno de cadena recta, opcionalmente teniendo uno o más sustituyentes metilo o etilo.

14. Un compuesto de acuerdo a la reivindicación 13, en donde X es metileno o etileno.

15. Un compuesto de acuerdo a la reivindicación 1, en donde Z es arilo, heteroarilo, C_{3-8} cicloalquilo o heterociclilo, cada uno de los cuales puede ser sustituido con uno o más sustituyentes seleccionados de C_{1-6} alquilo, halógeno, haloC_{1-6} alquilo, ciano, amino, C_{1-6} alcoxi, -COR4, -CONR12R13, arilo, y heteroarilo.

16. Un compuesto de acuerdo a la reivindicación 1, en donde Z es heteroarilo, dicho heteroarilo siendo seleccionado de los grupos tienilo, furilo, furazanilo, pirrolilo, triazolilo, tetrazolilo, imidazolilo, imidazopiridilo, oxazolilo, tiazolilo, oxadiazolilo, isotiazolilo, isoxazolilo, tiadiazolilo, piranilo, pirazolilo, pirimidilo, piridazinilo, pirazinilo, piridilo, triazinilo, tetrazinilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, pteridinilo, cinnolinilo, ftalazinilo, naftiridinilo, indolilo, isoindolilo, azaindolilo, indolizinilo, indazolilo, purinilo, pirrolopiridinilo, fluropiridinilo, benzofuranilo, isobenzofuranilo,

benzotienilo, benzimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzoxadiazolilo, y benzotiadiazolilo.

17. Un compuesto de acuerdo a la reivindicación 1 o a la reivindicación 2, en donde Z es arilo, dicho arilo es seleccionado de los grupos fenilo, naftilo y tetrahidronaftalenilo.

18. Un compuesto de acuerdo a la reivindicación 1, en donde Z es heterociclilo, dicho heterociclilo siendo seleccionado de los grupos pirrolidinilo, azetidinilo, pirazolidinilo, oxazolidinilo, piperidinilo, piperazinilo, morfolinilo, thiomorfolinilo, tiazolidinilo, hidantoinilo, valerolactamilo, oxiranilo, oxetanilo, dioxolanilo, dioxanilo, oxatiolanilo, oxatianilo, ditianilo, dihidrofuranilo, tetrahidrofuranilo, dihidropiranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidropirimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo, diazepanilo, azepanilo, indolinilo, isoindolinilo, benzopiranilo, quinuclidinilo, 2,3,4,5-tetrahidro-1H-3-benzazepina y tetrahidroisoquinolinilo.

19. Un compuesto de acuerdo a la reivindicación 1, en donde Z es cicloalquilo, dicho cicloalquilo siendo seleccionado de los grupos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo.

20. Un compuesto de acuerdo a las reivindicaciones de la 1 a la 3, en donde A es –CON(R2)-, y n es 0, 1 o 2.

21. Un compuesto de acuerdo a las reivindicaciones 1 o 2, en donde A es -OC(O)- o -C(O)O-, y n es 0, 1 o 2.

22. Un compuesto de acuerdo a las reivindicaciones 1 o 2, en donde A es -C(R2)(OR3)- o -CO-, y n es 0, 1 o 2.

23. Un compuesto de acuerdo a la reivindicación 20 o a la reivindicación 22, en donde R2 es H.

24. Un compuesto de acuerdo a la reivindicación 22 o a la reivindicación 23, en donde R3 es H o C_{1-4} alquilo.

25. Una composición farmacéutica que comprende un compuesto de acuerdo a cualquiera de las reivindicaciones precedentes, junto con uno o más excipientes aceptables para uso farmacéutico.

26. Un compuesto de acuerdo a cualquiera de las reivindicaciones de la 1 a la 24, o una composición de acuerdo a la reivindicación 25, para uso en terapia.

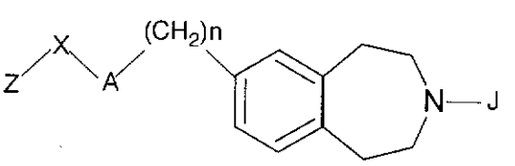
27. Un compuesto de acuerdo a cualquiera de las reivindicaciones de la 1 a la 24, o a una composición de acuerdo a la reivindicación 25, para uso en el tratamiento o prevención de una condición, cuyo desarrollo o síntomas están ligados a la actividad del receptor H3 de histamina, en donde las condiciones para la reivindicación 1 no aplican.

28. Un método de tratamiento o prevención de una condición, cuyo desarrollo o síntomas están ligados a la actividad del receptor H3 de histamina, el método comprende la administración, a un sujeto en necesidad de dicho tratamiento o prevención, de una cantidad terapéuticamente efectiva de un compuesto de acuerdo a cualquiera de las reivindicaciones de la 1 a la 24, en donde las condiciones a la reivindicación 1 no aplican.

29. Un compuesto de acuerdo a la reivindicación 27, o un método de acuerdo a la reivindicación 28, en donde la condición es un trastorno del sistema nervioso central.

30. Un compuesto o un método de acuerdo a la reivindicación 29, en donde el trastorno es seleccionado de la esquizofrenia, desórdenes neurodegenerativos (como la enfermedad de Alzheimer), desórdenes cognitivos (como la demencia), desórdenes del sueño, dolor, obesidad, desórdenes atencionales y epilepsia.

31. Un compuesto intermediario que tiene la fórmula:



en donde n, A, X y Z tienen el mismo significado que en la reivindicación 1, o Z-X-A- juntos representan C_{1-6} alquilsulfoniloxi, nitro, halógeno (como Br), carbaldehído O-C_{1-6}

alquil oxima, amino, amino ligado a un grupo amino protector o arilsulfonilo, y en donde J es un grupo amino protector o H, siempre que Z esté unido a X o A via un átomo de carbono cuando Z contiene una grupo piperazinilo, y siempre que:

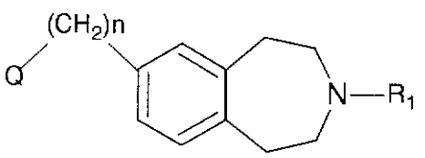
cuando A es -OC(O)-, J es H, n es 0 y X es $-CH_2CH_2-$, Z no es H;

cuando A es -OC(O)-, J es tert-butoxicarbonilo, n es 0 y X es $-CH_2-$, Z no es H;

cuando A es -NHCO-, J es tert-butoxicarbonilo, n es 0 y X es -isopropilo, Z no es H; y

cuando A es -NHCO-, J es tert-butoxicarbonilo, aminoiminometilo o H, n es 0 y X es $-CH_2-$ o $-CH_2CH_2-$, Z no es pirrolidin-2-il sustituido con oxo, fenilpropilo y sustituyentes de ácido acético.

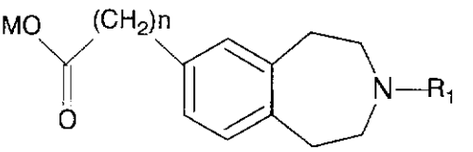
32. Un compuesto intermediario que tiene la fórmula:



en donde n y R1 tienen el mismo significado que en la reivindicación 1, y en donde Q es seleccionado de ciano, amino, amino ligado a un grupo protector de amino, arilsulfonilo y halógeno (como Br).

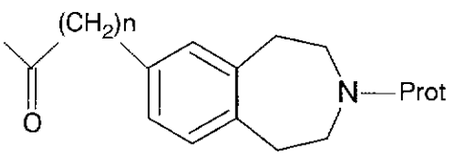
33. Uso de un compuesto intermediario de acuerdo a la reivindicación 31 o reivindicación 32 en la síntesis de un compuesto, de acuerdo a cualquiera de las reivindicaciones de la 1 a la 24, en donde las condiciones para la reivindicación 31, no aplican.

34. Un método de síntesis de un compuesto de acuerdo a la reivindicación 1, en donde A es -N(R2)CO-, el método comprende la reacción de un intermediario que tiene la fórmula:



con una amina (Z-X)(R2)NH en la presencia de un catalizador, en donde n, Z, X, R1 y R2 tienen el mismo significado que en la reivindicación 1, y en donde M representa H o un catión metálico monovalente.

35. Un método de síntesis de un compuesto de acuerdo a la reivindicación 1, en donde A es -CO- o -C(R2)(OR3)- y X está presente, el método comprende la reacción de un intermediario protegido:

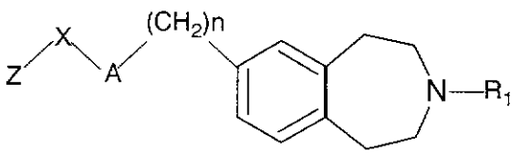


con un aldehído Z-CHO en la presencia de un catalizador, seguido de desprotección de la amina protegida y sustitución del mismo con R1 y opcionalmente, por hidrogenación catalítica, en donde n, Z, X, R1, R2 y R3 tienen el mismo significado que en la reivindicación 1, y en donde Prot representa un grupo protector de amina.

RESUMEN

DERIVADOS DE BENZAZEPINA Y SU USO COMO ANTAGONISTAS DE HISTAMINA H3

Un compuesto que tiene la fórmula:



en donde:

R1 es un grupo seleccionado de C_{3-8} cicloalquilo, C_{1-6} alquilo, C_{1-6} alquileno-C_{3-8} cicloalquilo, cada uno de los cuales puede ser opcionalmente sustituido con C_{1-6} alquilo, halógeno, haloC_{1-6} alquilo o OR15, o R1 es heterociclilo, opcionalmente sustituido con C_{1-6} alquilo, haloC_{1-6} alquilo o OR15;

n es 0, 1, 2, 3 o 4, el grupo alquileno $-(CH_2)_n-$ formado de ese modo, siendo opcionalmente sustituido con un grupo seleccionado de C_{1-4} alquilo, C_{3-8} cicloalquilo y arilsulfonilo;

A es un grupo seleccionado de -N(R2)CO-, -CON(R2)-, -OC(O)-, -C(O)O-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cicloalquileno-, -C(R2)(haloC_{1-6} alquilo)-, C_{1-4} alquileno y -C(OR3)(haloC_{1-6} alquilo)-;

R2 y R3 cada uno son independientemente seleccionados de H, C_{1-6} alquilo, y C_{3-8} cicloalquilo, o cuando A es -N(R2)CO- y X está ausente, R2 puede formar, junto con el átomo de nitrógeno adyacente y Z, un grupo heterociclilo que contiene N, el cual puede ser sustituido opcionalmente;

X está ausente o es C_{1-4} alquileno o C_{2-4} alquenileno, cada uno de los cuales puede ser opcionalmente sustituido con uno o más grupos C_{1-4} alquilo, OR16, halógeno o haloC_{1-6} alquilo;

Z es seleccionado de arilo, heteroarilo, C_{3-8} cicloalquilo, y heterociclilo, cada uno de los cuales puede ser opcionalmente sustituido por un grupo seleccionado de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo, o cuando X está presente, Z puede ser H, o cuando X está ausente y A es -C(R2)(OR3)- o -N(R2)CO-, Z puede ser H, o cuando A es -N(R2)CO- y X está ausente, Z puede formar, junto con el átomo de nitrógeno adyacente y R2, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido, en donde, cuando A es -CO-, Z está ligado a X o A via un átomo de carbono y en donde, cuando A es -N(R2)CO- y Z es H, R1 es C_{3-8} cicloalquilo; y

Y representa un enlace, C_{1-6} alquileno, CO, NR14, COC_{2-6} alquenileno, O, SO_2 o $NHCOC_{1-6}$ alquileno;

en donde dichos grupos Z cicloalquilo, arilo, heteroarilo y heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes y los cuales son seleccionados de halógeno, haloC_{1-6} alquilo, hidroxi, ciano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alquilo-NR5R6, -C_{3-8} cicloalquilo-NR5R6, -CONR12R13, -NR12COR13, -NR5SO_2R6, -OCONR5R6, -NR5CO_2R6, -NR4CONR5R6 o -SO_2NR5R6-SHR8, -alquilo-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, -alquilo-SO_2R9, -alquilo-CONHR9, -alquilo-SONHR9, -alquilo-COR10, -CO-alquilo-R10, -O-alquilo-R11 (en donde R4, R5 y R6 representan hidrógeno independientemente, C_{1-6} alquilo, -C_{3-8} cicloalquilo, -C_{1-6} alquileno-C_{3-8} cicloalquilo, aril, heterociclilo o heteroaril, en donde R8 representa C_{1-6} alquilo, en donde R9 representa C_{1-6} alquilo o arilo, en donde R10 representa aril, en donde R11 representa C_{3-8} cicloalquilo o aril, R12, R13, R14, R15 y R16 cada uno independientemente representa H o C_{1-6} alquilo, y en donde -NR5R6 y -NR12R13 pueden representar un grupo heterociclilo que contiene nitrógeno); en donde dichos grupos R4, R5, R6 R8, R9, R10 y R11 pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes, y los cuales se

han seleccionado del grupo que consiste en halógeno, hidroxi, C_{1-6} alquilo, C_{1-6} alcoxi, ciano, amino, =O o trifluorometilo;

y en donde los sustituyentes de Z seleccionados de -Y-arilo -Y-heteroarilo, -Y-C_{3-8}cicloalquilo y -Y-heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes seleccionados de =O, hidroxi, ciano, nitro, halógeno, haloC_{1-6} alquilo y C_{1-6} alquilo;

y en donde, cuando A es C_{1-4} alquileno, dicho grupo Z cicloalquilo, arilo, heteroarilo o heterociclilo (como un grupo Z heterociclilo) es sustituido al menos con hidroxi, CF_3, o =O;

y en donde, cuando A es CON(R2) n es 1;

o una sal aceptable para uso farmacéutico o un éster de la misma,

siempre que: cuando A es -CO-, R1 es CH_3, C_{3-8} cicloalquilo-sustituido C_{1-6} alquileno o n-butil, n es 0 y X es -CH_2CH_2-, Z no sea N-benzil sustituido 4-piperidinilo, N-(3-fluorobenzil)-sustituido 4-piperidinilo o N-acetil sustituido 4-piperidinilo;

cuando A es -OC(O)-, R1 es ciclobutilo, n es 0 y X es -CH_2CH_2-, Z no sea H;

cuando A es -OC(O)-, R1 es n-propilo, n es 0 y X es -CH_2-, Z no sea H; y

cuando A es –CO-, R1 es CH_3, n es 0 y X es CH_2, Z no sea H.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

JONES, Nicholas, Andrew
Withers & Rogers LLP
Goldings House
2 Hays Lane
London SE1 2HW
ROYAUME-UNI

Date of mailing *(day/month/year)*
16 December 2010 (16.12.2010)

Applicant's or agent's file reference
P523035PCT

IMPORTANT NOTIFICATION

International application No.
PCT/GB2009/001774

International filing date *(day/month/year)*
17 July 2009 (17.07.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
KERR, Catrina
Takeda Cambridge Ltd
418 Cambridge Science Park
Cambridge CB4 0PA
United Kingdom

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State of Residence: GB
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
KERR, Catrina, Morvern
Takeda Cambridge Ltd
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State of Residence: GB
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 Authority(ies) specified for supplementary search
☐ 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 87 40

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000428

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT __X__ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) **TAKEDA PHARMACEUTICAL COMPANY**

(72) Inventor(es) **PARMINDER KAUR POONI, KEVIN JOHN MERCHANT, CATRINA MORVERN KERR, STUART RICHARD CROSBY, TOMOHIRO OKAWA, MITSURU SASAKI, MIKA GOTOU, GRAHAM ANDREW SHOWELL, MARTIN RICHARD TEALL**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad	(31)	No. Prioridad	32)	Fecha	(33)	País
		0813254.0		18/07/2008		GB
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(85) Fecha inicio fase nacional:
Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **17/07/2009**
No. de solicitud **PCT/GB2009/001774**

(87) Publicación internacional
Fecha: **21/01/2010**
Nº publicación: **WO 2010/007382 A8**

(54) Titulo: **DERIVADOS DE BENZAZEPINA Y SU USO COMO ANTAGONISTAS DE HISTAMINA H3**

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

000129

(21) Nº de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) Nº Prioridad 32) Fecha (33) País
0813254.0 18/07/2008 GB
0905231.7 26/03/2009 GB

(51) Int. Cl.:

(71)Solicitante(s) **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

(72) Inventor(es) **PARMINDER KAUR POONI**
KEVIN JOHN MERCHANT
CATRINA MORVERN KERR
Y OTROS

(74) Apoderado: **MARGARITA CASTELLANOS ABONDANO**

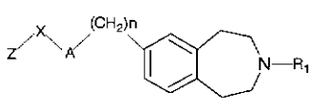
(85) Fecha limite inicio fase nacional:
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **17/07/2009**
Nº de solicitud **PCT/GB2009/001774**

(87) Publicación internacional
Fecha: **21/01/2010**
Nº publicación: **WO 2010/007382 A8**

(54) Titulo: **DERIVADOS DE BENZAZEPINA Y SU USO COMO ANTAGONISTAS DE HISTAMINA H3**

Reivindicación(es):

1. Un compuesto que tiene la fórmula:



en donde:
R1 es un grupo seleccionado de C_{3-8} cicloalquilo, C_{1-6} alquilo, C_{1-6} alquileno-C_{3-8} cicloalquilo, cada uno de los grupos pueden ser opcionalmente sustituidos con C_{1-6} alquilo, halógeno, haloC_{1-6} alquilo o OR15, o R1 es heterociclilo, opcionalmente sustituido con C_{1-6} alquilo, haloC_{1-6} alquilo o OR15;
n es 0, 1, 2, 3 o 4, el grupo alquileno -$(CH_2)_n$- formado de este modo siendo opcionalmente sustituido con un grupo seleccionado de C_{1-4} alquilo, C_{3-8} cicloalquilo y arilsulfonilo;
A es un grupo seleccionado de -N(R2)CO-, -CON(R2)-, -OC(O)-, -C(O)O-, -CO-, -C(R2)(OR3)-, -C(=N-O-R3)-, -C(=CR2R3)-, -C_{3-8} cicloalquileno-, -C(R2)(haloC_{1-6} alquilo)-, C_{1-4} alquileno y -C(OR3)(haloC_{1-6} alquilo)-;
R2 y R3 cada uno son independientemente seleccionados de H, C_{1-6} alquilo y C_{3-8} cicloalquilo, o cuando A es -N(R2)CO- y X está ausente, R2 puede formar, junto con el átomo de nitrógeno adyacente y Z, un grupo heterociclilo que contiene N, el cual puede ser sustituido opcionalmente;
X está ausente o es C_{1-4} alquileno o C_{2-4} alquenileno, cada uno de los cuales puede ser opcionalmente sustituido con uno o más grupos C_{1-4} alquilo, OR16, halógeno o haloC_{1-6} alquilo;
Z es seleccionado de arilo, heteroarilo, C_{3-8} cicloalquilo, y heterociclilo, cada uno de los cuales puede ser opcionalmente sustituido por un grupo seleccionado de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo, o cuando X está presente, Z puede ser H, o cuando X está ausente y A es -C(R2)(OR3)- o -N(R2)CO-, Z puede ser H, o cuando A es -N(R2)CO- y X está ausente, Z puede formar, junto con el átomo de nitrógeno adyacente y R2, un grupo heterociclilo que contiene N, el cual puede ser opcionalmente sustituido, en donde, cuando A es -CO-, Z está ligado a X o A via un átomo de carbono y en donde, cuando A es –N(R2)CO- y Z es H, R1 es C_{3-8} cicloalquilo; y
Y representa un enlace, C_{1-6} alquileno, CO, NR14, COC_{2-6} alquenileno, O, SO_2 o $NHCOC_{1-6}$ alquileno;
en donde dichos grupos Z cicloalquilo, arilo, heteroarilo y heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes, y los cuales son seleccionados de halógeno, haloC_{1-6} alquilo, hidroxi, ciano, nitro, =O, -R4, -CO_2R4, -COR4, -NR5R6, -C_{1-6} alquil-NR5R6, -C_{3-8} cicloalquil-NR5R6, -CONR12R13, -NR12COR13, -NR5SO_2R6, -OCONR5R6, -NR5CO_2R6, -NR4CONR5R6 o -SO_2NR5R6-SHR8, -alquil-OR8, -SOR8, -OR9, -SO_2R9, -OSO_2R9, -alquil-SO_2R9, -alquil-CONHR9, -alquil-SONHR9, -alquil-COR10, -CO-alquil-R10, -O-alquilo-R11 (en donde R4, R5 y R6 independientemente representan hidrógeno, C_{1-6} alquilo, -C_{3-8} cicloalquilo, -C_{1-6} alquileno-C_{3-8} cicloalquilo, arilo, heterociclilo o heteroarilo, en donde R8 representa C_{1-6} alquilo, en donde R9 representa C_{1-6} alquilo o arilo, en donde R10 representa arilo, en donde R11 representa C_{3-8} cicloalquilo o arilo, R12, R13, R14, R15 y R16, cada uno representa independientemente H o C_{1-6} alquilo, y en donde -NR5R6 y -NR12R13 pueden representar un grupo heterociclilo que contiene nitrógeno); en donde dichos grupos R4, R5, R6 R8, R9, R10 y R11 pueden ser opcionalmente sustituidos por uno o más sustituyentes, los cuales pueden ser los mismos o diferentes, y los cuales están seleccionados del grupo que consiste de halógeno, hidroxi, C_{1-6} alquilo, C_{1-6} alcoxi, ciano, amino, =O o trifluorometilo;
y en donde los sustituyentes de Z seleccionados de -Y-arilo, -Y-heteroarilo, -Y-C_{3-8} cicloalquilo y -Y-heterociclilo pueden ser opcionalmente sustituidos por uno o más sustituyentes seleccionados de =O, hidroxi, ciano, nitro, halógeno, haloC_{1-6} alquilo y C_{1-6} alquilo;
y en donde, cuando A es C_{1-4} alquileno, dicho grupo Z cicloalquilo, arilo, heteroarilo o heterociclilo (como un grupo heterociclilo Z) es sustituido al menos con hidroxi, CF_3, o =O;
y en donde, cuando A es CON(R2) n es 1;
o una sal aceptable para uso farmacéutico, o un éster de la misma,
siempre que: cuando A es -CO-, R1 es CH_3, C_{3-8} cicloalquilo-sustituido C_{1-6} alquileno o n-butilo, n es 0 y X es -CH_2CH_2-, Z no sea N-benzil sustituido 4-piperidinil, N-(3-fluorobenzil)-sustituido 4-piperidinil o N-acetil sustituido 4-piperidinil;
cuando A es -OC(O)-, R1 es ciclobutilo, n es 0 y X es -CH_2CH_2-, Z no sea H;
cuando A es -OC(O)-, R1 es n-propilo, n es 0 y X es -CH_2-, Z no sea H; y
cuando A es –CO-, R1 es CH_3, n es 0 y X es CH_2, Z no sea H.

...

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-003062- -00000-0000

Fecha: 2011-01-13 14:22:09 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 429

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO

ADMISION A TRAMITE - NUEVAS CREACIONES

PATENTE DE INVENCION [ ] **MODELO DE UTILIDAD** [ ] **Art. 33 Decisión 486/00**

- [ ] Indicación que se solicita una patente
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Descripción de la invención
- [ ] Dibujos de ser estos pertinentes
- [ ] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [ ] Incompleta [ ]

PATENTE DE INVENCION PCT [X] **MODELO DE UTILIDAD PCT** [ ] **Art. 33 Decisión 486/00 Circular Única**

- [X] Indicación que se solicita una PCT
- [X] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [X] Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- [ ] Dibujos de ser estos pertinentes
- [X] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [X] Incompleta [ ]

DISEÑO INDUSTRIAL [ ] **(Art. 119 Decisión 486/00)**

- [ ] Indicación que se solicita 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 [ ] **(Art. 92 Decisión 486/00)**

- [ ] Indicación que se solicita un esquema de trazado
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Representación gráfica de un esquema de trazado
- [ ] Comprobante de pago de las tasas establecidas

Completa [ ] Incompleta [ ]

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Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
MARGARITA CASTELLANOS ABONDANO
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA		
	Radicación No.	11 003062
	Solicitud internacional	PCT/GB2009/001774
	Fecha inicio fase nacional	18/02/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	03944

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se consideraró abandonada y perderá su prelación.

Continua en la página siguiente...

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 24 MAR 2011
adpa11