

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
Carlos Olarte
Apoderado

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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ASUNTO	Radicación	07 39099
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	102307
	Folios	006

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap.I	☒
		Cap. II	☐
No. Sol. Internacional		PCT/US2005/037576	
Fecha de Presentación Internal.		19/10/2006	

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios 129 - 224
- 1.2. Reivindicaciones: Folios 225 - 236
- 1.3. Prioridad: Presentada en Estados Unidos, el 19.10.04, bajo el número 60/620060 y la 0519957.5, presentada el 30.09.05 en Gran Bretaña

2. Objeto de la invención

- Título de la solicitud: "Derivados de pirazolo (1,5-alfa)-pirimidinilo útiles como antagonistas de receptores del factor liberador de corticotropina (CRF)".

Según las reivindicaciones 1-25 se refiere a compuestos derivados de pirazolo (1,5-alfa)-pirimidinil-oxadiazol-amina de fórmula (I), sus formas polimórficas y composiciones farmacéuticas que los contienen.

El problema planteado con la presente solicitud es la necesidad de más compuestos antagonistas CRF

Para solucionar este problema técnico la solicitud en estudio proporciona los compuestos de la presente solicitud que son activos en el tratamiento de desórdenes neurosiquiátricos.

- Clasificación Internacional de Patentes A 61 K 31/519

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

- Las expresiones “sustituido”, “alquilo”, “haloalquilo”, “alcoxialquilo”, “arilalquilo”, “heterocicloalquilo” no son limitativas y pueden comprender compuestos que no se encuentran revelados en la descripción.
- El término “profármacos” de la reivindicación 1 no se encuentra sustentado en la descripción, debido a que a lo largo de la misma no se describen procedimientos de síntesis que permitan la obtención de los mismos.

4. Excepciones a la patentabilidad (artículo 20 D 486)

El contenido de las reivindicaciones 18-25, que trata de “Método para tratar un individuo...”, no es patentable, debido a que se relaciona con métodos de tratamiento aplicado a seres humanos o a animales.

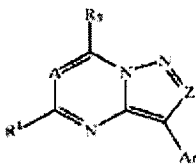
5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 19.10.04, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Nº	Documento	Título	Fecha de Publicación
D1	US 6060478	“Azolo triazinas y pirimidinas”	09.05.00

6. Análisis de patentabilidad (artículo 14 D486)

6.1. Nivel Inventivo (artículo 18 D486)



- D1 se relaciona con compuestos de fórmula (I) ,que son antagonistas CRF. La diferencia con los compuestos reivindicados radica en que D1 no revela de manera específica el radical oxadiazol.

Teniendo en cuenta el objeto de la solicitud, el cual es proveer más

compuestos antagonistas CRF, es una derivación del estado de la técnica, ya que una persona versada en la materia tomaría las enseñanzas del documento D1 y con sus conocimientos usuales en síntesis química, llegaría a los compuestos reivindicados con la expectativa de que también fueran antagonistas CRF

Finalmente, no se demuestra un efecto sorprendente o mejorado de los compuestos reivindicados en comparación con lo revelado en el estado de la técnica.

7. Conclusión:

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

Nº	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	US 6060478	1-17	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001.



José Luís Salazar López
Director de Nuevas Creaciones (e)

El anterior requerimiento fue notificado por fijación en lista, de fecha 7 FEB. 2011

CONCEPTO TECNICO No. 0355	EXAMINADOR TECNICO Código No.202024
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United States Patent [19]

Gilligan et al.

[11] Patent Number: 6,060,478
[45] Date of Patent: May 9, 2000

- [54] AZOLO TRIAZINES AND PYRIMIDINES
- [75] Inventors: Paul Gilligan, Wilmington, Del.;
Robert Chorvat, West Chester;
Argyrios Georgios Arvanitis, Kennett
Square, both of Pa.
- [73] Assignee: DuPont Pharmaceuticals, Wilmington,
Del.
- [21] Appl. No.: 09/015,001
- [22] Filed: Jan. 28, 1998

Related U.S. Application Data

- [63] Continuation-in-part of application No. 08/899,242, Jul. 23,
1997.
- [60] Provisional application No. 60/023,290, Jul. 24, 1996.
- [51] Int. Cl.⁷ A61K 31/505; C07D 487/04
- [52] U.S. Cl. 514/258; 514/241; 544/281;
544/180
- [58] Field of Search 544/180, 194,
544/281; 514/245, 246, 258, 241

References Cited

U.S. PATENT DOCUMENTS

3,910,907	10/1975	O'Brien et al.	260/310
3,920,652	11/1975	Springer et al.	260/310
3,995,039	11/1976	Rooney et al.	424/249
4,021,556	5/1977	Springer et al.	424/251
4,567,263	1/1986	Ficken et al.	544/250
4,892,576	1/1990	Kruger et al.	71/93
4,990,647	2/1991	Himmeler et al.	558/414
4,997,940	3/1991	Vinogradoff et al.	544/281
5,089,499	2/1992	Barker et al.	514/259
5,137,887	8/1992	Hashimoto et al.	514/246
5,397,774	3/1995	Nugent et al.	544/244
5,428,044	6/1995	Bantick et al.	514/341
5,463,071	10/1995	Himmelsbach et al.	548/251
5,464,847	11/1995	Courtemanche et al.	514/342
5,484,760	1/1996	Bussler et al.	504/103
5,486,531	1/1996	Schonafinger et al.	514/364
5,723,608	3/1998	Yuan	544/283

FOREIGN PATENT DOCUMENTS

0269859	6/1988	European Pat. Off.
0300688	1/1989	European Pat. Off.
0373891	12/1989	European Pat. Off.
0374448	6/1990	European Pat. Off.
0395144	10/1990	European Pat. Off.
0455545	11/1991	European Pat. Off.
0503099	9/1992	European Pat. Off.
0521622	1/1993	European Pat. Off.
0531901	3/1993	European Pat. Off.
0576350	12/1993	European Pat. Off.
0591528	4/1994	European Pat. Off.
0594149	4/1994	European Pat. Off.
0714898	6/1995	European Pat. Off.
0662477	7/1995	European Pat. Off.
0729758	9/1996	European Pat. Off.
0773023	5/1997	European Pat. Off.
0778277	6/1997	European Pat. Off.
0812831	12/1997	European Pat. Off.
4243279	12/1992	Germany
42/11753	7/1967	Japan
61/57587	3/1986	Japan

9210098	6/1992	WIPO
9220642	11/1992	WIPO
9409017	4/1994	WIPO
9413643	6/1994	WIPO
9413644	6/1994	WIPO
9413661	6/1994	WIPO
9413676	6/1994	WIPO
9413677	6/1994	WIPO
9500507	1/1995	WIPO
9511880	5/1995	WIPO
9532710	12/1995	WIPO
9533727	12/1995	WIPO
9533750	12/1995	WIPO
9534563	12/1995	WIPO
95/35298	2/1996	WIPO
9619452	6/1996	WIPO
9623783	8/1996	WIPO
9635689	11/1996	WIPO
9639388	12/1996	WIPO
9639400	12/1996	WIPO
9700868	1/1997	WIPO
9714684	4/1997	WIPO
9729109	8/1997	WIPO
9729110	8/1997	WIPO
9808821	3/1998	WIPO
9808846	3/1998	WIPO
9808847	3/1998	WIPO

OTHER PUBLICATIONS

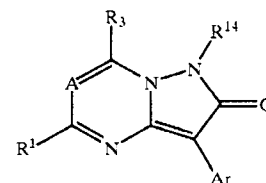
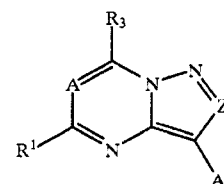
Arch. Pharm. (Weinheim) 320, 487-491 (1987).
Psychopharmacology (Britton, Lee, Koob) 94:306-311
(1988).
Life Sciences (Britton, Koob, Rivier, Vale) 31:363-367
(1982).

(List continued on next page.)

Primary Examiner—John M. Ford
Attorney, Agent, or Firm—Maureen P. O'Brien; Kenneth B.
Rubin

[57] ABSTRACT

Corticotropin releasing factor (CRF) antagonists of formula I or II:

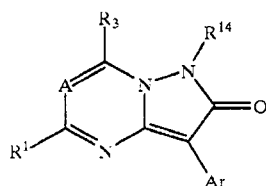
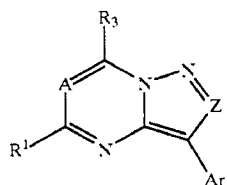


and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

28 Claims, No Drawings

What is claimed is:

1. A compound of Formulae (1) or (2):



and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein:

Z is N or CR²;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R⁴ groups and each Ar is attached to an unsaturated carbon atom;

R is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl, halo, CN, C₁-C₄ haloalkyl;

R¹ is independently selected at each occurrence from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo, CN, C₁-C₄ haloalkyl, C₁-C₁₂ hydroxyalkyl, C₂-C₁₂ alkoxyalkyl, C₂-C₁₀ cyanoalkyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, NR⁹R¹⁰, C₁-C₄ alkyl-NR⁹R¹⁰, NR⁹COR¹⁰, OR¹¹, SH or S(O)_nR¹²;

R² is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₀ cycloalkylalkyl, C₁-C₄ hydroxyalkyl, halo, CN, —NR⁶R⁷, NR⁹COR¹⁰, —NR⁶S(O)_nR⁷, S(O)_nNR⁶R⁷, C₁-C₄ haloalkyl, —OR⁷, SH or —S(O)_nR¹²;

R³ is selected from:

—H, OR⁷, SH, S(O)_nR¹³, COR⁷, CO₂R⁷, OC(O)R¹³, NR⁸COR⁷, N(COR⁷)₂, NR⁸CONR⁶R⁷, NR⁸CO₂R¹³, NR⁶R⁷, NR^{6a}R^{7a}, N(OR⁷)R⁶, CONR⁶R⁷, aryl, heteroaryl and heterocyclyl, or —C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, C₄-C₁₂ cycloalkylalkyl or C₆-C₁₀ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵, aryl, heteroaryl and heterocyclyl;

R⁴ is independently selected at each occurrence from:

C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, NO₂, halo, CN, C₁-C₄ haloalkyl, NR⁶R⁷, NR⁸COR⁷, NR⁸CO₂R⁷, COR⁷, OR⁷, CONR⁶R⁷, CO(NOR⁹)R⁷, CO₂R⁷, or

S(O)_nR⁷, where each such C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, NO₂, halo, CN, NR⁶R⁷, NR⁸COR⁷, NR⁸CO₂R⁷, COR⁷ OR⁷, CONR⁶R⁷, CO₂R⁷, CO(NOR⁹)R⁷, or S(O)_nR⁷;

R⁶, R⁷, R^{6a} and R^{7a} are independently selected at each occurrence from:

—H,

—C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₁-C₁₀ haloalkyl with 1-10 halogens, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, C₅-C₁₀ cycloalkenyl, or C₆-C₁₄ cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, aryl, heteroaryl or heterocyclyl,

—aryl, aryl(C₁-C₄ alkyl), heteroaryl, heteroaryl(C₁-C₄ alkyl), heterocyclyl or heterocyclyl(C₁-C₄ alkyl),

alternatively, NR⁶R⁷ and NR^{6a}R^{7a} are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C₁-C₄ alkyl groups;

R⁸ is independently selected at each occurrence from H or C₁-C₄ alkyl;

R⁹ and R¹⁰ are independently selected at each occurrence from H, C₁-C₄ alkyl, or C₃-C₆ cycloalkyl;

R¹¹ is selected from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

R¹² is C₁-C₄ alkyl or C₁-C₄ haloalkyl;

R¹³ is selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heteroaryl or heteroaryl(C₁-C₄ alkyl)-;

R¹⁴ is selected from C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, C₃-C₈ cycloalkyl, or C₄-C₁₂ cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, CONR¹⁶R¹⁵, and C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl and C₁-C₆ alkylsulfonyl;

R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₄-C₁₆ cycloalkylalkyl, except that for S(O)_nR¹⁵, R¹⁵ cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, cyano, OR¹⁵, SH, S(O)_nR¹⁵, COR¹⁵, CO₂R¹⁵, OC(O)R¹⁵, NR⁸COR¹⁵, N(COR¹⁵)₂, NR⁸CONR¹⁶R¹⁵, NR⁸CO₂R¹⁵, NR¹⁶R¹⁵, and CONR¹⁶R¹⁵;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranal, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substitu-

ents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15} , SH , $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15} , $OC(O)R^{15}$, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15} , SH , $S(O)_nR^{15}$, COR^{15} , CO_2R^{15} , $OC(O)R^{15}$, NR^8COR^{15} , $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2;

with the provisos that:

- (1) when Z is CR^2 , then R^2 is not $-NR^6SO_2R^7$ or $-SO_2NR^6R^7$;
- (2) when Z is CR^2 and R^2 is H, phenyl or alkyl and R^3 is NR^8COR^7 and Ar is phenyl or phenyl substituted with phenylthio, then R^7 is not aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);
- (3) when Z is CR^2 and R^2 is H or alkyl and Ar is phenyl and R^3 is SR^{13} or $NR^{6a}R^{7a}$, then R^{13} is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or
- (4) when Z is CR^2 and R^1 is OR^{11} and R^2 is H and R^3 is OR^7 and R^7 and R^{11} are both H, then Ar is not phenyl, p-Br-phenyl, p-Cl-phenyl, p-NHCOCH₃-phenyl, p-ClI₃-phenyl, pyridyl or naphthyl;
- (5) when Z is CR^2 and R^2 is H and Ar is unsubstituted phenyl and R^3 is CH_3 , C_2H_5 , CF_3 or C_6H_4F , then R_1 is not CF_3 or C_2F_5 ;
- (6) when R is H and Z is CR^2 and R^2 is OH and R^1 and R^3 are H, then Ar is not phenyl;
- (7) when R is H and Z is CR^2 and R^2 is OH or NH_2 and R^1 and R^3 are CH_3 , then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl; and
- (7) when R is H and Z is CR^2 and R^1 and R^2 are CH_3 and Ar is 2-methyl-4-methoxyphenyl, then R^3 is not 3-pentylamino.

2. A compound of claim 1 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 2.

5. A compound of Formula (2) of claim 1 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof.

6. A compound of claim 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

7. A compound of claim 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7 .

8. A compound of claim 5 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7 .

9. A compound of Formula (1) of claim 1 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein Z is CR^2 .

10. A compound of claim 9 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

11. A compound of claim 9 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7 .

12. A compound of claim 9 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7 .

13. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15} , SH , $S(O)_nR^{13}$, COR^{15} , CO_2R^{15} , $OC(O)R^{13}$, NR^8COR^{15} , $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

14. A compound of claim 9 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein

—Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents,

— R^3 is $NR^{6a}R^{7a}$ or OR^7 and

— R^1 and R^2 are independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl.

15. A compound of claim 14 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15} , SH , $S(O)_nR^{13}$, COR^{15} , CO_2R^{15} , $OC(O)R^{13}$, NR^8COR^{15} , $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

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