



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-071259- -00002-0000

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Act. 400 OPOSIOBSERVTER Folios: 96

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

Numero del expediente: 08-71259

Solicitante: WYETH

SOLICITUD

PUBLICADA

Apoderado: ALVARO CORREA ORDONEZ

Título de la nueva creación o denominación del signo: COMBINACIÓN DE UN INHIBIDOR DE ACETILCOLINESTERASA Y UN ANTAGONISTA DE 5-HT6 PARA EL TRATAMIENTO DE LA DISFUNCIÓN COGNITIVA

Gaceta: 599

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: GYNOPHARM S.A	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78B -201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual: _____	
	Telefono: (571)3719900 Fax: (571)3730818	Numero	802.006.279-4
	E-mail: negocios@optimum-co.com		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95 104	C.C. ☒	NIT ☐
	Telefono: (571) 2131213 Fax: (571) 6121979	C.E. ☐	Otro ☐
	E-mail: negocios@optimum-co.com	Cual: 51'975.664 - 83823	
		Numero	TP: _____

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: La presente solicitud no cumple con los requisitos patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

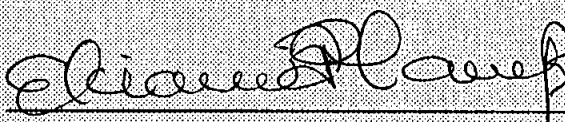
⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA:



C.C. 51.975.664

TP. 83823

Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 08 071.259
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMBINACIÓN DE UN INHIBIDOR DE ACETIL
COLINESTERASA Y UN ANTAGONISTA DE 5-HT6
PARA EL TRATAMIENTO DE LA DISFUNCIÓN
COGNITIVA"

Solicitante : WYETH
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 599 del 31 de Diciembre de 2008

Yo, **ELIANA ISaura MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de agente oficioso de la sociedad **GYNOPHARM S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada **"COMBINACIÓN DE UN INHIBIDOR DE ACETIL COLINESTERASA Y UN ANTAGONISTA DE 5-HT6 PARA EL TRATAMIENTO DE LA**

DISFUNCIÓN COGNITIVA", cuyo titular es **WYETH**, y pido a Usted declarar fundada ésta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR ✓

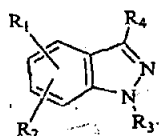
Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular qalantamina. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 10 de julio de 2008 reivindicando prioridad bajo la solicitud US20060758841P del 2006-01-13; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 599 del 31 de Diciembre de 2008, cuya publicación internacional corresponde a la WO2007087151 del 2007-08-02.

2.2. La solicitud colombiana 08 071.259 objeto de la presente oposición, se refiere a un método para el tratamiento de un trastorno cognitivo tal como la enfermedad de Alzheimer en un paciente que lo necesita que comprende suministrar a dicho

paciente una cantidad terapéuticamente efectiva de una combinación de un inhibidor de acetilcolinesterasa y un antagonista 5-hidroxitriptamina-6; método de tratamiento para un trastorno cognitivo en un paciente que lo necesita que comprende suministrar a dicho paciente una cantidad terapéuticamente efectiva de una combinación de un inhibidor de acetilcolinesterasa y un antagonista de 5-hidroxitriptamina; en donde el inhibidor de acetilcolinesterasa se selecciona del grupo que consiste esencialmente de: donepezil; galantamina; rivastigmina; y una sal farmacéuticamente aceptable de ellos; en donde el antagonista 5-hidroxitriptamina-6 es un compuesto de fórmula I



(I)

en donde E1 es W(CR5R6)NR7R8, W es O, S, NR, CH2, CO, CH2Y, CH2CO, CONR o NRCO, entre otros.

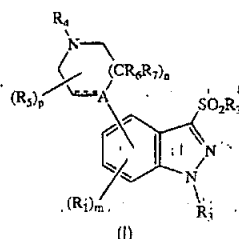
2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)", los usos no están contemplados como patentables; y, Artículo 20.- "No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la

norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: WO2004074243 publicada el 2 de septiembre de 2004.
- D2: NORDBERG A. ET AL: 'CHOLINESTERASE INHIBITORS IN THE TREATMENT OF ALZHEIMER'S DISEASE A COMPARISON OF TOLERABILITY AND PHARMACOLOGY' DRUG SAFETY vol. 19, no. 6, pages 465 - 480; publicada el 1° de diciembre de 1998.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela compuestos de fórmula I



para el tratamiento terapéutico de desórdenes relacionados con o afectado por el receptor 5-HT6. Como tal, esta anterioridad D1 revela que los antagonistas de 5-HT6 tienen un efecto terapéutico para el tratamiento de desórdenes cognitivos. En

la descripción define que el receptor 5-hidroxitriptamina-6 (5-HT6) es uno de los receptores más recientes para ser identificados por la reproducción molecular. Según D1, se define su capacidad de atar una amplia gama de compuestos terapéuticos usados en psiquiatría, la disfunción cognoscitiva, la función motora y el control, la memoria, el humor y otros por similares.

2.6. Ahora bien, el documento D2 revela inhibidores de colinesterasa en el tratamiento en Alzheimer. Este documento D2 revela para 1998, el uso de donepezil (ítem 5, página 472), galantamina (ítem 6, página 473) y rivastigmina (ítem 10, página 475) sólo o en combinación, efectivos para el tratamiento terapéutico de desordenes cognitivos.

2.7. Por lo tanto, cualquier persona versada en la materia puede llegar de manera consecuente a crear una combinación que incluye una cantidad terapéuticamente efectiva de un antagonista 5-hidroxitriptamina-6-inhibidor con base en lo revelado en el documento D1, combinado con un acetilcolinesterasa según lo ilustrado en el documento D2, para el tratamiento de un trastorno cognitivo en un paciente, llegando obvia y de manera evidente a una composición tal y como aquella revelada en la presente solicitud. Por lo tanto, visto dicho documento D2 en combinación con el documento D1, la presente solicitud carece evidentemente de altura inventiva.

2.8. Por lo tanto, este documento objeto de oposición a la luz del documento D1 y el documento D2, carece de ALTURA INVENTIVA.

2.9. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 071.259 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.10. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.10.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 13 de febrero de 2006, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a un compuesto farmacéutico que combine un antagonista 5-hidroxitriptamina-6inhibidor y un acetilcolinesterasa para el tratamiento de un trastorno cognitivo en un paciente, sobre el cual busca protección en el capítulo reivindicatorio.

2.10.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.11. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán*

patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.12. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"COMBINACIÓN DE UN INHIBIDOR DE ACETIL COLINESTERASA Y UN ANTAGONISTA DE 5-HT6 PARA EL TRATAMIENTO DE LA DISFUNCIÓN COGNITIVA"**, cuyo titular es **WYETH**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 599 del 31 de diciembre de 2008.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO2004074243 publicada el 2 de septiembre de 2004.
- D2: NORDBERG A. ET AL: 'CHOLINESTERASE INHIBITORS IN THE TREATMENT OF ALZHEIMER'S DISEASE A COMPARISON OF TOLERABILITY AND PHARMACOLOGY' DRUG SAFETY vol. 19, no. 6, pages 465 - 480; publicada el 1° de diciembre de 1998.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

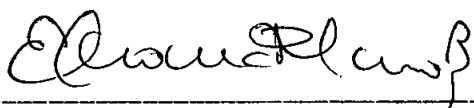
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente. ☒
2. Documento que acredita al representante legal de GYNOPHARM S.A. ☒
3. Recibo de caja del respectivo pago de tasa. ☒
4. Copias de los documentos:
 - D1: WO2004074243 publicada el 2 de septiembre de 2004.
 - D2: NORDBERG A. ET AL: 'CHOLINESTERASE INHIBITORS IN THE TREATMENT OF ALZHEIMER'S DISEASE, A COMPARISON OF TOLERABILITY AND PHARMACOLOGY' DRUG SAFETY vol. 19, no. 6, pages 465 - 480; publicada el 1º de diciembre de 1998.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

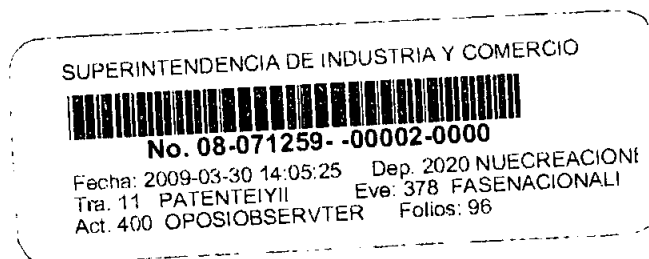
T.P.A. 83823 del C.S. de la J.

13

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 24,454
FECHA : MARZO 30 DE 2009



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	398134	17/02/2009	1,722,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	287,000.00
		TOTAL :	\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

(19) World Intellectual Property
Organization
International Bureau



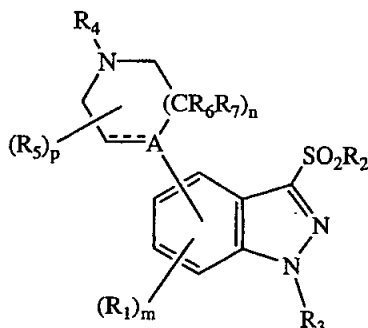
(43) International Publication Date
2 September 2004 (02.09.2004)

PCT

(10) International Publication Number
WO 2004/074243 A2

- (51) International Patent Classification⁷: **C07D**
- (21) International Application Number:
PCT/US2004/003926
- (22) International Filing Date: 10 February 2004 (10.02.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/447,613 14 February 2003 (14.02.2003) US
- (71) Applicant (for all designated States except US): **WYETH**
[US/US]; Five Giralda Farms, Madison, NJ 07940 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **BERNOTAS, Ronald, Charles** [US/US]; 908 Morgan Drive, Royersford, PA 19468 (US). **YAN, Yinfu** [CN/US]; 362 Wren Lane, Bedminster, NJ 07921 (US). **ROBICHAUD, Albert, Jean** [US/US]; 3 Riverview Court, Ringoes, NJ 08551 (US). **LIU, Guangcheng** [CN/US]; 7 Greenfield Drive, North, Princeton Junction, NJ 08550 (US).
- (74) Agent: **LENCES, Barbara, L.**; Wyeth, Patent Law Department, Five Giralda Farms, Madison, NJ 07940 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NI, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROCYCLYL-3-SULFONYLINDAZOLES AS 5-HYDROXYTRYPTAMINI-6 LIGANDS



(I)

(57) Abstract: The invention provides compounds of formula (I) and the use thereof in the therapeutic treatment of disorders related to or affected by the 5-HT₆ receptor.

WO 2004/074243 A2

**HETEROCYCLYL-3-SULFONYLINDAZOLES AS 5-HYDROXYTRYPTAMINE-6
LIGANDS**

5

BACKGROUND OF THE INVENTION

Serotonin (5-Hydroxytryptamine)(5-HT) receptors play a critical role in many physiological and behavioral functions in humans and animals. These functions are mediated through various 5-HT receptors distributed throughout the body. There are
10 now approximately fifteen different human 5-HT receptor subtypes that have been cloned, many with well-defined roles in humans. One of the most recently identified 5-HT receptor subtypes is the 5-HT6 receptor, first cloned from rat tissue in 1993 (Monsma, F. J.; Shen, Y.; Ward, R. P.; Hamblin, M. W. *Molecular Pharmacology* 1993, 43, 320-327) and subsequently from human tissue (Kohen, R.; Metcalf, M. A.;
15 Khan, N.; Druck, T.; Huebner, K.; Sibley, D. R. *Journal of Neurochemistry* 1996, 66, 47-56). The receptor is a G-protein coupled receptor (GPCR) positively coupled to adenylate cyclase (Ruat, M.; Traiffort, E.; Arrang, J-M.; Tardivel-Lacombe, L.; Diaz, L.; Leurs, R.; Schwartz, J-C. *Biochemical Biophysical Research Communications* 1993, 193, 268-276). The receptor is found almost exclusively in the central nervous
20 system (CNS) areas both in rat and in human. *In situ* hybridization studies of the 5-HT6 receptor in rat brain using mRNA indicate principal localization in the areas of 5-HT projection including striatum, nucleus accumbens, olfactory tubercle, and hippocampal formation (Ward, R. P.; Hamblin, M. W.; Lachowicz, J. E.; Hoffman, B. J.; Sibley, D. R.; Dorsa, D. M. *Neuroscience* 1995, 64, 1105-1111).

25 There are many potential therapeutic uses for 5-HT6 ligands in humans based on direct effects and on indications from available scientific studies. These studies include the localization of the receptor, the affinity of ligands with known *in vivo* activity, and various animal studies conducted so far.

One potential therapeutic use of modulators of 5-HT6 receptor function is in
30 the enhancement of cognition and memory in human diseases such as Alzheimer's. The high levels of receptor found in important structures in the forebrain, including the caudate/putamen, hippocampus, nucleus accumbens, and cortex

suggest a role for the receptor in memory and cognition since these areas are known to play a vital role in memory (Gerard, C.; Martres, M.-P.; Lefevre, K.; Miquel, M.C.; Verge, D.; Lanfumey, R.; Doucet, E.; Hamon, M.; El Mestikawy, S. *Brain Research*, 1997, 746, 207-219). The ability of known 5-HT6 receptor ligands to enhance
5 cholinergic transmission also supported the potential cognition use (Bentley, J. C.; Boursson, A.; Boess, F. G.; Kone, F. C.; Marsden, C. A.; Petit, N.; Sleight, A. J. *British Journal of Pharmacology*, 1999, 126(7), 1537-1542). Studies have found that a known 5-HT6 selective antagonist significantly increased glutamate and aspartate levels in the frontal cortex without elevating levels of noradrenaline, dopamine, or 5-
10 HT. This selective elevation of neurochemicals known to be involved in memory and cognition strongly suggests a role for 5-HT6 ligands in cognition (Dawson, L. A.; Nguyen, H. Q.; Li, P. *British Journal of Pharmacology*, 2000, 130(1), 23-26). Animal studies of memory and learning with a known selective 5-HT6 antagonist found some positive effects (Rogers, D. C.; Hatcher, P. D.; Hagan, J. J. *Society of Neuroscience*,
15 *Abstracts* 2000, 26, 680). Further support for the role of a selective 5-HT6 ligand in cognition can be found in Woolley, M. L.; Marsden, C. A.; Sleight, A. J.; and Fone, K. C. F., *Psychopharmacology*, 2003, 170(4), 358-367.

A related potential therapeutic use for 5-HT6 ligands is the treatment of attention deficit disorders (ADD, also known as Attention Deficit Hyperactivity
20 Disorder or ADHD) in both children and adults. Because 5-HT6 antagonists appear to enhance the activity of the nigrostriatal dopamine pathway and because ADHD has been linked to abnormalities in the caudate (Ernst, M.; Zametkin, A. J.; Matochik, J. H.; Jons, P. A.; Cohen, R. M. *Journal of Neuroscience* 1998, 18(15), 5901-5907), 5-HT6 antagonists may attenuate attention deficit disorders.

25 Early studies examining the affinity of various CNS ligands with known therapeutic utility or a strong structural resemblance to known drugs suggests a role for 5-HT6 ligands in the treatment of schizophrenia and depression. For example, clozapine (an effective clinical antipsychotic) has high affinity for the 5-HT6 receptor subtype. Also, several clinical antidepressants have high affinity for the receptor as
30 well and act as antagonists at this site (Branchek, T. A.; Blackburn, T. P. *Annual Reviews in Pharmacology and Toxicology* 2000, 40, 319-334).

Further, recent *in vivo* studies in rats indicate 5-HT6 modulators may be useful in the treatment of movement disorders including epilepsy (Stean, T.;

Routledge, C.; Upton, N. *British Journal of Pharmacology* 1999, 127 Proc.

Supplement 131P and Routledge, C.; Bromidge, S. M.; Moss, S. F.; Price, G. W.;

Hirst, W.; Newman, H.; Riley, G.; Gager, T.; Stean, T.; Upton, N.; Clarke, S. E.;

Brown, A. M. *British Journal of Pharmacology* 2000, 130(7), 1606-1612).

5 Taken together, the above studies strongly suggest that compounds which are 5-HT6 receptor modulators, i.e. ligands, may be useful for therapeutic indications including: the treatment of diseases associated with a deficit in memory, cognition, and learning such as Alzheimer's and attention deficit disorder; the treatment of personality disorders such as schizophrenia; the treatment of behavioral disorders,
10 e.g., anxiety, depression and obsessive compulsive disorders; the treatment of motion or motor disorders such as Parkinson's disease and epilepsy; the treatment of diseases associated with neurodegeneration such as stroke and head trauma; or withdrawal from drug addiction including addiction to nicotine, alcohol, and other substances of abuse.

15 Therefore, it is an object of this invention to provide compounds which are useful as therapeutic agents in the treatment of a variety of central nervous system disorders related to or affected by the 5-HT6 receptor.

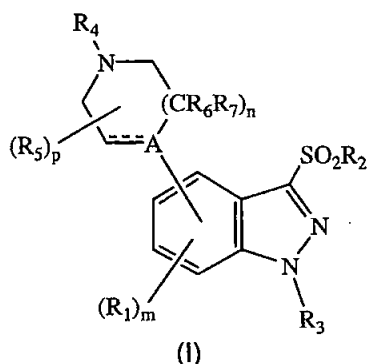
It is another object of this invention to provide therapeutic methods and pharmaceutical compositions useful for the treatment of central nervous system
20 disorders related to or affected by the 5-HT6 receptor.

It is a feature of this invention that the compounds provided may also be used to further study and elucidate the 5-HT6 receptor.

SUMMARY OF THE INVENTION

25

The present invention provides a compound of formula I



wherein

5

A is C, CR₈ or N;

R₁ is H, halogen, CN, COR₉, OCO₂R₁₀, CO₂R₁₁, CONR₁₂R₁₃, SO_xR₁₄, NR₁₅R₁₆, OR₁₇ or a C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl or heteroaryl group each optionally substituted;

10

R₂ is an optionally substituted C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl, or heteroaryl group or an optionally substituted 8- to 13-membered bicyclic or tricyclic ring system having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S ;

R₃ is H or a C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl or heteroaryl group each optionally substituted;

15

R₄ is H or a C₁-C₆alkyl or C₃-C₇cycloalkyl group each optionally substituted;

R₅, R₆ and R₇ are each independently H or a C₁-C₆alkyl or C₃-C₇cycloalkyl group each optionally substituted;

m and p are each independently an integer of 1, 2 or 3;

n is an integer of 1 or 2;

20

R₈ is H, OH or an optionally substituted C₁-C₆alkoxy group;

R₉, R₁₀, R₁₁ and R₁₇ are each independently H or a C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

25

R₁₂, R₁₃, R₁₅ and R₁₆ are each independently H or an optionally substituted C₁-C₄alkyl group or R₁₂ and R₁₃ or R₁₅ and R₁₆ may be taken together with the atom to which they are attached to form a 5- to 7-membered

ring optionally containing another heteroatom selected from O, NR₁₈
or SO_x;

R₁₄ is a C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl,
cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

5 R₁₈ is H or a C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₇cycloalkyl,
cycloheteroalkyl, aryl or heteraryl group each optionally substituted;
x is 0 or an integer of 1 or 2; and

--- represents a single bond or a double bond; or

the stereoisomes thereof or the pharmaceutically acceptable salts thereof.

10 The present invention also provides methods and compositions useful in the
treatment of central nervous system disorders.

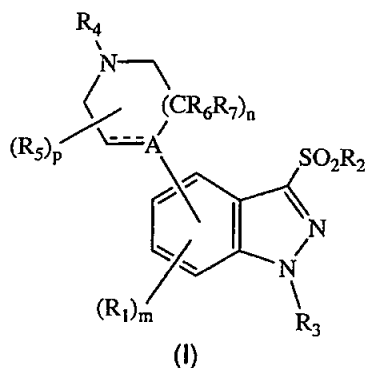
DETAILED DESCRIPTION OF THE INVENTION

15

The 5-hydroxytryptamine-6 (5-HT₆) receptor is one of the most recent
receptors to be identified by molecular cloning. Its ability to bind a wide range of
therapeutic compounds used in psychiatry, coupled with its intriguing distribution in
the brain has stimulated significant interest in new compounds which are capable of
20 interacting with or affecting said receptor. Significant efforts are being made to
understand the possible role of the 5-HT₆ receptor in psychiatry, cognitive
dysfunction, motor function and control, memory, mood and the like. To that end,
compounds which demonstrate a binding affinity for the 5-HT₆ receptor are earnestly
sought both as an aid in the study of the 5-HT₆ receptor and as potential therapeutic
25 agents in the treatment of central nervous system disorders, for example see C.
Reavill and D. C. Rogers, Current Opinion in Investigational Drugs, 2001, 2(1):104-
109, Pharma Press Ltd.

Surprisingly, it has now been found that heterocyclyl-3-sulfonylindazoles of
formula I demonstrate 5-HT₆ affinity along with significant sub-type selectivity.

30 Advantageously, said formula I indazoles are effective therapeutic agents for the
treatment of central nervous system (CNS) disorders associated with or affected by
the 5-HT₆ receptor. Accordingly, the present invention provides 1-heterocyclyl-3-
sulfonylindazole compounds of formula I



wherein

5

A is C, CR_8 or N;

R_1 is H, halogen, CN, COR_9 , OCO_2R_{10} , CO_2R_{11} , $CONR_{12}R_{13}$, SO_xR_{14} , $NR_{15}R_{16}$, OR_{17} or a C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl or heteroaryl group each optionally substituted;

10

R_2 is an optionally substituted C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, or heteroaryl group or an optionally substituted 8- to 13-membered bicyclic or tricyclic ring system having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S;

R_3 is H or a C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl or heteroaryl group each optionally substituted;

15

R_4 is H or a C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl group each optionally substituted;

R_5 , R_6 and R_7 are each independently H or a C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl group each optionally substituted;

m and p are each independently an integer of 1, 2 or 3;

n is an integer of 1 or 2;

20

R_8 is H, OH or an optionally substituted C_1 - C_6 alkoxy group;

R_9 , R_{10} , R_{11} and R_{17} are each independently H or a C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

25

R_{12} , R_{13} , R_{15} and R_{16} are each independently H or an optionally substituted C_1 - C_4 alkyl group or R_{12} and R_{13} or R_{15} and R_{16} may be taken together with the atom to which they are attached to form a 5- to 7-membered

21

ring optionally containing another heteroatom selected from O, NR₁₈ or SO_x;

R₁₄ is a C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl,

cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

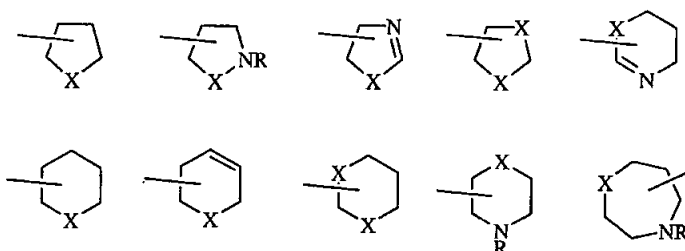
5 R₁₈ is H or a C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₇cycloalkyl, cycloheteroalkyl, aryl or heteraryl group each optionally substituted;

x is 0 or an integer of 1 or 2; and

---- represents a single bond or a double bond; or

the stereoisomes thereof or the pharmaceutically acceptable salts thereof.

- 10 As used in the specification and claims, the term halogen designates F, Cl, Br or I and the term cycloheteroalkyl designates a five- to seven-membered cycloalkyl ring system containing 1 or 2 heteroatoms, which may be the same or different, selected from N, O or S and optionally containing one double bond. Exemplary of the cycloheteroalkyl ring systems included in the term as designated herein are the
- 15 following rings wherein X is NR, O or S; and R is H or an optional substituent as described hereinbelow:

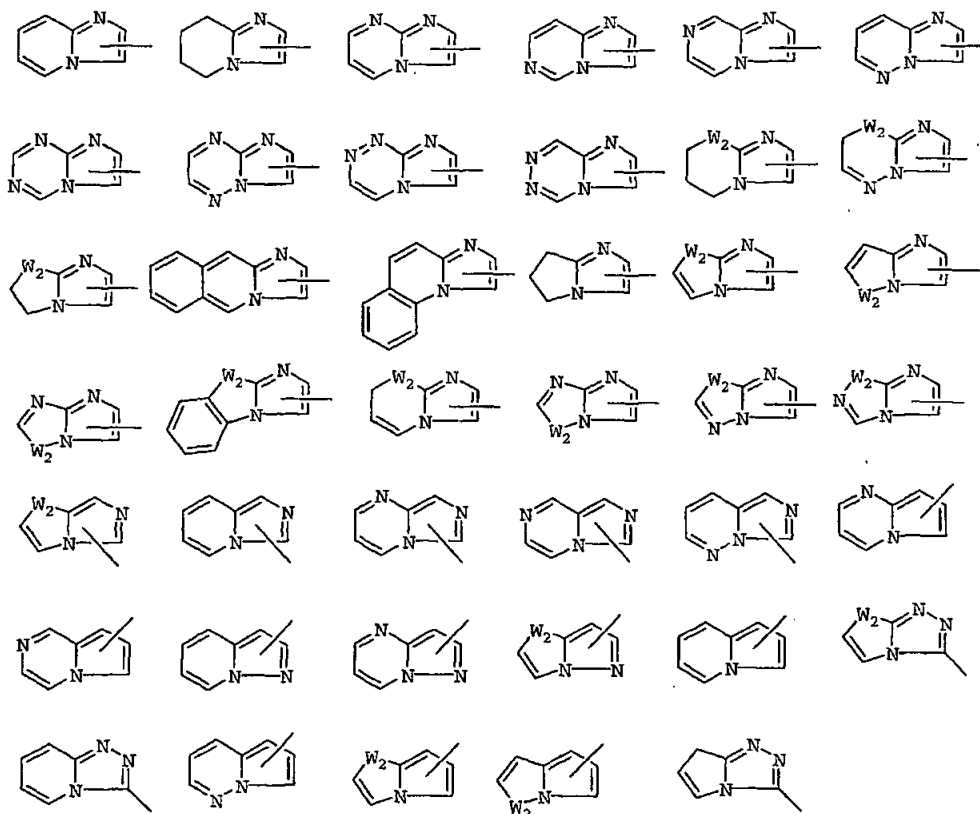


Similarly, as used in the specification and claims, the term heteroaryl

- 20 designates a five- to ten-membered aromatic ring system containing 1, 2 or 3 heteroatoms, which may be the same or different, selected from N, O or S. Such heteroaryl ring systems include pyrrolyl, azoly, oxazoly, thiazoly, imidazoly, furyl, thienyl, quinolinyl, isoquinolinyl, indolyl, benzothienyl, benzofuranyl, benzisoxazoly or the like. The term aryl designates a carbocyclic aromatic ring system such as
- 25 phenyl, naphthyl, anthracenyl or the like. The term haloalkyl as used herein designates a C_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different and the term haloalkoxy as used herein designates an OC_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different.

Exemplary of the 8- to 13-membered bicyclic or tricyclic ring systems having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S included in the term as designated herein are the following ring systems wherein W_2 is NR, O or S; and R is H or an optional substituent as

5 described hereinbelow:



In the specification and claims, when the terms C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, cycloheteroalkyl, aryl or heteroaryl are designated as
 10 being optionally substituted, the substituent groups which are optionally present may be one or more of those customarily employed in the development of pharmaceutical compounds, or the modification of such compounds, to influence their structure/activity, persistence, absorption, stability or other beneficial property.
 Specific examples of such substituents include halogen atoms, nitro, cyano,
 15 thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio,

alkylsulphinyl, alkylsulphonyl, carbamoyl, alkylaminocarbonyl, phenyl and substituted phenyl (where the substituents are as defined herein), phenoxy, benzyl, benzyloxy, heteroaryl, indolyl, heterocyclyl (e.g., heteroaryl, cycloheteroalkyl) or cycloalkyl groups, preferably halogen atoms or lower alkyl or lower alkoxy groups. Typically, 0-
5 3 substituents may be present. When any of the foregoing substituents represents or contains an alkyl substituent group, this may be linear or branched and may contain up to 12, preferably up to 6, more preferably up to 4 carbon atoms.

Pharmaceutically acceptable salts may be any acid addition salt formed by a compound of formula I and a pharmaceutically acceptable acid such as phosphoric,
10 sulfuric, hydrochloric, hydrobromic, citric, maleic, malonic, mandelic, succinic, fumaric, acetic, lactic, nitric, sulfonic, p-toluene sulfonic, methane sulfonic acid or the like.

Compounds of the invention include esters, carbamates or other conventional prodrug forms, which in general, are functional derivatives of the compounds of the
15 invention and which are readily converted to the inventive active moiety *in vivo*. Correspondingly, the method of the invention embraces the treatment of the various conditions described hereinabove with a compound of formula I or with a compound which is not specifically disclosed but which, upon administration, converts to a compound of formula I *in vivo*. Also included are metabolites of the compounds of
20 the present invention defined as active species produced upon introduction of these compounds into a biological system.

Compounds of the invention may exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers, atropisomers and geometric isomers. One skilled in the art will appreciate that one stereoisomer may
25 be more active or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich or selectively prepare said stereoisomers. Accordingly, the present invention comprises compounds of formula I, the stereoisomers thereof and the pharmaceutically acceptable salts thereof. The
30 compounds of the invention may be present as a mixture of stereoisomers, individual stereoisomers, or as an optically active or enantiomerically pure form.

Examples of R₃ are hydrogen, phenyl and C₁-C₄alkyl which may be substituted by optionally substituted phenyl, e.g., R₃ is methyl, phenyl or 3-chlorobenzyl. An example of A is N. Examples of R₂ are phenyl, 1-naphthyl, 2-naphthyl, cyanophenyl, 2, 3, or 4-halophenyl, 2-phenethyl, 2-chloro-4-fluorophenyl, aminophenyl and thienyl. Examples of R₄ are H, methyl, ethyl, propyl and phenethyl.

Preferred compounds of the invention are those compounds of formula I wherein n is 1. Another group of preferred compounds are those compounds of formula I wherein R₄ is H or an optionally substituted C₁-C₄alkyl group. A further group of preferred compounds of the invention are those compounds of formula I wherein R₂ is an optionally substituted phenyl, naphthyl or heteroaryl group. Also preferred are those compounds of formula I wherein R₅, R₆ and R₇ are H.

More preferred compounds of the invention are those compounds of formula I wherein A is N and R₄ is H or an optionally substituted C₁-C₄alkyl group. Another group of more preferred compounds are those compounds of formula I wherein A is N; n is 1 and R₂ is an optionally substituted phenyl, naphthyl or heteroaryl group. Further more preferred compounds of the invention are those compounds of formula I wherein the 6- or 7-membered azacyclic ring is attached to the indazole in the 5 or 7 position.

Among the preferred compounds of the invention are:

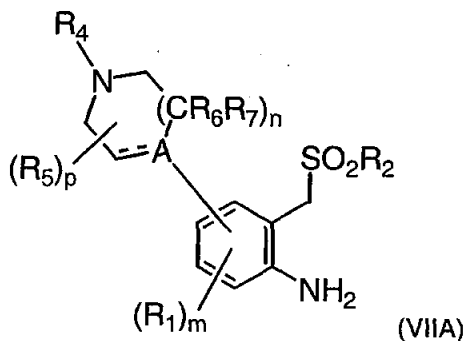
- 20 5-(4-methylpiperazin-1-yl)-3-(1-naphthylsulfonyl)-1H-indazole;
- 3-(1-naphthylsulfonyl)-5-piperazin-1-yl-1H-indazole;
- 1-(3-chlorobenzyl)-5-(4-methylpiperazin-1-yl)-3-(1-naphthylsulfonyl)-1H-indazole;
- 7-(4-methylpiperazin-1-yl)-3-(phenylsulfonyl)-1H-indazole;
- 3-(phenylsulfonyl)-7-(4-propylpiperazin-1-yl)-1H-indazole;
- 25 3-(phenylsulfonyl)-7-piperazin-1-yl-1H-indazole;
- 5-(4-methylpiperazin-1-yl)-3-(phenylsulfonyl)-1H-indazole;
- 3-(phenylsulfonyl)-5-(4-propylpiperazin-1-yl)-1H-indazole;
- 3-(phenylsulfonyl)-5-piperazin-1-yl-1H-indazole;
- 5-piperazin-1-yl-3-[(3-cyanophenyl)sulfonyl]-1H-indazole;
- 30 7-(4-methylpiperazin-1-yl)-3-[(2-phenethyl)sulfonyl]-1H-indazole;
- 3-(1-naphthylsulfonyl)-7-(4-propylpiperazin-1-yl)-1H-indazole;
- 5-(4-phenethylpiperazin-1-yl)-3-(1-naphthylsulfonyl)-1H-indazole;
- 5-(4-methylpiperazin-1-yl)-3-(2-naphthylsulfonyl)-1H-indazole;

- 3-[(2-chloro-4-fluorophenyl)sulfonyl]-5-piperazin-1-yl-1*H*-indazole;
1-methyl-3-(phenylsulfonyl)-5-piperazin-1-yl-1*H*-indazole;
1-phenyl-3-(phenylsulfonyl)-5-piperazin-1-yl-1*H*-indazole;
1-methyl-3-(phenylsulfonyl)-7-piperazin-1-yl-1*H*-indazole;
5 1-phenyl-3-(phenylsulfonyl)-7-(piperazin-1-yl)-1*H*-indazole;
7-piperazin-1-yl-3-[(3-fluorophenyl)sulfonyl]-1*H*-indazole;
3-[(4-fluorophenyl)sulfonyl]-7-(4-methylpiperazin-1-yl)-1*H*-indazole;
3-[(2-chlorophenyl)sulfonyl]-7-piperazin-1-yl-1*H*-indazole;
3-[(4-aminophenyl)sulfonyl]-7-(piperazin-1-yl)-1*H*-indazole;
10 5-piperazin-1-yl-3-[(3-fluorophenyl)sulfonyl]-1*H*-indazole;
3-[(4-fluorophenyl)sulfonyl]-5-(4-methylpiperazin-1-yl)-1*H*-indazole;
3-[(2-chlorophenyl)sulfonyl]-5-(4-propylpiperazin-1-yl)-1*H*-indazole;
3-[(4-aminophenyl)sulfonyl]-5-piperazin-1-yl-1*H*-indazole;
3-[(5-chlorothien-2-yl)sulfonyl]-5-piperazin-1-yl-1*H*-indazole;
15 3-[(5-chlorothien-2-yl)sulfonyl]-7-piperazin-1-yl-1*H*-indazole;
4-chloro-3-(phenylsulfonyl)-7-piperazin-1-yl-1*H*-indazole;
5-fluoro-3-(phenylsulfonyl)-7-piperazin-1-yl-1*H*-indazole;
6-fluoro-3-(phenylsulfonyl)-7-piperazin-1-yl-1*H*-indazole;
4-chloro-3-(phenylsulfonyl)-5-piperazin-1-yl-1*H*-indazole;
20 7-fluoro-3-(phenylsulfonyl)-5-piperazin-1-yl-1*H*-indazole;
6-fluoro-3-(phenylsulfonyl)-5-piperazin-1-yl-1*H*-indazole;
6-(4-phenethylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
6-(4-methylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
6-(4-propylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
25 3-(phenylsulfonyl)-6-piperazin-1-yl-1*H*-indazole;
4-piperazin-1-yl-3-(phenylsulfonyl)-1*H*-indazole;
4-(4-methylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
4-(4-propylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
3-(phenylsulfonyl)-4-piperazin-1-yl-1*H*-indazole;
30 3-[(5-chlorothien-2-yl)sulfonyl]-5-piperidin-1-yl-1*H*-indazole;
3-[(5-chlorothien-2-yl)sulfonyl]-7-piperidin-1-yl-1*H*-indazole;
1-methyl-3-(phenylsulfonyl)-5-piperidin-1-yl-1*H*-indazole;
3-[(3-fluorophenyl)sulfonyl]-5-piperidin-1-yl-1*H*-indazole;

- 1-methyl-3-(phenylsulfonyl)-7-(4-methylpiperidin-1-yl)-1*H*-indazole;
 3-[(3-fluorophenyl)sulfonyl]-7-piperidin-1-yl-1*H*-indazole;
 3-[(3-fluorophenyl)sulfonyl]-5-piperidin-1-yl-1*H*-indazole;
 3-(phenylsulfonyl)-5-piperidin-1-yl-1*H*-indazole;
 5 1-methyl-3-[(3-fluorophenyl)sulfonyl]-7-piperidin-1-yl-1*H*-indazole;
 3-(phenylsulfonyl)-7-piperidin-1-yl-1*H*-indazole;
 the stereoisomers thereof; or
 the pharmaceutically acceptable salts thereof.

- 10 This invention also provides processes for preparing compounds of formula (I) or salts thereof, which processes include one of the following

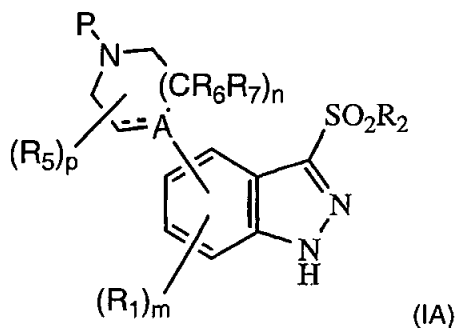
- (a) diazotising and cyclising a compound of formula (VIIA):



wherein the dotted line, m, n, p, A, R₁, R₂, R₄, R₅, R₆ and R₇ are as defined herein,

- 15 e.g. with NaNO₂/acid to give a compound of formula (I) wherein R₃ is hydrogen,
 or

- (b) alkylating or arylating a protected compound of formula (IA)



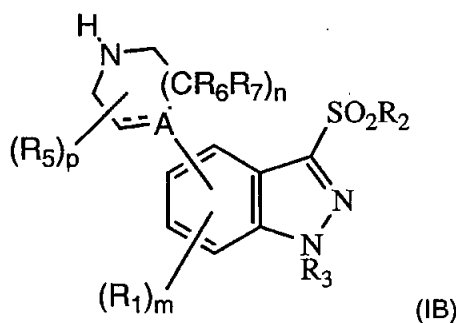
wherein the dotted line, m, n, p, A, R₁, R₂, R₅, R₆ and R₇ are as defined herein and P is a protecting group or R₄ where R₄ is as defined herein excepting hydrogen, with an alkylating or arylating agent of formula R₃-LG where LG is a leaving group and R₃ is a C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl or heteroaryl group each optionally substituted;

- 5 and if required removing the protecting group, to give a corresponding compound of formula (I) where R₃ is a C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl or heteroaryl group each optionally substituted;

or

- (c) alkylating a compound of formula (IB)

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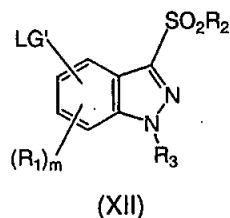


wherein the dotted line, m, n, p, A, R₁, R₂, R₃, R₅, R₆ and R₇ are as defined herein, with an alkylating agent of formula R₄-LG where LG is a leaving group and R₄ is a C₁-C₆alkyl or C₃-C₇cycloalkyl group each optionally substituted, to give a corresponding compound of formula (I) where R₄ is a C₁-C₆alkyl or C₃-C₇cycloalkyl group each optionally substituted;

- 15 or

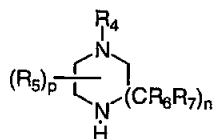
or

- (d) reacting a compound of formula (XII):



20

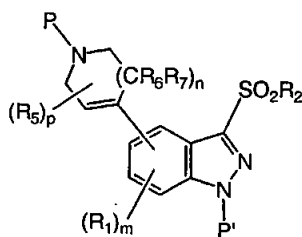
wherein m, R₁, R₂ and R₃ are as defined herein, and LG' is a leaving group such as Cl, Br, I or an activated hydroxyl group such as triflate, with a compound of formula (V):



(V)

wherein n, p, R₄, R₅, R₆ and R₇ are as defined herein, in the presence of a catalyst, e.g., a palladium or nickel catalyst, to give a corresponding compound of formula (I); or

- 5 (e) reducing a compound of formula (XII):

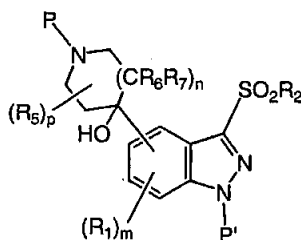


(XVI)

- wherein m, n, p, R₁, R₂, R₅, R₆ and R₇ are as defined herein, P is a protecting group or R₄ as defined in claim 1 and P' is a protecting group or R₃ as defined herein, if
10 required removing any protecting group, to give a corresponding compound of formula (I) wherein A is CH;

or

- 15 (f) acidifying a compound of formula (XII):



(XV)

wherein m, n, p, R₁, R₂, R₅, R₆ and R₇ are as defined herein, P is a protecting group or R₄ as defined herein and P' is a protecting group or R₃ as defined herein, if

required removing any protecting group, to give a corresponding compound of formula (I) wherein A is C and ---- represents a double bond;

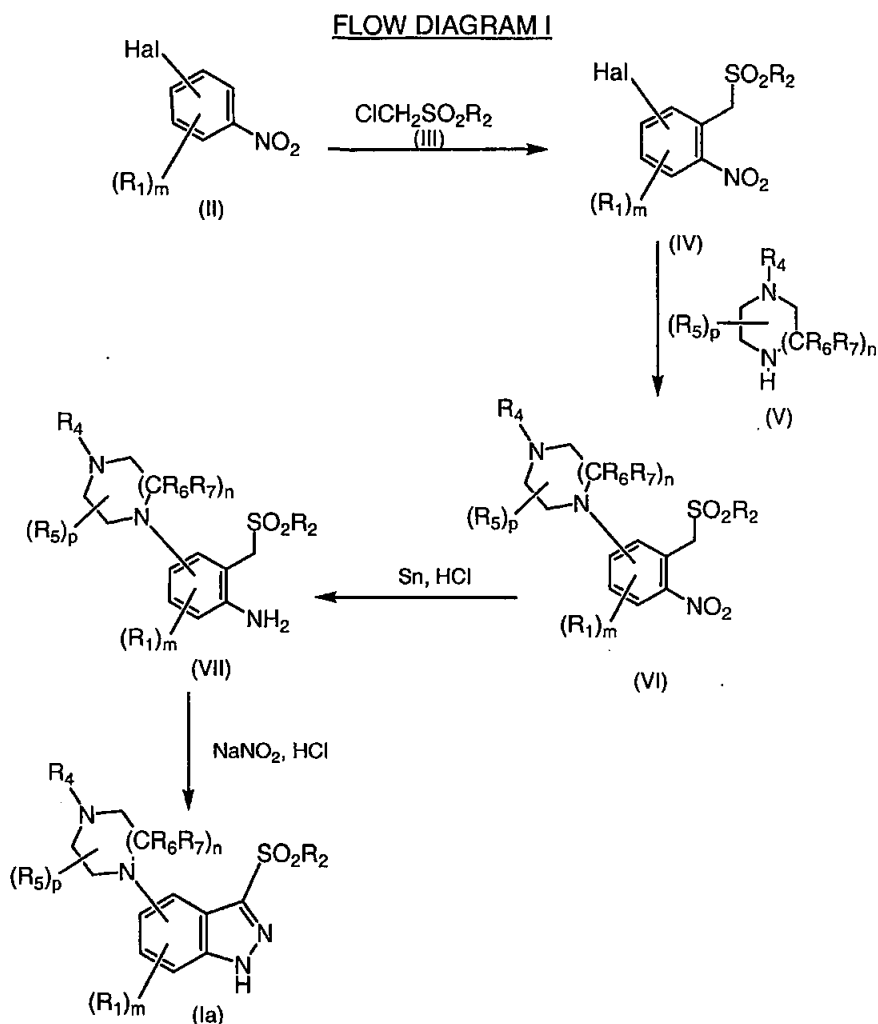
or

- 5 (g) converting a basic compound of formula (I) as defined herein to an acid addition salt thereof or vice versa.

or

- (h) separating a stereoisomer of a compound of formula (I) from a mixture thereof.

- 10 In particular compounds of the invention may be conveniently prepared using conventional synthetic methods and, if required, standard separation or isolation techniques. For example, compounds of formula I wherein A is N; R₃ is H; and ---- represents a single bond (Ia) may be prepared by reacting a halonitrobenzene compound of formula II with a chloromethylsulfone of formula III in the presence of
15 strong base, such as KO-t-Bu or KOH, to give the benzylsulfonyl compound of formula IV; reacting said formula IV compound with a piperazine or homopiperazine of formula V in the presence of a base such as K₂CO₃ to give the compound of formula VI; reacting said formula VI compound with a reducing agent such as Sn, Fe or Zn in the presence of an acid to give the corresponding amine of formula VII; and
20 reacting said amine with NaNO₂ in the presence of an acid to give the desired compound of formula Ia. The reaction is illustrated in flow diagram I wherein Hal represents Cl or F.



5

Compounds of formula Ia wherein R₃ is other than H may be prepared using conventional alkylation/deprotection procedures. For example, compounds of formula I wherein A is N; R₃ is other than H; and --- represents a single bond (Ib) may be prepared by reacting a protected compound of formula VIII with an alkylating agent of formula IX in the presence of a base and a solvent optionally in the presence of a phase-transfer agent to give the protected alkylated compound of formula X and deprotecting said formula X compound to give the desired compound

10

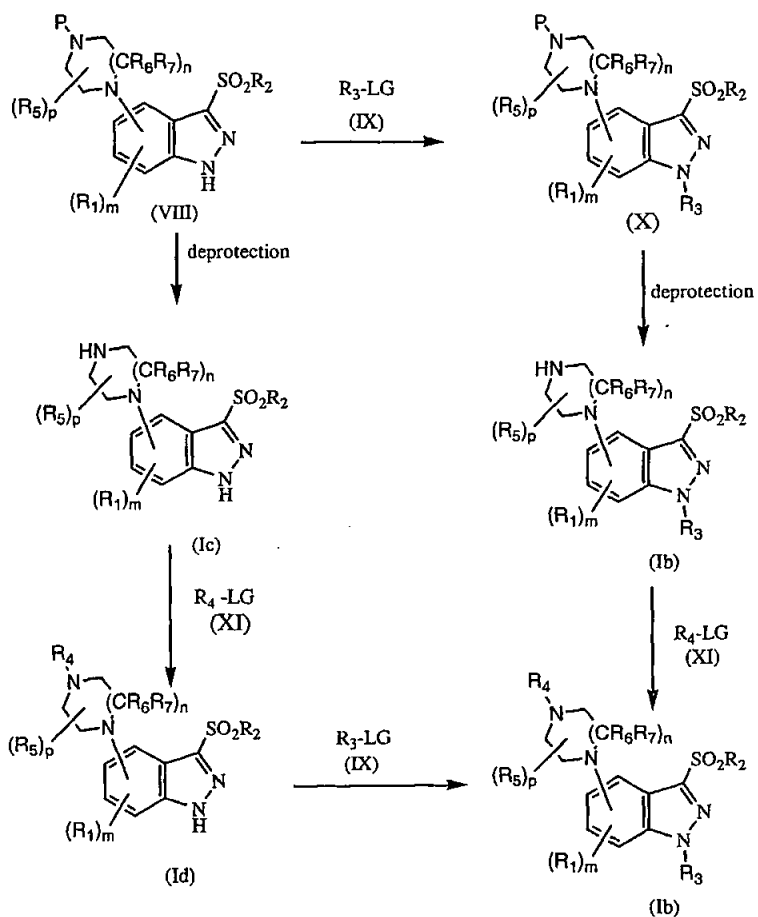
of formula Ib wherein R_4 is H. Alternatively, for those compounds wherein R_3 is an aryl or heteroaryl group, the agent of formula IX may be an aryl or heteroaryl boronic acid and may be coupled with the formula VIII indazole in the presence of a catalyst, e.g., $Cu(OCOCH_3)_2$ to give the corresponding protected compound of formula X

5 wherein R_3 is an aryl or heteroaryl group. Optionally the formula Ib compound may be reacted with an alkylating agent of formula XI under standard alkylation conditions to give the compound of formula Ib wherein R_4 is other than H. If desired, the sequence may be reversed by deprotecting the formula VIII compound to give the compound of formula Ia wherein R_3 and R_4 are H (Ic) and alkylating the formula Ic

10 compound with the formula XI alkylating agent to give the compound of formula Id. Optionally, the formula Id compound may be reacted with a formula IX alkylating agent, as described hereinabove, to give the compound of formula Ib. The reactions are shown in flow diagram II wherein P is a protecting group and LG is a leaving group such as Cl, Br, I, OH, $B(OH)_2$, tosyl, mesyl or the like.

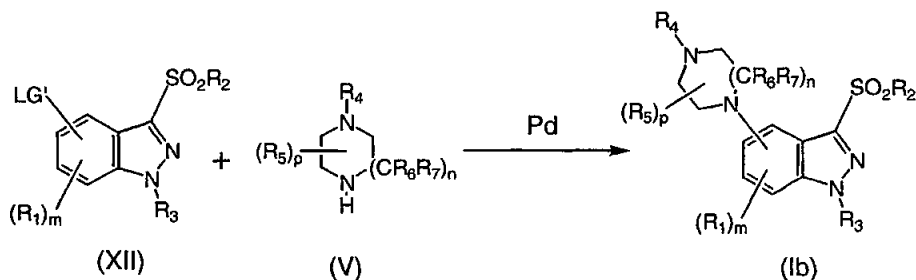
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FLOW DIAGRAM II

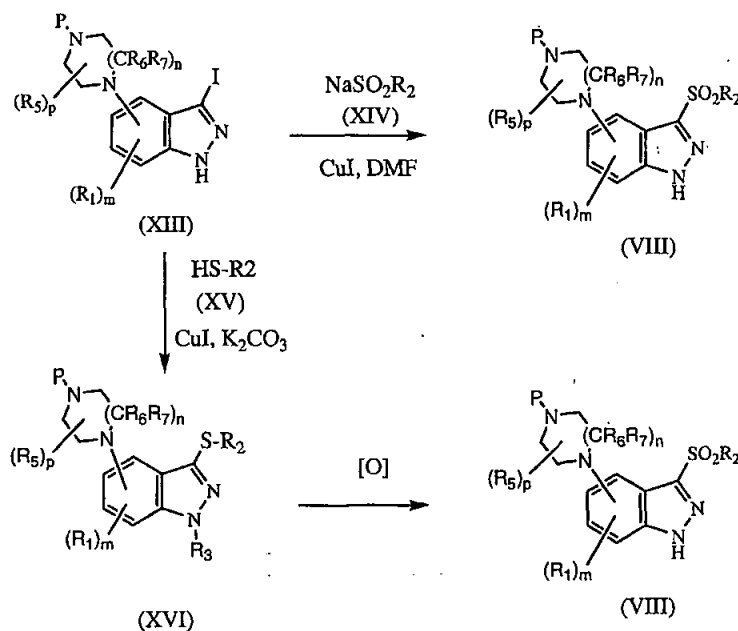


5 Alternatively, compounds of formula Ib may be prepared directly from an indazole compound of formula XII by coupling said formula XII compound with the appropriate piperazine or homopiperazine compound of formula V in the presence of a catalyst such as a palladium or nickel catalyst. The reaction is shown in flow

10 diagram III wherein LG' is a leaving group such as Cl, Br, I or an activated hydroxyl group such as CF_3SO_3 (triflate).

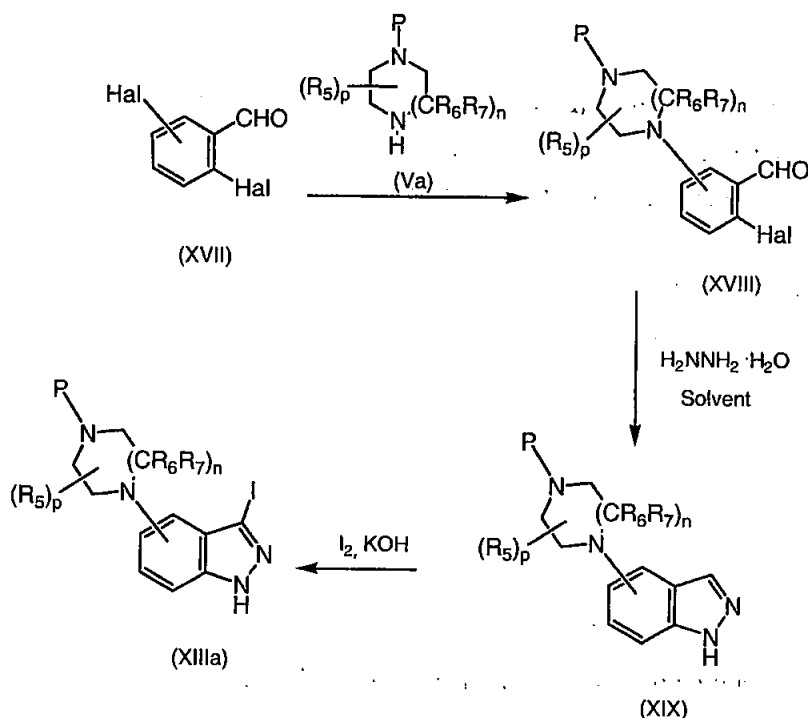
FLOW DIAGRAM III

- 5 Compounds of formula VIII may also be prepared by reacting a protected 3-iodoindazole of formula XIII with a sodium sulfinate of formula XIV in the presence of copper iodide and dimethyl formamide (DMF) to give the desired compound of formula VIII or by reacting the formula XIII compound with a thiol of formula XV in the presence of copper iodide and a base, such as K₂CO₃, to give the thio ether of
- 10 formula XVI and oxidizing said formula XVI compound to give the desired compound of formula VIII. The reactions are shown in flow diagram IV wherein P represents a protecting group.

FLOW DIAGRAM IV

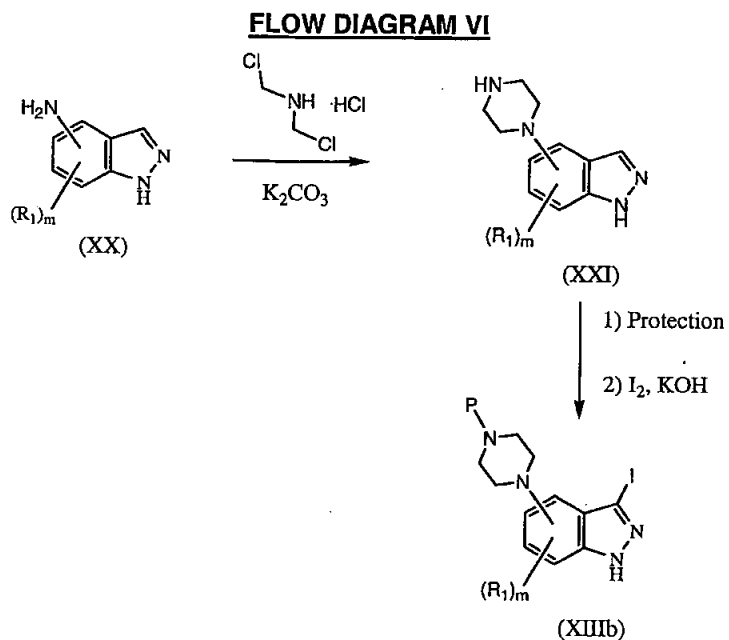
Compounds of formula XIII wherein R_1 is H (XIIIa) may be prepared by reacting a dihalobenzaldehyde of formula XVII with the piperazine or homopiperazine compound of formula V wherein R_4 is a protecting group (Va) to give the ortho halobenzaldehyde compound of formula XVIII, reacting the formula XVIII compound with hydrazine hydrate to give the indazole of formula XIX and reacting the formula XIX indazole with iodine in the presence of a base, such as KOH, to give the desired formula XIIIa compounds. The reactions are shown in flow diagram V wherein P is a protecting group and Hal is F, Cl, Br, or I, preferably F.

10

FLOW DIAGRAM V

Compounds of formula XIII wherein n is 1 and R_5 , R_6 and R_7 are H (XIIIb) may be prepared by reacting an indazole amine of formula XX with di(2-chloroethyl)amine hydrochloride to give the corresponding piperaziny indazole of formula XXI, protecting said formula XXI compound and reacting the protected formula XXI compound with iodine in the presence of a base, such as KOH, to give the desired

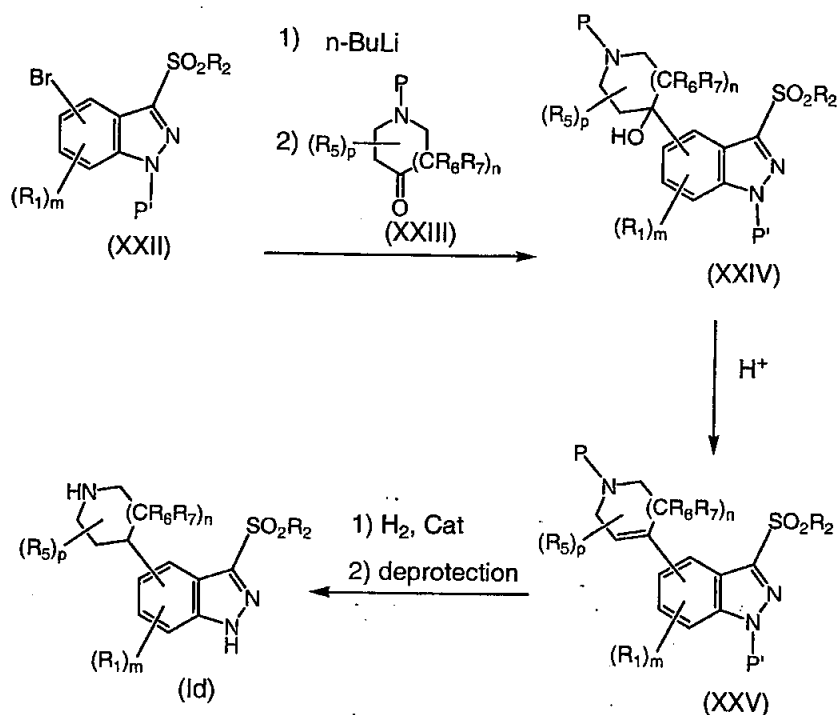
compound of formula XIIIb. The reactions are shown in flow diagram VI whereing P represents a protecting group.



5

Compounds of XIIIa and XIIIb may be converted to compounds of formula Ia, Ib, or Ic as shown hereinabove in flow diagrams II and III.

Corresponding compounds of the invention wherein A is CR₈ may be obtained, for example, by lithiating a protected bromoindazole of formula XXII, and
 10 reacting the lithiated compound *in situ* with an N-protected azacyclic ketone of formula XXIII to give the protected hydroxy compound of formula XXIV, said hydroxy compound may then be dehydrated to give the protected compound of formula XXV. Catalytic hydrogenation and subsequent deprotection of said formula XXV compound gives the desired compounds of formula I wherein A is CR₈; R₃ and R₄ are H; and ---
 15 represents a single bond (Id). The reaction sequence is shown in flow diagram VII wherein P and P' each independently represent a protecting group.

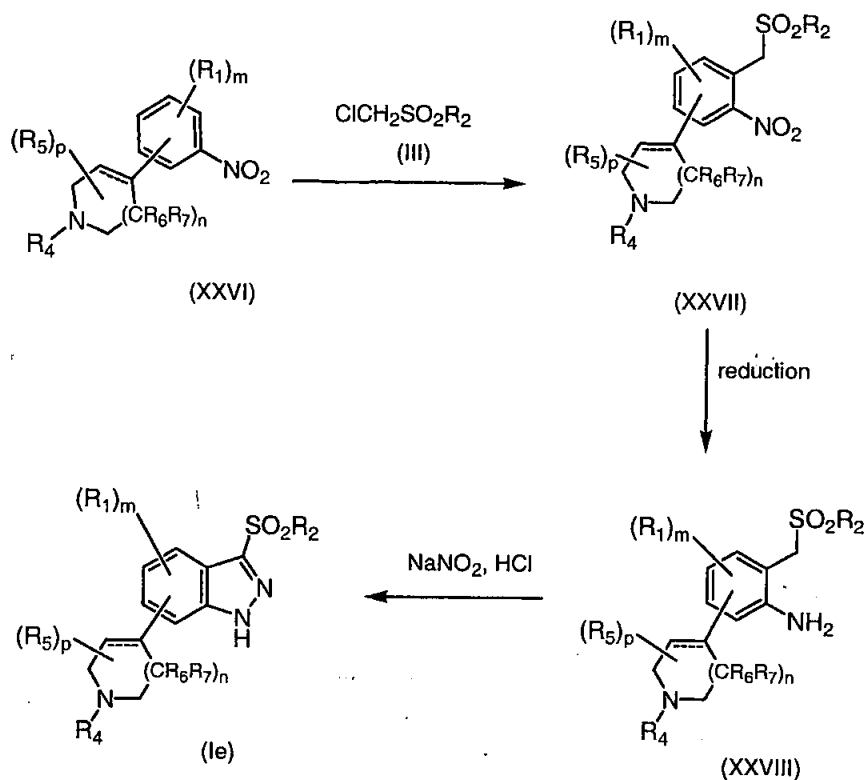
FLOW DIAGRAM VII

5 Using the procedures shown in flow diagram II hereinabove, the compounds of formulas XXIV, XXV and Id may be readily converted to compounds of formula I wherein A is CR₈ and R₃ or R₄ are other than H.

Alternatively, compounds of formula I wherein A is C or CR₈ and R₃ is H (Ie) may be prepared by reacting a chloromethylsulfonyl compound of formula III with a nitrobenzene derivative of formula XXVI in the presence of a strong base, such as KO-t-Bu or KOH, to provide the compound of formula XXVII; reducing said formula XXVII compound with a reducing agent such as Sn, Fe or Zn in the presence of an acid to give the corresponding amine of formula XXVIII; and reacting said amine with NaNO₂ in the presence of an acid to give the desired indazole compound of formula

10

15 Ie. The reactions are shown in flow diagram VIII.

FLOW DIAGRAM VIII

5 Compounds of formula Ie may be converted to the corresponding compounds of formula I wherein A is C or CR₆ and R₃ is other than H by reacting said formula Ie compound with an alkylating agent as shown hereinabove in flow diagram II.

Protecting groups suitable for use in the reactions shown hereinabove include t-butyloxycarbonyl, benzyl, acetyl, benzyloxycarbonyl, or any conventional group
 10 known to protect a basic nitrogen in standard synthetic procedures.

Advantageously, the formula I compounds of the invention are useful for the treatment of CNS disorders relating or affected by 5-HT₆ receptor including motor, mood, personality, behavioral, psychiatric, cognitive, neurodegenerative, or the like disorders, for example Alzheimer's disease, Parkinson's disease, attention deficit
 15 disorder, anxiety, epilepsy, depression, obsessive compulsive disorder, sleep disorders, neurodegenerative disorders (such as head trauma or stroke), feeding disorders (such as anorexia or bulimia), schizophrenia, memory loss, disorders

38

associated with withdrawal from drug or nicotine abuse, or the like or certain gastrointestinal disorders such as irritable bowel syndrome. Accordingly, the present invention provides a method for the treatment of a disorder of the central nervous system related to or affected by the 5-HT₆ receptor in a patient in need thereof which comprises providing said patient a therapeutically effective amount of a compound of formula I as described hereinabove. The compounds may be provided by oral or parenteral administration or in any common manner known to be an effective administration of a therapeutic agent to a patient in need thereof.

The term "providing" as used herein with respect to providing a compound or substance embraced by the invention, designates either directly administering such a compound or substance, or administering a prodrug, derivative or analog which forms an equivalent amount of the compound or substance within the body.

The therapeutically effective amount provided in the treatment of a specific CNS disorder may vary according to the specific condition(s) being treated, the size, age and response pattern of the patient, the severity of the disorder, the judgment of the attending physician or the like. In general, effective amounts for daily oral administration may be about 0.01 to 1,000 mg/kg, preferably about 0.5 to 500 mg/kg and effective amounts for parenteral administration may be about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg.

In actual practice, the compounds of the invention are provided by administering the compound or a precursor thereof in a solid or liquid form, either neat or in combination with one or more conventional pharmaceutical carriers or excipients. Accordingly, the present invention provides a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I as described hereinabove.

Solid carriers suitable for use in the composition of the invention include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aides, binders, tablet-disintegrating agents or encapsulating materials. In powders, the carrier may be a finely divided solid which is in admixture with a finely divided compound of formula I. In tablets, the formula I compound may be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. Said powders and tablets may contain up to 99% by weight of the formula I compound.

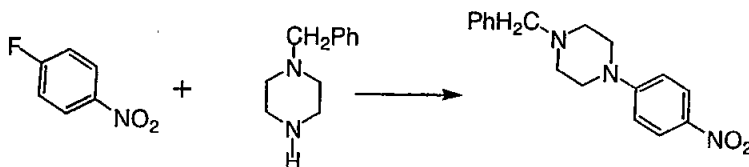
Solid carriers suitable for use in the composition of the invention include calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

- 5 Any pharmaceutically acceptable liquid carrier suitable for preparing solutions, suspensions, emulsions, syrups and elixirs may be employed in the composition of the invention. Compounds of formula I may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a pharmaceutically acceptable oil or fat, or a mixture thereof. Said liquid
- 10 composition may contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, coloring agents, viscosity regulators, stabilizers, osmo-regulators, or the like. Examples of liquid carriers suitable for oral and parenteral administration include water (particularly containing additives as
- 15 above, e.g., cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) or their derivatives, or oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier may also be an oily ester such as ethyl oleate or isopropyl myristate.
- 20 Compositions of the invention which are sterile solutions or suspensions are suitable for intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions may also be administered intravenously. Inventive compositions suitable for oral administration may be in either liquid or solid composition form.

- For a more clear understanding, and in order to illustrate the invention more
- 25 clearly, specific examples thereof are set forth hereinbelow. The following examples are merely illustrative and are not to be understood as limiting the scope and underlying principles of the invention in any way.

- Unless otherwise stated, all parts are parts by weight. The term NMR designates proton nuclear magnetic resonance. The terms THF, DMF and DMSO
- 30 designate tetrahydrofuran, dimethyl formamide and dimethylsulfoxide, respectively. In the chemical drawings, the term Ph represents a phenyl group.

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EXAMPLE 1**Preparation of 1-Benzyl-4-(4-nitrophenyl)piperazine**

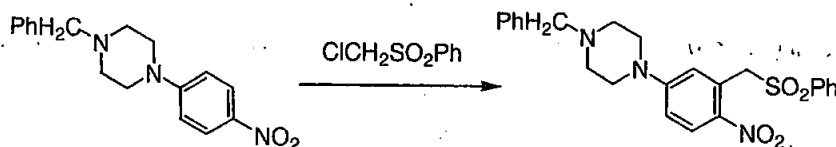
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A stirred solution of 1-benzylpiperazine (8.81 g, 50.0 mmol), 4-fluoronitrobenzene (5.31 mL, 50.0 mmol), and K_2CO_3 (6.90 g, 50.0 mmol) in ethanol is heated at reflux temperature under nitrogen for 18 h, cooled, diluted with water, and extracted with CH_2Cl_2 . The combined extracts are dried over $MgSO_4$ and concentrated *in vacuo* to give a solid residue. The solid is triturated with 20:80 ethyl acetate:hexanes and filtered. The filtercake is air-dried to afford the title compound as orange crystals, 8.45 g (57% yield), mp 218-219°C, characterized by NMR and mass spectral analyses.

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EXAMPLE 2**Preparation of 1-Benzyl-4-[4-nitro-3-[(phenylsulfonyl)methyl]phenyl]piperazine**

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A stirred solution of 1-benzyl-4-(4-nitrophenyl)piperazine (5.95 g, 20.0 mmol) and chloromethylphenylsulfone (3.82 g, 20.0 mmol) in dry THF under nitrogen at $-60^\circ C$ is treated with 1.0M KO-t-Bu in THF (44.0 mL, 44.0 mmol), warmed to $-20^\circ C$ over a 1 h period, quenched with acetic acid and treated sequentially with water, saturated aqueous $NaHCO_3$ and ether. The phases are separated and the aqueous phase is extracted with ether. The combined ethers are washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is

30

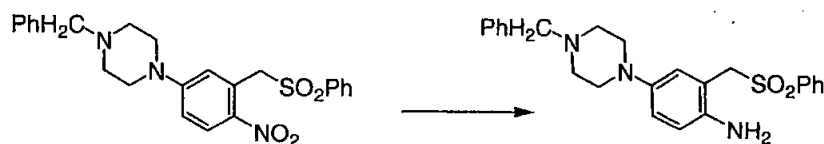
chromatographed (silica gel, 1:1 and 1:0 ethyl acetate:hexanes as eluent) to give the title compound as a yellow solid, 7.52 g (83% yield), mp 145-146°C, characterized by NMR and mass spectral analyses.

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EXAMPLE 3

Preparation of 4-(4-Benzylpiperazin-1-yl)-2-[(phenylsulfonyl)methyl]aniline

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A mixture of 1-benzyl-4-{4-nitro-3-[(phenylsulfonyl)methyl]phenyl}piperazine (6.77 g, 15.0 mmol) and granular tin (7.48 g, 63.0 mmol) in methanol and conc. hydrochloric acid is heated at 45°C for 4 h, stirred at ambient temperature for 18 h, carefully poured into saturated aqueous NaHCO₃, treated with ether and stirred for 0.5 h. The phases are separated and the aqueous phase is extracted sequentially with ether and CH₂Cl₂. The extracts and organic phase are combined, dried over MgSO₄ and concentrated *in vacuo*. The resultant residue is dissolved in CH₂Cl₂ and filtered through Celite®. The filtrate is concentrated *in vacuo* to afford the title compound as a pale yellow solid, 6.11 g (97% yield), mp 141-143°C, characterized by NMR and mass spectral analyses

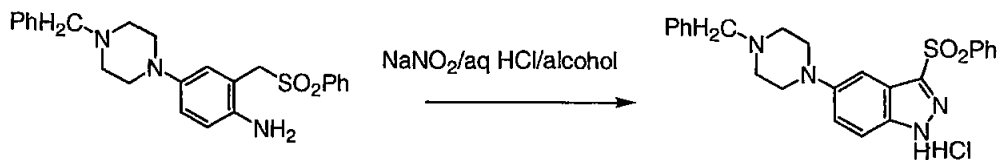
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EXAMPLE 4

Preparation of 5-(4-Benzylpiperazin-1-yl)-3-(phenylsulfonyl)-1H-indazole hydrochloride

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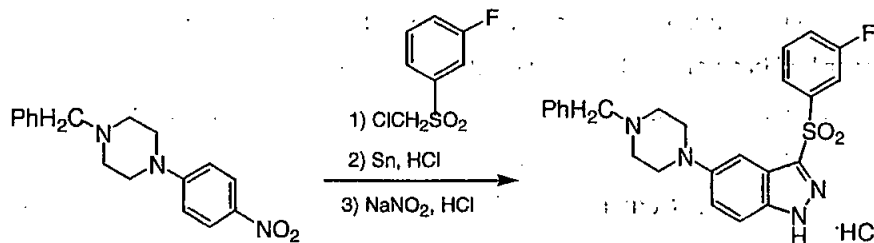


A stirred solution of 4-(4-benzylpiperazin-1-yl)-2-[(phenylsulfonyl)methyl]-
 5 aniline (0.371 g, 0.88 mmol) in 4.0 M aqueous hydrochloric acid is cooled in an ice
 bath, treated dropwise with NaNO_2 (91 mg, 1.32 mmol) in water, stirred for 40 min,
 treated with 2.5 M aqueous NaOH to pH ~ 14 and filtered. The filtercake is dissolved
 in CH_2Cl_2 , and chromatographed (silica gel, ethyl acetate as eluent) to afford the free
 indazole of the title product as a yellow solid (276 mg, 64%). The solid is dissolved in
 10 a mixture of ethanol and CH_2Cl_2 , treated with 4.0 M HCl in dioxane, and concentrated
in vacuo to give a solid residue. The residue is triturated with ethyl acetate to afford
 the title product as an off-white solid, 278 mg (57% yield), mp 177-180°C, identified
 by NMR and mass spectral analyses.

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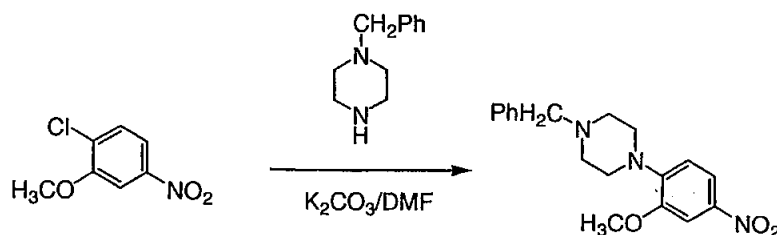
EXAMPLE 5**Preparation of 5-(4-Benzylpiperazin-1-yl)-3-[(3-fluorophenyl)sulfonyl]-1H-indazole hydrochloride**

20

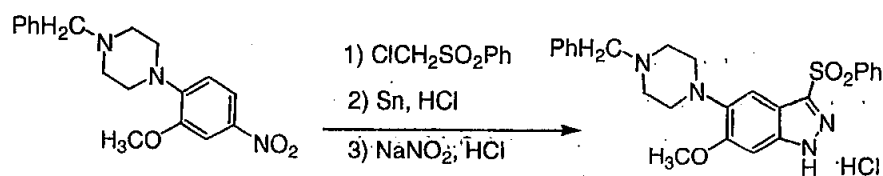


Using essentially the same procedures described hereinabove for Examples
 25 2 - 4 and employing chloromethyl-(3-fluorophenyl)sulfone, the title compound is
 obtained as an off-white solid, mp 157-160°C, identified by NMR and mass spectral
 analyses.

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EXAMPLE 6**5 Preparation of 1-Benzyl-4-(3-methoxy-4-nitrophenyl)piperazine**

A stirred solution of 1-benzylpiperazine (3.53 g, 20.0 mmol), 4-chloro-3-methoxy-nitrobenzene (3.75 g, 20.0 mmol), and K_2CO_3 (2.76 g, 20.0 mmol) in DMF is heated at 85° to 100°C under nitrogen for 23 h, cooled to room temperature, treated with 2M aqueous hydrochloric acid, diluted with water and extracted with ether. The combined extracts are washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is chromatographed (silica gel, 30:70 ethyl acetate:hexanes and 50:50 ethyl acetate:hexanes as eluent) to afford the title compound as a yellow-orange oil 2.64 g (57% yield), identified by NMR analysis.

EXAMPLE 7**20 Preparation of 5-(4-Benzylpiperazin-1-yl)-6-methoxy-3-(phenylsulfonyl)-1H-indazole hydrochloride**

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Using essentially the same procedures described hereinabove for Examples 2 - 4 and employing 1-benzyl-4-(2-methoxy-4-nitrophenyl)piperazine as starting

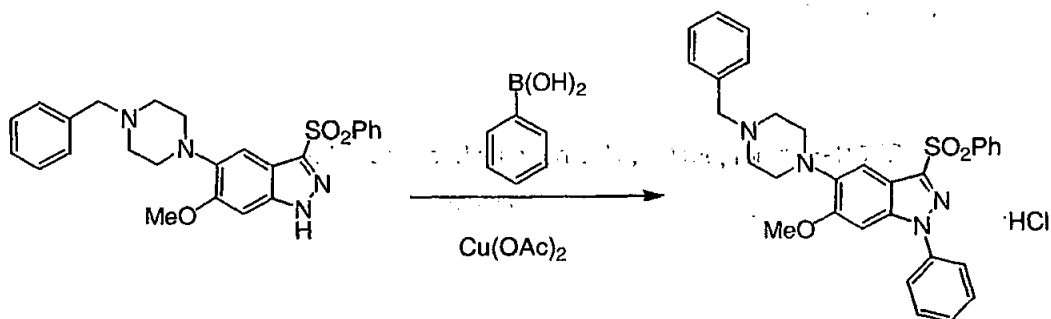
substrate, the title compound is obtained as a tan solid, 70 mg, mp 185-187°C, identified by NMR and mass spectral analyses.

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EXAMPLE 8

Preparation of 5-(4-Benzylpiperazin-1-yl)-6-methoxy-1-phenyl-3-(phenylsulfonyl)-1H-indazole hydrochloride

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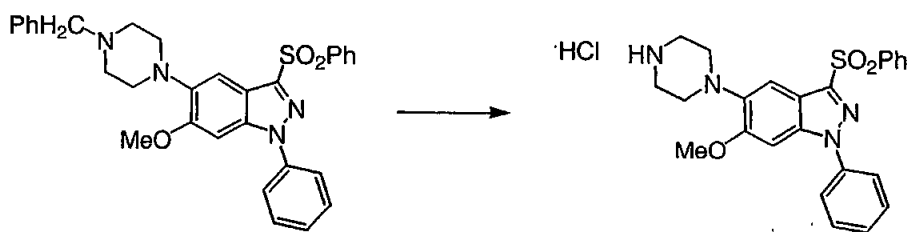


A mixture of 5-(4-benzylpiperazin-1-yl)-6-methoxy-3-(phenylsulfonyl)-1H-indazole (448 mg, 0.97 mmol), phenylboronic acid (242 mg, 1.94 mmol), copper(II) acetate (271 mg, 1.50 mmol), pyridine (160 mg, 2.00 mmol) and 4Å molecular sieves (1.0 g) in methylene chloride is stirred at room temperature for 48 h and filtered. The filtercake is washed with THF. The filtrates are combined and concentrated *in vacuo*. The resultant residue is chromatographed (silica gel, 60:40 and 80:20 ethyl acetate:hexanes as eluents) to afford the free amine of the title product as a white solid, 130 mg (25% yield). The free amine is dissolved in ethanol, treated with 4.0 M HCl in dioxane, and concentrated *in vacuo* to a solid residue. This solid is triturated with ethyl acetate to afford the title product as a white solid, mp: 210-212°C, identified by NMR and mass spectral analyses.

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EXAMPLE 9**Preparation of 6-Methoxy-1-phenyl 3-(phenylsulfonyl)-5-piperazin-1-yl-1H-indazole hydrochloride**

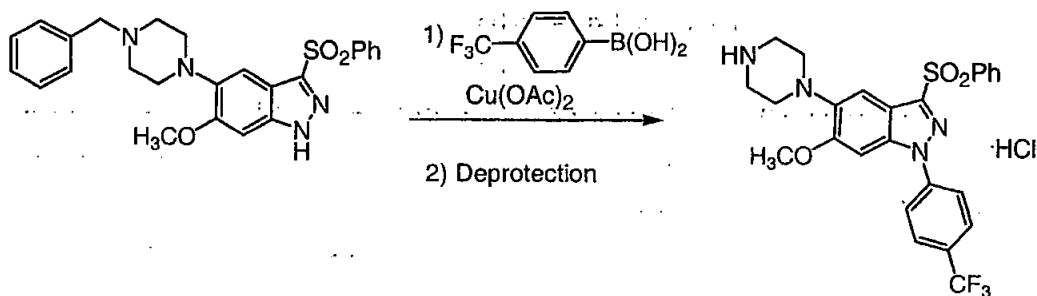
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- A mixture of 5-(4-benzylpiperazin-1-yl)-6-methoxy-1-phenyl-3-(phenylsulfonyl)-1H-indazole (190 mg, 0.353 mmol) and 1-chloroethylchloroformate (250 mg, 1.77 mmol) in 1,2-dichloroethane is heated at reflux temperature for 4 h, cooled to room temperature and concentrated to dryness. The resultant residue is dissolved in ethanol, heated at reflux temperature for 16 h and concentrated *in vacuo* to give the title compound as a white solid, 130 mg, (82% yield). This compound is purified by recrystallization from ethanol/ether to afford a white solid, mp 167-170°C, identified by NMR and mass spectral analyses.

EXAMPLE 10

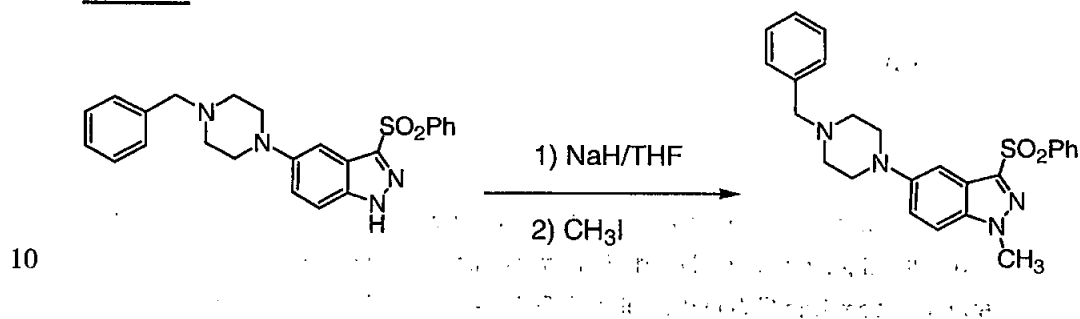
- 20 **Preparation of 6-Methoxy-3-(phenylsulfonyl)-5-(piperazin-1-yl)-1-[4-(trifluoromethyl)phenyl]-1H-indazole hydrochloride**



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Using essentially the same procedures described in Examples 8 and 9 hereinabove and employing 4-(trifluoromethyl)phenyl boronic acid, the title product is obtained as a white solid, mp 175-177°C, identified by NMR and mass spectral analyses.

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EXAMPLE 11**Preparation of 5-(4-Benzylpiperazin-1-yl)-1-methyl-3-(phenylsulfonyl)-1H-indazole**

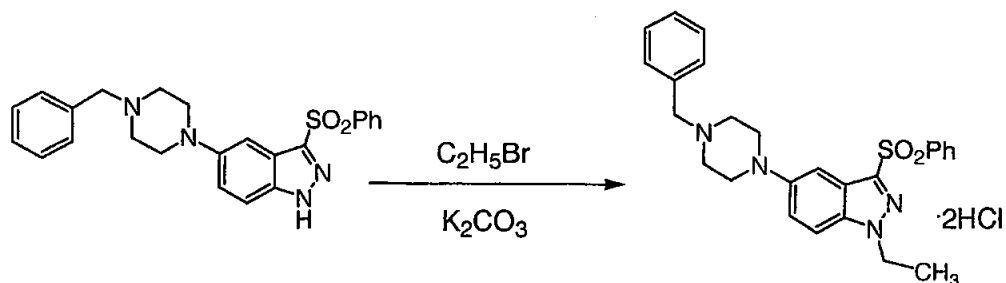
15 A solution of 5-(4-benzylpiperazin-1-yl)-3-(phenylsulfonyl)-1H-indazole (433 mg, 1.00 mmol) in THF at room temperature is treated with NaH (80 mg, 60% in mineral oil, 2.00 mmol), stirred for 0.5 h, treated with methyl iodide (142 mg, 1.00 mmol), stirred for 16 h, and diluted with water and EtOAc. The organic phase is separated, dried over MgSO₄, and concentrated *in vacuo*. The resultant residue is chromatographed (SiO₂, 90:10 EtOAc:hexanes as eluent) to afford the title compound as a white solid, 190 mg (43% yield), mp 195-197°C, identified by mass spectral and NMR analyses.

20

EXAMPLE 12

25 **Preparation of 5-(4-Benzylpiperazin-1-yl)-1-ethyl-3-(phenylsulfonyl)-1H-indazole dihydrochloride**

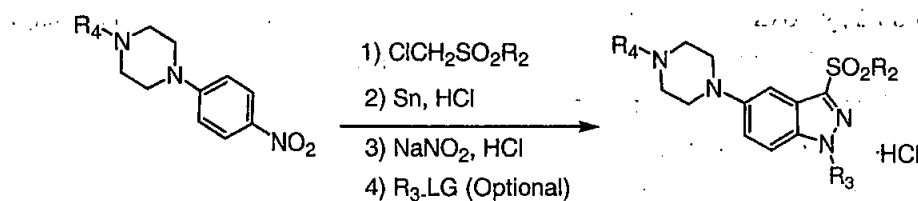
47



A mixture of 5-(4-benzylpiperazin-1-yl)-3-(phenylsulfonyl)-1H-indazole (400 mg, 0.92 mmol), bromoethane (108 mg, 1.00 mmol) and K₂CO₃ (276 mg, 2.00 mmol) in DMF is stirred for 16 h at room temperature and diluted water and EtOAc. The organic phase is separated, dried over MgSO₄, and concentrated *in vacuo*. The resultant residue is chromatographed (SiO₂, 80:20, then 90:10 EtOAc:hexanes as eluent) to afford the free amine of the title product as a white solid, 230 mg. A portion of this solid (115 mg, 0.25 mmol) is dissolved in ethanol, treated with 4M HCl in dioxane and concentrated *in vacuo* to give the title compound as a white solid, mp >250°C, identified by mass spectral and NMR analyses.

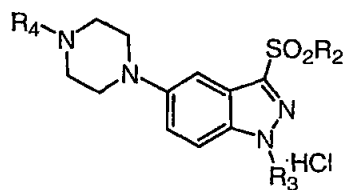
EXAMPLES 13 - 93

Preparation of 3-Arylsulfonyl-5-piperaziny lindazole Derivatives



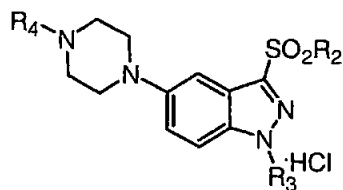
Using essentially the same procedures described in Examples 2 - 12 hereinabove and employing the appropriate 4-nitrophenylpiperazine as substrate and suitable chloromethylarylsulfone as reactant, the compounds shown on Table I are obtained and identified by HNMR and mass spectral analyses.

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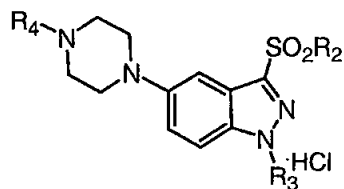
TABLE I

Ex No	R2	R3	R4	mp °C
13	phenyl	H	methyl	>250
14	1-naphthyl	H	methyl	>250
15	5-chlorothiophen-2-yl	H	methyl	>250**
16	phenyl	H	methyl	208-210
17	4-bromophenyl	H	methyl	>250**
18	2-fluorophenyl	H	methyl	160-161
19	3-fluorophenyl	H	methyl	>250
20	phenyl	phenyl	benzyl	148-151
21	phenyl	4-trifluoromethylphenyl	benzyl	169-171
22	phenyl	4-ethoxyphenyl	benzyl	140-144
23	phenyl	3-fluorophenyl	benzyl	146-149
24	phenyl	3-methoxyphenyl	benzyl	135-138
25	phenyl	4-fluorophenyl	benzyl	206-208
26	phenyl	3-chloro-4-fluorophenyl	benzyl	157-161
27	phenyl	4-methylthiophenyl	benzyl	156-160
28	phenyl	3-trifluoromethylphenyl	benzyl	146-150
29	phenyl	3,4-dimethoxyphenyl	benzyl	>200
30	phenyl	4-iodophenyl	benzyl	196-199
31	phenyl	2-phenethyl	H	127-130
32	phenyl	phenyl	H	>200

TABLE I, cont.

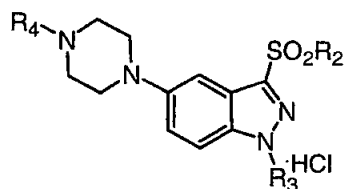


Ex No	R2	R3	R4	mp °C
33	phenyl	4-trifluoromethylphenyl	H	170-172
34	phenyl	4-ethoxyphenyl	H	>200
35	phenyl	3-fluorophenyl	H	139-142
36	phenyl	3-methoxyphenyl	H	132-135
37	phenyl	4-fluorophenyl	H	159-161
38	phenyl	3-chloro-4-fluorophenyl	H	>200
39	phenyl	4-methylthiophenyl	H	160-164
40	phenyl	3-trifluoromethylphenyl	H	139-142
41	phenyl	3,4-dimethoxyphenyl	H	156-158
42	phenyl	4-iodophenyl	H	>200
43	phenyl	ethyl	H	>200
44	phenyl	methyl	H	>200
45	1-naphthyl	1-propyl	methyl	**
46	1-naphthyl	ethyl	methyl	**
47	1-naphthyl	methyl	methyl	**
48	1-naphthyl	1-butyl	methyl	**
49	1-naphthyl	3-chlorobenzyl	methyl	**
50	1-naphthyl	2-propyl	methyl	**
51	1-naphthyl	1-(2-methylpropyl)	methyl	**
52	1-naphthyl	benzyl	methyl	**
53	1-naphthyl	H	H	**

TABLE I, cont.

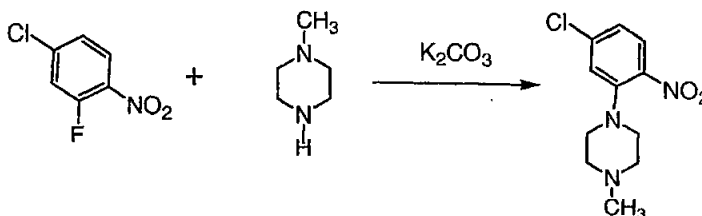
Ex No	R2	R3	R4	mp °C
54	2-thienyl	H	methyl	**
55	3-methylphenyl	H	methyl	**
56	4-methylphenyl	H	methyl	**
57	benzyl	H	methyl	**
58	2-fluorophenyl	H	methyl	**
59	3-fluorophenyl	H	methyl	**
60	4-fluorophenyl	H	methyl	**
61	3-cyanophenyl	H	methyl	**
62	4-cyanophenyl	H	methyl	**
63	3-methoxyphenyl	H	methyl	**
64	4-methoxyphenyl	H	methyl	**
65	2-chlorophenyl	H	methyl	**
66	3-chlorophenyl	H	methyl	**
67	4-chlorophenyl	H	methyl	**
68	2,4-difluorophenyl	H	methyl	**
69	3,4-difluorophenyl	H	methyl	**
70	5-chlorothien-2-yl	H	methyl	**
71	4-isopropylphenyl	H	methyl	**
72	2-naphthyl	H	methyl	**
73	3-chloro-4-fluorophenyl	H	methyl	**
74	4-n-butylphenyl	H	methyl	**
75	4-t-butylphenyl	H	methyl	**

TABLE I, cont.



Ex No	R2	R3	R4	mp °C
76	4-aminophenyl	H	methyl	**
77	5-chloro-2-methoxyphenyl	H	methyl	**
78	2,5-dichlorophenyl	H	methyl	**
79	3,5-dichlorophenyl	H	methyl	**
80	4-methylsulfonylphenyl	H	methyl	**
81	4-bromophenyl	H	methyl	**
82	3,5-bis(trifluoromethyl)phenyl	H	methyl	**
83	2-methylphenyl	H	methyl	**
84	2-cyanophenyl	H	methyl	**
85	4-n-propylphenyl	H	methyl	**
86	3-(difluoromethoxy)phenyl	H	methyl	**
87	4-acetylphenyl	H	methyl	**
88	2,3,4-trifluorophenyl	H	methyl	**
90	2,4,5-trichlorophenyl	H	methyl	**
91	2,6-dichlorophenyl	H	methyl	**
92	2,5-dichlorothien-3-yl	H	methyl	**
93	2-propyl	H	methyl	**

5 ** Free Amine

EXAMPLE 94**Preparation of 1-(5-Chloro-2-nitrophenyl)-4-methylpiperazine**

5

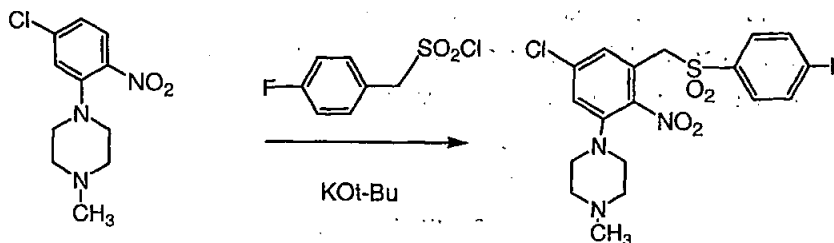
A mixture of 4-chloro-2-fluoro-nitrobenzene (28.5 mmol), 1-methylpiperazine (28.5 mmol) and K_2CO_3 (37.0 mmol) in DMF is stirred at 100° C for 16 h and diluted with water and EtOAc. The phases are separated and the aqueous phase is extracted with EtOAc. The organic phase and the extracts are combined, washed sequentially with water and brine, dried over Na_2SO_4 and dried *in vacuo*. The resultant residue is chromatographed (SiO_2 , 10% methanol in EtOAc as eluent) to afford the title product.

10

15

EXAMPLE 95**Preparation of 1-{5-Chloro-2-nitro-3-[(4-fluorophenyl)sulfonyl]methyl}phenyl}-4-methylpiperazine**

20



25

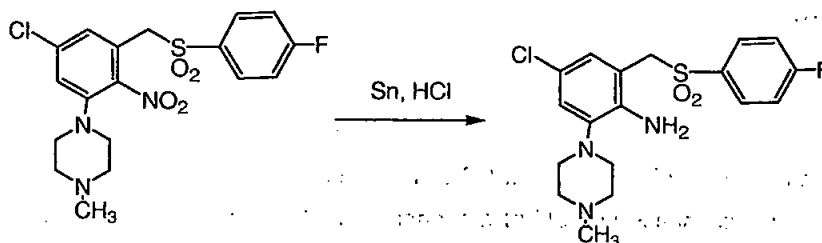
A stirred mixture of 1-(5-chloro-2-nitrophenyl)-4-methylpiperazine (1.0 mmol) and 4-fluorobenzylsulfonyl chloride (1.0 mmol) in THF is treated with 2.2 mL of a 1M $KOt-Bu$ (2.2 mmol) solution in THF at -78° C, warmed to room temperature over a 2 h period, quenched with acetic acid and concentrated *in vacuo*. The resultant residue is partitioned between EtOAc and aqueous Na_2CO_3 . The phases are separated and

the aqueous phase is extracted with EtOAc. The organic phase is combined with the extracts, dried over Na₂SO₄ and concentrated to dryness *in vacuo* to afford the title product.

5

EXAMPLE 96**Preparation of 4-Chloro-2-[(4-fluorophenyl)sulfonylmethyl]-6-(4-methylpiperazin-1-yl)aniline**

10

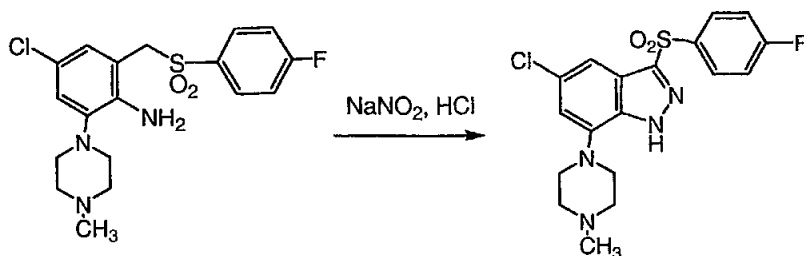


A solution of 4-chloro-2-[(4-fluorophenyl)sulfonylmethyl]-6-(4-methylpiperazin-1-yl)aniline (1.0 mmol) in methanol is treated with Sn foil (593.3 mg), followed by 5.8 mL of 12 M HCl, heated at 60° C for 4 h (until reaction is complete by thin layer chromatography), cooled to 0° C, treated with solid NaOH to pH >10 and extracted with CH₂Cl₂. The extracts are combined, washed with water and concentrated to dryness *in vacuo* to give the title compound.

20

EXAMPLE 97**Preparation of 5-Chloro-3[(4-fluorophenyl)sulfonyl]-7-(4-methylpiperazin-1-yl)-1H-indazole**

25



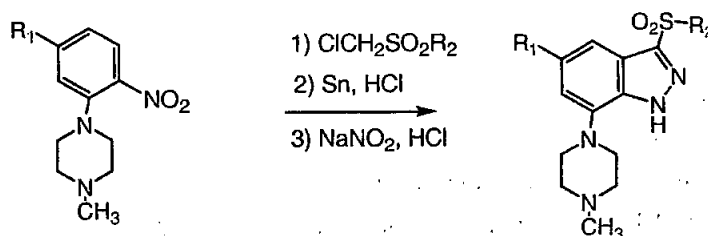
- 5 A solution of NaNO_2 (2.0 mg) in water at 0° is treated dropwise with a solution of 4-chloro-2-[[[(4-fluorophenyl)sulfonyl]methyl]-6-(4-methylpiperazin-1-yl)aniline (102.2 mg, 0.25 mmol) in 1M HCl , allowed to warm to room temperature over a 2 h period, treated with saturated Na_2CO_3 to pH >10 and filtered. The filtercake is washed with water and dried in vacuo to give the title compound, identified by mass spectral and NMR analyses.

10

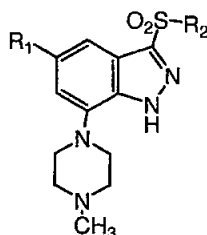
EXAMPLE 98-101

Preparation of 3 (Arylsulfonyl)-7-(4-methylpiperazin-1-yl)-1H-indazole Derivatives

15



- 20 Using essentially the same procedures described hereinabove in Examples 95-97 and employing the appropriate arylsulfonyl chloride, the compounds shown in Table II are obtained and identified by mass spectral and NMR analyses.

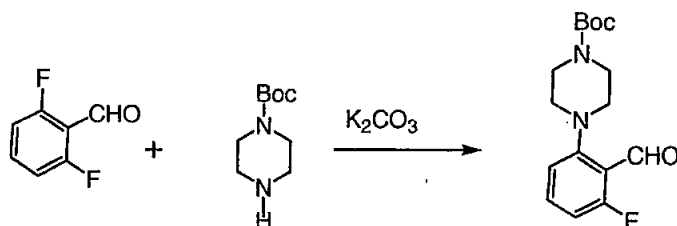
TABLE II

Ex. No.	R1	R2	% Yield (Over 3 Steps)
98	Cl	4-(isopropyl)phenyl	74
99	Cl	3-(trifluoromethyl)phenyl	65
100	Cl	1-naphthyl	7.7
101	H	1-naphthyl	--

5

EXAMPLE 102Preparation of 1-Fluoro-3-[4-(*t*-butoxycarbonyl)piperazin-1-yl]benzaldehyde

10



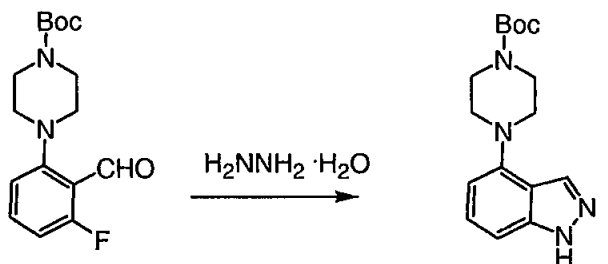
15 A stirred solution of 2,6-difluorobenzaldehyde **5** (10.0 g, 70 mmol) in *N,N*-dimethylformamide is treated with *tert*-butyl piperazine-1-carboxylate (Boc) **6** (14.4 g, 77.0 mmol) and potassium carbonate (11.7 g, 85.0 mmol), stirred at 80 °C for 16 h, cooled to ambient temperature, diluted with water and extracted with methylene chloride. The extracts are combined, washed sequentially with water and brine, dried over sodium sulfate, and concentrated *in vacuo* to afford a crude oil. This oil is purified by column chromatography (silica gel, 15:85 ethyl acetate/hexanes) to afford

the title compound as a yellow solid, 15.5g (71% yield), identified by NMR and mass spectral analyses.

EXAMPLE 103

5

Preparation of 4-[4-(t-Butoxycarbonyl)piperazin-1-yl]-1H-indazole

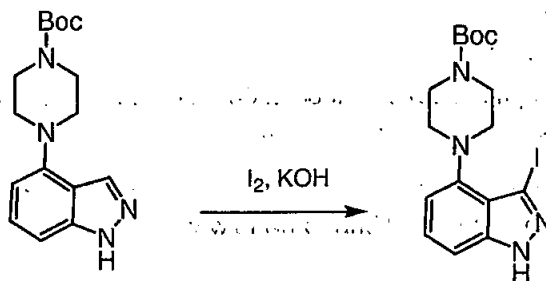


A solution of 7 (20.0 g, 64.9 mmol) and hydrazine monohydrate (30 mL) in methyl sulfoxide is stirred at 95 °C for 96 h, cooled to room temperature, partitioned between saturated sodium bicarbonate and ether. The phases are separated and the aqueous phase is extracted with ether. The extracts are combined with the organic phase, washed sequentially with water and brine, dried over sodium sulfate and concentrated *in vacuo* to a crude residue. This residue is purified by column chromatography (silica gel, 10:90 to 30:70 ethyl acetate/hexanes) to afford the title compound as a light yellow solid, 12.3 g (57% yield), identified by NMR and mass spectral analyses.

EXAMPLE 104

20

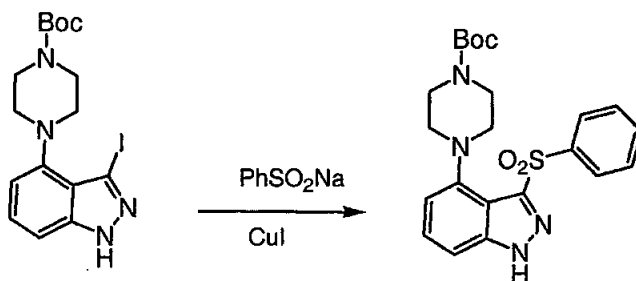
Preparation of 4-[4-(t-Butoxycarbonyl)piperazin-1-yl]-3-iodo-1H-indazole



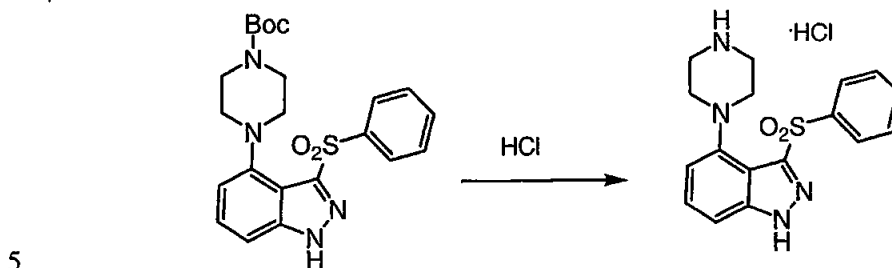
A solution of 4-[4-(t-butoxycarbonyl)piperazin-1-yl]-1H-indazole (5.00 g, 16.5 mmol) in *N,N*-dimethylformamide is treated with powdered potassium hydroxide

(1.85 g, 33.07 mmol) and iodine (4.61 g, 18.2 mmol), stirred at room temperature for 16 h, diluted with ethyl acetate and quenched with 15% aqueous sodium metabisulfite. The phases are separated and the aqueous phase is extracted with ethyl acetate. The extracts and the organic phase are combined, washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford a crude solid. This solid is purified by column chromatography (silica gel, 10:90 to 15:85 to 20:80 ethyl acetate/hexanes) to afford the title product as a yellow solid, 2.40 g (35% yield) identified by HNMR and mass spectral analyses.

10

EXAMPLE 105Preparation of 4-[4-(t-Butoxycarbonyl)piperazin-1-yl]-3-(phenylsulfonyl)-1H-indazole

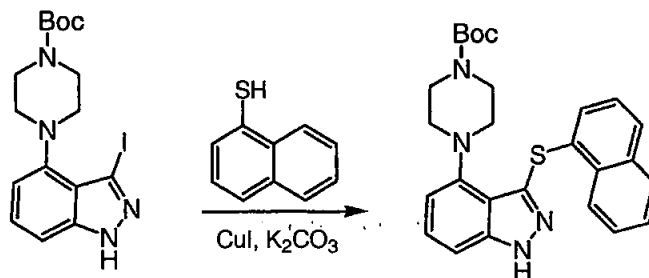
15 A mixture of 4-[4-(t-butoxycarbonyl)piperazin-1-yl]-3-iodo-1H-indazole (0.110 g, 0.257 mmol), sodium benzene sulfinate (0.068 g, 0.411 mmol), copper(I) iodide (0.073 g, 0.386 mmol) and *N,N*-dimethylformamide is added to a screw-capped test-tube with Teflon-lined septum. The tube is evacuated and backfilled with argon. This procedure is repeated twice, then the tube is heated to 125 °C for 4 h. The reaction mixture is cooled, partitioned between ethyl acetate and water and filtered through a pad of diatomaceous earth. The filtrate is separated. The organic phase is washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The resulting crude material is purified by column chromatography (silica gel, 40:60 ethyl acetate/hexanes) to afford the title compound as a pale yellow foam, 0.022 g (18% yield), identified by NMR and mass spectral analyses.

EXAMPLE 106Preparation of 3-(Phenylsulfonyl)-4-piperazin-1-yl-1H-indazole Hydrochloride

10 A solution of 4-[4-(t-butoxycarbonyl)piperazin-1-yl]-3-(phenylsulfonyl)-1H-indazole (0.022 g, 0.050 mmol) in methanol is treated with a 2 M solution of HCl in ether (0.4 mL), heated at reflux temperature for 1 h, cooled to room temperature and evaporated to dryness. The residue is re-dissolved in methanol and concentrated. Repeating this procedure three more times affords the title product as a white solid, 0.009 g (40% yield), identified by NMR and mass spectral analyses.

EXAMPLE 107

15 Preparation of 4-[4-t-Butoxycarbonyl)piperazin-1-yl]-3-(1-naphthylthio)-1H-indazole

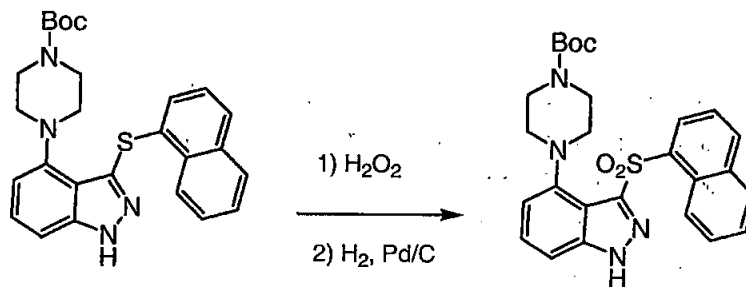


20 A mixture of 4-[4-(t-butoxycarbonyl)piperazin-1-yl]-3-iodo-1H-indazole (0.068 g, 0.159 mmol) copper(I) iodide (0.005 g, 0.024 mmol) and potassium carbonate (0.044 g, 0.318 mmol) are added to a screw-capped test tube with a Teflon-lined septum. The tube is evacuated and backfilled with argon and this procedure repeated twice more. The reaction mixture is treated sequentially with 2-propanol

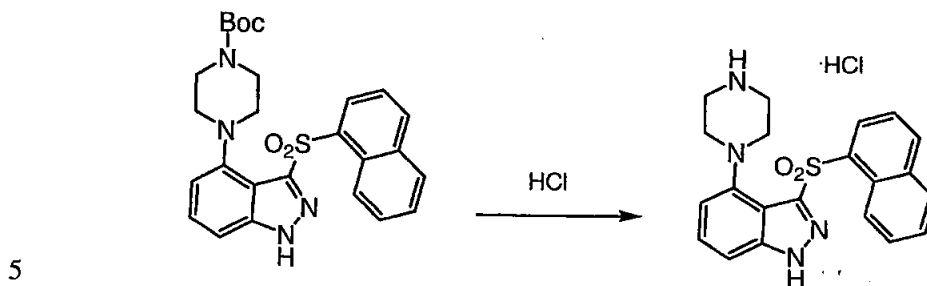
(1.5 mL), ethylene glycol (19 μ L, 0.318 mmol) and 1-naphthalenethiol (0.051 g, 0.318 mmol), heated at 130°–140° C for 8 h, cooled to room temperature, diluted with ethyl acetate and filtered through diatomaceous earth. The filtrate is concentrated under reduced pressure. The resultant crude material is purified by flash chromatography (silica gel, 40:60 ethyl acetate/hexanes) to afford the title compound as a colorless oil, 0.033 g (45% yield), identified by NMR and mass spectral analyses.

EXAMPLE 108

Preparation of 4-[4-(t-Butoxycarbonyl)piperazin-1-yl]-3-(1-naphthylsulfonyl)-1H-indazole



A stirred solution of 4-[4-t-butoxycarbonyl)piperazin-1-yl]-3-(1-naphthylthio)-1H-indazole (0.030 g, 0.065 mmol) in glacial acetic acid is treated with 35% aqueous hydrogen peroxide (0.127 g, 1.30 mmol) stirred for 24 h, quenched with 10% aqueous sodium metabisulfite solution (1 mL) and concentrated *in vacuo*. The resulting solid is directly added to a suspension of 10% palladium-on-carbon (3 mg) in methanol (10 mL) and the mixture is shaken on a Parr hydrogenator under a 40 psi hydrogen atmosphere for 2 h and filtered through diatomaceous earth. The filtrate is concentrated *in vacuo*. Purification of the resulting crude material by flash chromatography (silica gel, 30:70 ethyl acetate/hexanes) affords the title compound as a colorless oil, 0.011 g (35% yield), identified by NMR and mass spectral analyses.

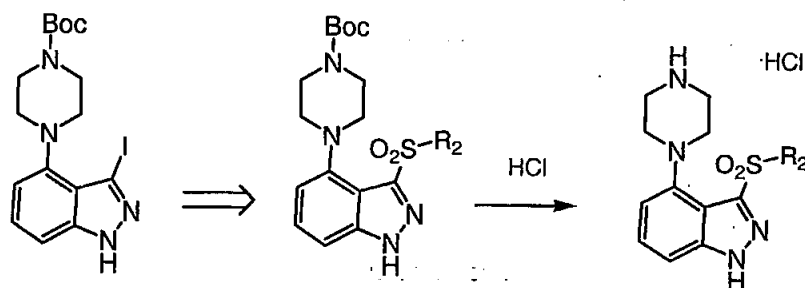
EXAMPLE 109Preparation of 3-(1-Naphthylsulfonyl)-4-piperazin-1-yl-1H-indazole Hydrochloride

Using essentially the same procedure described in Example 106 hereinabove and employing 4-[4-(t-butoxycarbonyl)piperazin-1-yl]-3-(1-naphthylsulfonyl)-1H-indazole as substrate, the title product is obtained as a light yellow solid (74% yield), mp 220°C dec, identified by NMR and mass spectral analyses.

10

EXAMPLES 110-114Preparation of 3-(Arylsulfonyl)-4-piperazin-1-yl-1H-indazole HydrochlorideDerivatives

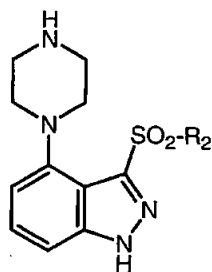
15



Using essentially the same procedures described in Examples 102-109 hereinabove and employing the appropriate arylthiol or arylsulfinate, the compounds shown on Table III are obtained and identified by NMR and mass spectral analyses.

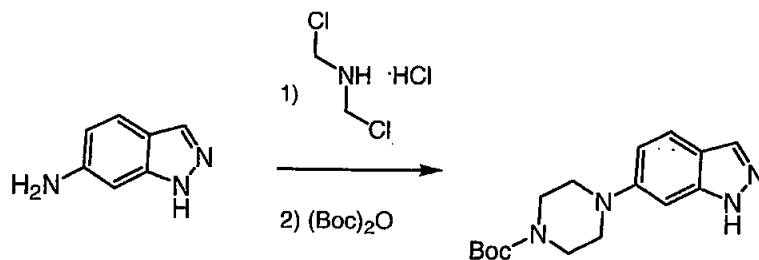
20

TABLE III



Ex. No.	R2	mp °C
110	4-methylphenyl	190-192
111	4-chlorophenyl	230 dec
112	3-fluorophenyl	180-183
113	4-methoxyphenyl	178-182
114	2-naphthyl	200-202

5

EXAMPLE 115Preparation of 6-[4-t-Butoxycarbonyl]piperazin-1-yl]-1H-indazole

10

A stirred solution of 6-aminoindazole (13.3 g, 100 mmol) in *n*-butanol is treated with bis(2-chloroethyl)amine hydrochloride (28.6 g, 160 mmol) and potassium carbonate (34.6 g, 250 mmol), heated to reflux temperature for 72 h, cooled to room temperature and concentrated *in vacuo*. A stirred solution of the resultant crude material in 1,4-dioxane at 0° C is treated with 1 N sodium hydroxide solution (200 mL) and di-*tert*-butyldicarbonate (34.9 g, 160 mmol), stirred at ambient temperature for 24 h and concentrated *in vacuo* to afford a crude oil. This oil is partitioned between

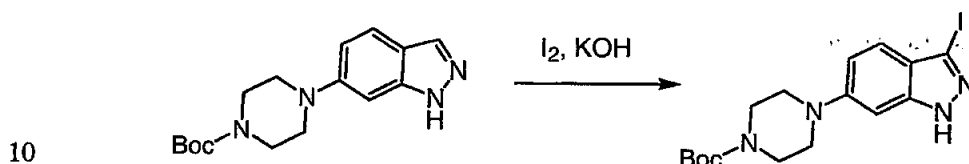
15

82

ethyl acetate and water. The organic layer is separated, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Further purification of this resultant residue by flash chromatography (silica gel, 40:60 ethyl acetate/hexanes) affords the title compound as a colorless oil, 11.5 g (38% yield) identified by NMR and mass spectral analyses.

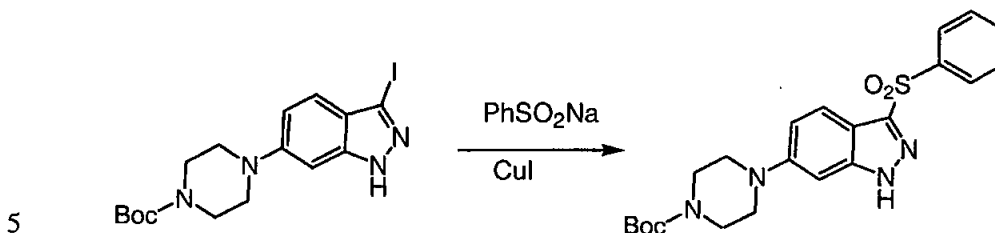
EXAMPLE 116

Preparation of 6-[4-t-Butoxycarbonyl]piperazin-1-yl]-3-iodo-1H-indazole



A stirred solution of 6-[4-(tert-butoxycarbonyl)piperazin-1-yl]-1H-indazole (7.20 g, 23.8 mmol) in *N,N*-dimethylformamide at 0 °C is treated with powdered potassium hydroxide (5.40 g, 95.4 mmol) followed by the dropwise addition of a solution of iodine (10.9 g, 42.9 mmol) in *N,N*-dimethylformamide, stirred at ambient temperatures for 16 h, diluted with ethyl acetate and quenched with 10% aqueous sodium metabisulfite solution. The phases are separated. The aqueous phase is extracted with ethyl acetate. The extracts are combined with the organic phase, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The resulting crude material is purified by flash chromatography (silica gel, 30:70 ethyl acetate/hexanes) to afford the title compound as a yellow solid, 11.5 g (38% yield) identified by NMR and mass spectral analyses.

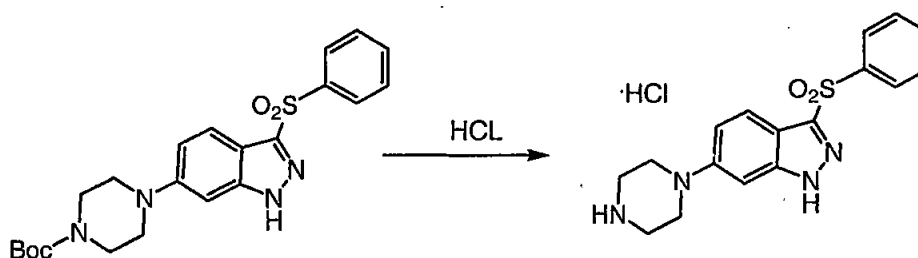
25

EXAMPLE 117Preparation of 6-[4-t-butoxycarbonyl]piperazin-1-yl]-3-(phenylsulfonyl)-1H-indazole

Using essentially the same procedure described in Example 105 hereinabove and employing of 6-[4-t-butoxycarbonyl]piperazin-1-yl]-3-iodo-1H-indazole and sodium benzenesulfinate affords the title compound as a colorless foam (80% yield), identified by NMR and mass spectral analyses.

EXAMPLE 118

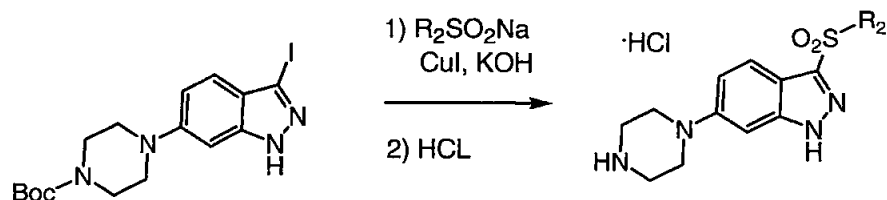
15 Preparation of 3-(Phenylsulfonyl)- 6-piperazin-1-yl]-1H-indazole Hydrochloride



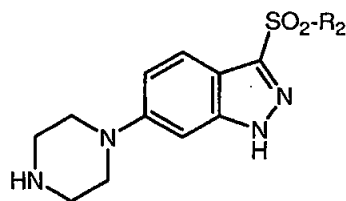
20 Using essentially the same procedure described in Example 106 hereinabove and employing 6-[4-t-butoxycarbonyl]piperazin-1-yl]-3-(phenylsulfonyl)-1H-indazole as substrate, the title compound is obtained as an off-white solid (81% yield), identified by NMR and mass spectral analyses.

EXAMPLES 119-124**Preparation of 3-(Arylsulfonyl)-6-piperazin-1-yl-1H-indazole Hydrochloride Compounds**

5



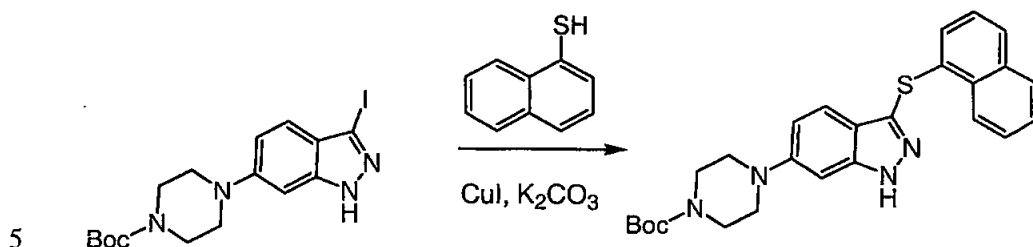
Using essentially the same procedures described in Examples 117 and 118
 10 hereinabove and employing the appropriate arylsulfinate, the compounds shown in Table IV are obtained and identified by NMR and mass spectral analyses.

TABLE IV

15

Ex. No.	R ₂	mp °C
119	4-methylphenyl	172-175
120	4-(trifluoromethyl)phenyl	189-191
121	4-chlorophenyl	175-178
122	3-fluorophenyl	260 dec
123	4-methoxyphenyl	165-170
124	2-naphthyl	260 dec

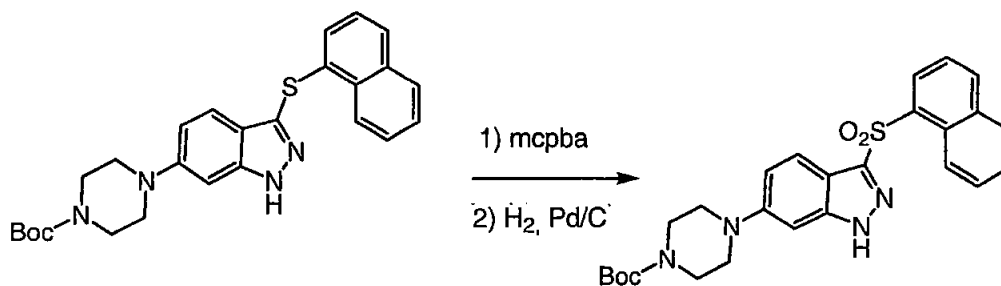
65

EXAMPLE 125Preparation of 6-[4-t-Butoxycarbonyl]piperazin-1-yl)-3-(1-naphthylthio)-1H-indazole

Using essentially the same procedure described in Example 107 hereinabove and employing 6-[4-t-butoxycarbonyl]piperazin-1-yl)-3-iodo-1H-indazole as substrate,
 10 the title compound is obtained as a colorless oil (78% yield), identified by NMR and mass spectral analyses.

EXAMPLE 126

15 Preparation of 6-[4-t-Butoxycarbonyl]piperazin-1-yl)-3-(1-naphthylsulfonyl)-1H-indazole



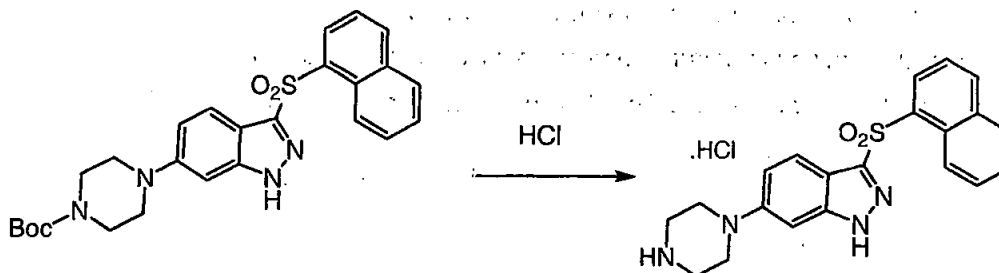
20

A stirred solution of 6-[4-t-butoxycarbonyl]piperazin-1-yl)-3-(1-naphthylthio)-1H-indazole (0.240 g, 0.521 mmol) in methylene chloride is treated with meta-chloroperoxybenzoic acid (mcpba) (77% pure, 0.350 g, 1.56 mmol) and sodium

bicarbonate (0.219 g, 2.61 mmol), stirred at ambient temperatures for 16 h and partitioned between ethyl acetate and water. The phases are separated and the aqueous phase is extracted with methylene chloride. The extracts and the organic phase are combined, washed sequentially with 10% aqueous sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated *in vacuo* to afford a crude oil. This oil is added to a suspension of 10% palladium-on-carbon (40 mg) in methanol and shaken on a Parr hydrogenator under a 40 psi hydrogen atmosphere for 2 h and filtered through diatomaceous earth. The filtrate is concentrated *in vacuo*. The resulting crude material is purified by flash chromatography (silica gel, 50:50 ethyl acetate/hexanes) to afford the title compound as a colorless oil, 0.106 g (41% yield), identified by NMR and mass spectral analyses.

EXAMPLE 127

15 Preparation of 3-(1-Naphthylsulfonyl)-6-piperazin-1-yl-1H-indazole Hydrochloride



20 Using essentially the same procedure described in Example 106 hereinabove and employing of 6-[4-t-butoxycarbonyl]piperazin-1-yl)-3-(1-naphthylsulfonyl)-1H-indazole as substrate, the title product is obtained as a white solid (98% yield), mp 205-210 °C, identified by NMR and mass spectral analyses.

25

67

EXAMPLE 128Comparative Evaluation of 5-HT6 Binding Affinity of Test Compounds

5 The affinity of test compounds for the serotonin 5-HT6 receptor is evaluated in the following manner. Cultured Hela cells expressing human cloned 5-HT6 receptors are harvested and centrifuged at low speed (1,000 x g) for 10.0 min to remove the culture media. The harvested cells are suspended in half volume of fresh physiological phosphate buffered saline solution and recentrifuged at the same
10 speed. This operation is repeated. The collected cells are then homogenized in ten volumes of 50 mM Tris.HCl (pH 7.4) and 0.5 mM EDTA. The homogenate is centrifuged at 40,000 x g for 30.0 min and the precipitate is collected. The obtained pellet is resuspended in 10 volumes of Tris.HCl buffer and recentrifuged at the same speed. The final pellet is suspended in a small volume of Tris.HCl buffer and the
15 tissue protein content is determined in aliquots of 10-25 μ l volumes. Bovine Serum Albumin is used as the standard in the protein determination according to the method described in Lowry et al., J. Biol. Chem., 193:265 (1951). The volume of the suspended cell membranes is adjusted to give a tissue protein concentration of 1.0 mg/ml of suspension. The prepared membrane suspension (10 times concentrated)
20 is aliquoted in 1.0 ml volumes and stored at -70° C until used in subsequent binding experiments.

 Binding experiments are performed in a 96 well microtiter plate format, in a total volume of 200 μ l. To each well is added the following mixture: 80.0 μ l of incubation buffer made in 50 mM Tris.HCl buffer (pH 7.4) containing 10.0 mM MgCl₂
25 and 0.5 mM EDTA and 20 μ l of [³H]-LSD (S.A., 86.0 Ci/mmol, available from Amersham Life Science), 3.0 nM. The dissociation constant, K_D of the [³H]LSD at the human serotonin 5-HT6 receptor is 2.9 nM, as determined by saturation binding with increasing concentrations of [³H]LSD. The reaction is initiated by the final addition of 100.0 μ l of tissue suspension. Nonspecific binding is measured in the presence of
30 10.0 μ M methiothepin. The test compounds are added in 20.0 μ l volume.

 The reaction is allowed to proceed in the dark for 120 min at room temperature, at which time, the bound ligand-receptor complex is filtered off on a 96 well unifilter with a Packard Filtermate® 196 Harvester. The bound complex caught

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on the filter disk is allowed to air dry and the radioactivity is measured in a Packard TopCount® equipped with six photomultiplier detectors, after the addition of 40.0µl Microscint®-20 scintillant to each shallow well. The unifilter plate is heat-sealed and counted in a PackardTopCount® with a tritium efficiency of 31.0%.

- 5 Specific binding to the 5-HT6 receptor is defined as the total radioactivity bound less the amount bound in the presence of 10.0µM unlabeled methiothepin. Binding in the presence of varying concentrations of test compound is expressed as a percentage of specific binding in the absence of test compound. The results are plotted as log % bound versus log concentration of test compound. Nonlinear
- 10 regression analysis of data points with a computer assisted program Prism® yields both the IC₅₀ and the K_i values of test compounds with 95% confidence limits.

The amount of displacement by the test compound is given in percent (%) inhibition and is derived from the following equation:

15

$$\% \text{ inhibition} = \left(1 - \frac{B_0 - \text{NSB}}{\text{TB} - \text{NSB}} \right) 100$$

- where B₀ is the amount of CPM bound in the presence of the testing agent. NSB
- 20 represents the CPM bound in the presence of a saturating concentration of a displacer and TB represents the total amount of CPM bound at zero (0) concentration of test compound.

- Alternatively, a linear regression line of data points is plotted, from which the IC₅₀ value is determined and the K_i value is determined based upon the following
- 25 equation:

$$K_i = \text{IC}_{50} / (1 + L/K_D)$$

where L is the concentration of the radioactive ligand used and K_D is the dissociation constant of the ligand for the receptor, both expressed in nM.

- Using this assay, the % inhibition and K_i values are determined and
- 30 compared to those values obtained by representative compounds known to demonstrate binding to the 5-HT6 receptor. The data are shown in TableV, below.

70

TABLE V, cont.

EX. No.	5-HT ₆ Binding K _i (nM)	% Inhibition at 1 μ M
35	38	--
36	20	--
37	4	--
38	73	--
39	69	--
40	62	--
41	13	--
42	117	--
43	3	--
44	--	67
45	2	--
46	2	--
47	2	--
48	4	--
49	6	--
50	2	--
51	1	--
52	2	--
53	1	--
54	8	--
55	1	--
56	5	--
58	3	--
59	2	--
60	5	--
63	1	--
64	12	--
65	4	--
66	1	--

71

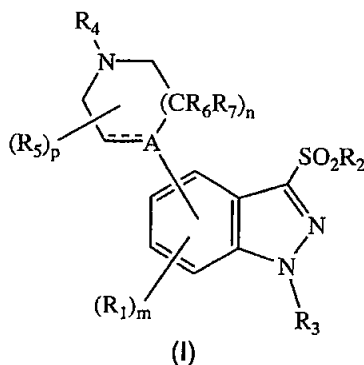
TABLE V, cont.

EX. No.	5-HT6 Binding Ki (nM)	% Inhibition at 1μM
67	8	--
68	14	--
69	28	--
70	3	--
71	4	--
72	2	--
74	26	--
77	2	--
80	62	--
81	7	--
83	4	--
85	10	--
86	1	--
89	10	--
91	6	--
92	1	--
97	12	--
98	22	--
99	20	--
100	5	--
101	5	--

Comparative Examples	5-HT6 binding Ki (nM)
Clozapine	6.0
Loxapine	41.4
Bromocriptine	23.0
Methiothepin	8.3
Mianserin	44.2
Olanzapine	19.5

CLAIMS:

1. A compound of formula I



wherein

A is C, CR₈ or N;

R₁ is H, halogen, CN, COR₉, OCO₂R₁₀, CO₂R₁₁, CONR₁₂R₁₃, SO_xR₁₄, NR₁₅R₁₆, OR₁₇ or a C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl or heteroaryl group each optionally substituted;

R₂ is an optionally substituted C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl, or heteroaryl group or an optionally substituted 8- to 13-membered bicyclic or tricyclic ring system having a N atom at the bridgehead and optionally containing 1, 2 or 3 additional heteroatoms selected from N, O or S;

R₃ is H or a C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl or heteroaryl group each optionally substituted;

R₄ is H or a C₁-C₆alkyl or C₃-C₇cycloalkyl group each optionally substituted;

R₅, R₆ and R₇ are each independently H or a C₁-C₆alkyl or C₃-C₇cycloalkyl group each optionally substituted;

m and p are each independently an integer of 1, 2 or 3;

n is an integer of 1 or 2;

R₈ is H, OH or an optionally substituted C₁-C₆alkoxy group;

R₉, R₁₀, R₁₁ and R₁₇ are each independently H or a C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

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- R₁₂, R₁₃, R₁₅ and R₁₆ are each independently H or an optionally substituted C₁-C₄alkyl group or R₁₂ and R₁₃ or R₁₅ and R₁₆ may be taken together with the atom to which they are attached to form a 5- to 7-membered ring optionally containing another heteroatom selected from O, NR₁₈ or SO_x;
- 5 R₁₄ is a C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;
- R₁₈ is H or a C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₇cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;
- 10 x is 0 or an integer of 1 or 2; and
- represents a single bond or a double bond; or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.
2. A compound according to claim 1 wherein n is 1.
- 15 3. A compound according to claim 1 or claim 2 wherein R₄ is H or an optionally substituted C₁-C₄alkyl group.
4. A compound according to any one of claims 1 to 3 wherein R₂ is an optionally substituted phenyl, naphthyl or heteroaryl group.
- 20 5. A compound according to any one of claims 1 to 4 wherein the 6- or 7-membered azacyclic ring is attached to the indazole in the 5 or 7 position.
- 25 6. A compound according to any one of claims 1 to 5 wherein A is N.
7. A compound according to any one of claims 1 to 6 wherein R₃ is selected from hydrogen, phenyl and C₁-C₄alkyl which may be substituted by optionally substituted phenyl.
- 30 8. A compound according to any one of claims 1 to 7 wherein m is 1 and R₁ is hydrogen or halogen.

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9. A compound according to claim 1 which is one of the following:
- 5-(4-methylpiperazin-1-yl)-3-(1-naphthylsulfonyl)-1H-indazole;
 - 3-(1-naphthylsulfonyl)-5-piperazin-1-yl-1H-indazole;
 - 1-(3-chlorobenzyl)-5-(4-methylpiperazin-1-yl)-3-(1-naphthylsulfonyl)-1H-indazole;
 - 5 7-(4-methylpiperazin-1-yl)-3-(phenylsulfonyl)-1H-indazole;
 - 3-(phenylsulfonyl)-7-(4-propylpiperazin-1-yl)-1H-indazole;
 - 3-(phenylsulfonyl)-7-piperazin-1-yl-1H-indazole;
 - 5-(4-methylpiperazin-1-yl)-3-(phenylsulfonyl)-1H-indazole;
 - 3-(phenylsulfonyl)-5-(4-propylpiperazin-1-yl)-1H-indazole;
 - 10 3-(phenylsulfonyl)-5-piperazin-1-yl-1H-indazole;
 - 5-piperazin-1-yl-3-[(3-cyanophenyl)sulfonyl]-1H-indazole;
 - 7-(4-methylpiperazin-1-yl)-3-[(2-ethylphenyl)sulfonyl]-1H-indazole;
 - 3-(1-naphthylsulfonyl)-7-(4-propylpiperazin-1-yl)-1H-indazole;
 - 5-(4-phenethylpiperazin-1-yl)-3-(1-naphthylsulfonyl)-1H-indazole;
 - 15 5-(4-methylpiperazin-1-yl)-3-(2-naphthylsulfonyl)-1H-indazole;
 - 3-[(2-chloro-4-fluorophenyl)sulfonyl]-5-piperazin-1-yl-1H-indazole;
 - 1-methyl-3-(phenylsulfonyl)-5-piperazin-1-yl-1H-indazole;
 - 1-phenyl-3-(phenylsulfonyl)-5-piperazin-1-yl-1H-indazole;
 - 1-methyl-3-(phenylsulfonyl)-7-piperazin-1-yl-1H-indazole;
 - 20 1-phenyl-3-(phenylsulfonyl)-7-(piperazin-1-yl)-1H-indazole;
 - 7-piperazin-1-yl-3-[(3-fluorophenyl)sulfonyl]-1H-indazole;
 - 3-[(4-fluorophenyl)sulfonyl]-7-(4-methylpiperazin-1-yl)-1H-indazole;
 - 3-[(2-chlorophenyl)sulfonyl]-7-piperazin-1-yl-1H-indazole;
 - 3-[(4-aminophenyl)sulfonyl]-7-(piperazin-1-yl)-1H-indazole;
 - 25 5-piperazin-1-yl-3-[(3-fluorophenyl)sulfonyl]-1H-indazole;
 - 3-[(4-fluorophenyl)sulfonyl]-5-(4-methylpiperazin-1-yl)-1H-indazole;
 - 3-[(2-chlorophenyl)sulfonyl]-5-(4-propylpiperazin-1-yl)-1H-indazole;
 - 3-[(4-aminophenyl)sulfonyl]-5-piperazin-1-yl-1H-indazole;
 - 3-[(5-chlorothien-2-yl)sulfonyl]-5-piperazin-1-yl-1H-indazole;
 - 30 3-[(5-chlorothien-2-yl)sulfonyl]-7-piperazin-1-yl-1H-indazole;
 - 4-chloro-3-(phenylsulfonyl)-7-piperazin-1-yl-1H-indazole;
 - 5-fluoro-3-(phenylsulfonyl)-7-piperazin-1-yl-1H-indazole;
 - 6-fluoro-3-(phenylsulfonyl)-7-piperazin-1-yl-1H-indazole;

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- 4-chloro-3-(phenylsulfonyl)-5-piperazin-1-yl-1*H*-indazole;
 7-fluoro-3-(phenylsulfonyl)-5-piperazin-1-yl-1*H*-indazole;
 6-fluoro-3-(phenylsulfonyl)-5-piperazin-1-yl-1*H*-indazole;
 6-(4-phenethylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
 5 6-(4-methylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
 6-(4-propylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
 3-(phenylsulfonyl)-6-piperazin-1-yl-1*H*-indazole;
 4-piperazin-1-yl-3-(phenylsulfonyl)-1*H*-indazole;
 4-(4-methylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
 10 4-(4-propylpiperazin-1-yl)-3-(phenylsulfonyl)-1*H*-indazole;
 3-(phenylsulfonyl)-4-piperazin-1-yl-1*H*-indazole;
 3-[(5-chlorothien-2-yl)sulfonyl]-5-piperidin-1-yl-1*H*-indazole;
 3-[(5-chlorothien-2-yl)sulfonyl]-7-piperidin-1-yl-1*H*-indazole;
 1-methyl-3-(phenylsulfonyl)-5-piperidin-1-yl-1*H*-indazole;
 15 3-[(3-fluorophenyl)sulfonyl]-5-piperidin-1-yl-1*H*-indazole;
 1-methyl-3-(phenylsulfonyl)-7-(4-methylpiperidin-1-yl)-1*H*-indazole;
 3-[(3-fluorophenyl)sulfonyl]-7-piperidin-1-yl-1*H*-indazole;
 3-[(3-fluorophenyl)sulfonyl]-5-piperidin-1-yl-1*H*-indazole;
 3-(phenylsulfonyl)-5-piperidin-1-yl-1*H*-indazole;
 20 1-methyl-3-[(3-fluorophenyl)sulfonyl]-7-piperidin-1-yl-1*H*-indazole;
 3-(phenylsulfonyl)-7-piperidin-1-yl-1*H*-indazole;
 or a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

10. A method for the treatment of a central nervous system disorder related to or
 25 affected by the 5-HT₆ receptor in a patient in need thereof which comprises providing
 to said patient a therapeutically effective amount of a compound of formula I as
 claimed in any one of claims 1 to 9 or a stereoisomer thereof; or a pharmaceutically
 acceptable salt thereof.

- 30 11. A method according to claim 10 wherein said disorder is a motor
 disorder, anxiety disorder or cognitive disorder.

12. A method according to claim 10 wherein said disorder is a neurodegenerative disorder.

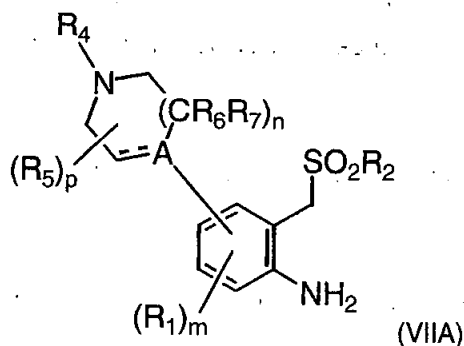
13. A method according to claim 11 wherein said disorder is selected from the group consisting of: attention deficit disorder; obsessive compulsive disorder; withdrawal from drug, alcohol or nicotine addiction; schizophrenia; depression; and Alzheimer's disease.

14. A method according to claim 12 wherein said disorder is selected from the group consisting of: stroke; head trauma; and neuropathic pain.

15. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of formula I as claimed in any one of claims 1 to 9 or a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

16. A process for preparing a compound of formula (I) according to claim 1 which comprises one of the following

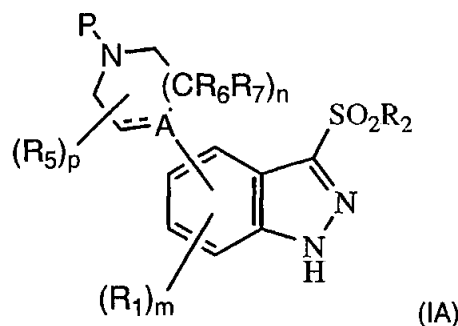
(a) diazotising and cyclising a compound of formula (VIIA):



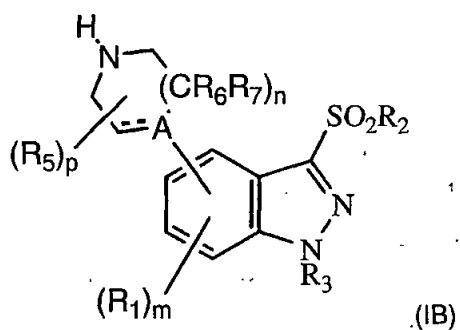
20 wherein the dotted line, m, n, p, A, R₁, R₂, R₄, R₅, R₆ and R₇ are as defined in claim 1, e.g. with NaNO₂/acid to give a compound of formula (I) wherein R₃ is hydrogen, or

(b) alkylating or arylating a protected compound of formula (IA)

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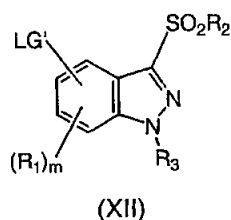


- wherein the dotted line, m, n, p, A, R₁, R₂, R₅, R₆ and R₇ are as defined in claim 1 and P is a protecting group or R₄ where R₄ is as defined in claim 1 excepting
- 5 hydrogen, with an alkylating or arylating agent of formula R₃-LG where LG is a leaving group and R₃ is a C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl or heteroaryl group each optionally substituted; and if required removing the protecting group, to give a corresponding compound of formula (I) where R₃ is a C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl or heteroaryl group each optionally substituted;
- 10 or
- (c) alkylating a compound of formula (IB)

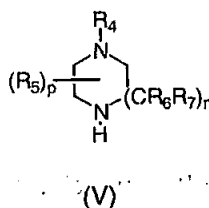


- 15 wherein the dotted line, m, n, p, A, R₁, R₂, R₃, R₅, R₆ and R₇ are as defined in claim 1, with an alkylating agent of formula R₄-LG where LG is a leaving group and R₄ is a C₁-C₆alkyl or C₃-C₇cycloalkyl group each optionally substituted, to give a corresponding compound of formula (I) where R₄ is a C₁-C₆alkyl or C₃-C₇cycloalkyl group each optionally substituted;
- 20 or

(d) reacting a compound of formula (XII):



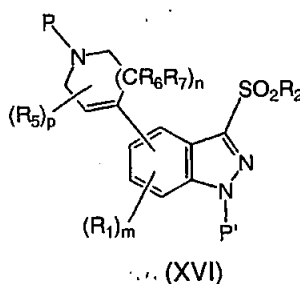
wherein m, R₁, R₂ and R₃ are as defined in claim 1, and LG' is a leaving group such as Cl, Br, I or an activated hydroxyl group such as triflate, with a compound of
5 formula (V):



wherein n, p, R₄, R₅, R₆ and R₇ are as defined in claim 1, in the presence of a catalyst, e.g., a palladium or nickel catalyst, to give a corresponding compound of formula (I);

10 or

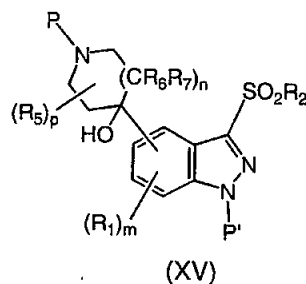
(e) reducing a compound of formula (XII):



wherein m, n, p, R₁, R₂, R₅, R₆ and R₇ are as defined in claim 1, P is a protecting group or R₄ as defined in claim 1 and P' is a protecting group or R₃ as defined in claim 1, if required removing any protecting group, to give a corresponding compound of formula (I) wherein A is CH;

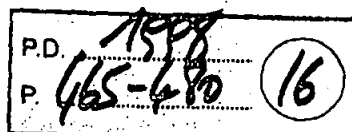
or

20 (f) acidifying a compound of formula (XII):



- wherein m, n, p, R₁, R₂, R₅, R₆ and R₇ are as defined in claim 1, P is a protecting group or R₄ as defined in claim 1 and P' is a protecting group or R₃ as defined in claim 1, if required removing any protecting group, to give a corresponding compound of formula (I) wherein A is C and represents a double bond;
- 5 or
- (g) converting a basic compound of formula (I) as defined in claim 1 to an acid addition salt thereof or vice versa.
- 10 or
- (h) separating a stereoisomer of a compound of formula (I) from a mixture thereof.

ANEXO 2



DRUG EXPERIENCE

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Cholinesterase Inhibitors in the Treatment of Alzheimer's Disease

A Comparison of Tolerability and Pharmacology

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Abstract

Cholinesterase inhibitors are currently the most established treatment strategy in Alzheimer's disease. The treatment effect appears mainly to be symptomatic. Effects on progression of the disease following long term treatment, and possible neuroprotective effects, have been investigated. Delay until nursing home placement has been reported. Three cholinesterase inhibitors: tacrine, donepezil and rivastigmine, are in clinical use. Other cholinesterase inhibitors, such as galantamine (galanthamine), metrifonate, physostigmine, eptastigmine, are currently under clinical evaluation. So far, the efficacy appears to be comparable between the various cholinesterase inhibitors: treatment for up to 6 months has produced an improvement in Alzheimer's Disease Assessment Scale - Cognitive Subscale score (ADAS-cog) of between 1.8 and 4.9 in patients with Alzheimer's disease.

Tacrine, donepezil, galantamine and physostigmine are reversible inhibitors of acetylcholinesterase and butyrylcholinesterase, while metrifonate is considered to be an irreversible inhibitor and rivastigmine a pseudoirreversible inhibitor. Tacrine and physostigmine have lower bioavailability, 17 to 37% and 3 to 8%, respectively, than the other cholinesterase inhibitors such as rivastigmine, galantamine and donepezil (40 to 100%). The elimination half-life is considerably longer for donepezil (70 to 80h) in comparison to most of the other cholinesterase inhibitors (0.3 to 12h). Donepezil is therefore administered once daily in comparison to rivastigmine which is administered twice daily and tacrine which is administered 4 times daily.

Simultaneous food intake lowers the plasma concentration of tacrine and reduces the adverse effects of rivastigmine. Drugs like theophylline and cimetidine have been reported to change the pharmacokinetics of tacrine and donepezil. In contrast, concomitant medication with various drugs with rivastigmine does not seem to cause any drug interactions in patients with Alzheimer's disease. Tacrine, donepezil and galantamine are metabolised via the cytochrome P450 (CYP) liver enzymes. Active metabolites are known for tacrine and galantamine. Rivastigmine is not metabolised via CYP enzymes, but via esterases and is excreted in the urine.

Tacrine is associated with hepatotoxicity while other cholinesterase inhibitors seem devoid this adverse effect. Increased liver enzyme values have been observed in 49% of patients with Alzheimer's disease treated with tacrine. Rechallenge with tacrine reduces the incidence of elevated liver enzyme levels. Peripheral cholinergic adverse effects are common for the cholinesterase inhibitors, with an incidence ranging between 7 to 30%. For some cholinesterase inhibitors, such as rivastigmine, the cholinergic adverse effects such as nausea, vomiting, dizziness, diarrhoea and abdominal pain can be reduced by slowing the rate of dose titration.

Alzheimer's disease is the most common form of dementia and represents about 40 to 60% of late onset dementia syndrome. It is a progressive and costly disease that causes suffering over a long period for both the patients and their families. The disease is characterised by memory loss and other cognitive symptoms producing occupational and

social disabilities. Genetic causes have been reported to be involved in familial cases of Alzheimer's disease but the disease probably has a much more complex and heterogeneous aetiology.^[1,2] Although a great deal of progress has been made in recent years in further understanding the genetical aberrations as well as the pathophysio-

logical processes of Alzheimer's disease, there is still no cure for the disease.

Cognition is known to be dependent on several mental functions, such as awareness, memory, language, mental tempo and visuospatial function. It is still an open question as to whether memory can be improved by cognition-enhancing substances.

Transmitter replacement therapy is one of several possible treatment strategies; others being anti-amyloid drugs, nerve growth factors, anti-inflammatory drugs, and antioxidants.^[3,4] The cholinergic hypothesis claims that low levels of acetylcholine lead to cognitive decline.^[5] Cholinesterase inhibitors inhibit the metabolism of acetylcholine and treatment with these drugs has so far been the most fruitful treatment strategy in Alzheimer's disease. Clinical experience with cholinesterase inhibitors, such as tacrine, indicates that these compounds have positive effects on cognitive function, especially in attention^[6] and that long term treatment also has effects on primary memory, episodic memory, visuospatial ability and psychomotor speed.^[7-9]

Tacrine was the first cholinesterase inhibitor to be approved for use in Alzheimer's disease (in the US in 1993 and in Europe in 1994). Modest palliative effects have been observed, as well as some slowing or arresting of the disease course.^[9-11] The second cholinesterase inhibitor donepezil was approved in 1996 in the US and in 1997 in Europe, and in 1998 rivastigmine was approved in several European countries. Other cholinesterase inhibitors, including galantamine (galanthamine), metrifonate and eptastigmine, are currently under clinical evaluation.

The aim of this paper is to compare these cholinesterase inhibitors with respect to specificity of cholinesterase inhibition, pharmacokinetic properties and metabolism, efficacy, tolerability and possible drug interactions.

1. Evaluation of Drug Treatment Efficacy in Alzheimer's Disease

Because of the genetic, biological and clinical heterogeneity of Alzheimer's disease it can be as-

sumed that a specific treatment strategy may not be helpful for all patients. Patients may show different rates of progression of deterioration during the course of the untreated disease. The disease involves changes not only in cognition but also in behaviour, social and overall global functioning. Different types of outcome measures have been used in clinical trials to evaluate improvement and measure the effect of treatment with cholinesterase inhibitors. The cognitive tests include the Mini-Mental State Examination and the Alzheimer's Disease Assessment Scale, while other scales, such as the clinician's global assessment of severity, change, behavioural ratings and functional scales, have also been used.^[12] A valuable complement to these scales are studies of the functional effects of therapies on the brain as evaluated by neuropsychological measurements, electroencephalogram (EEG), and imaging techniques including positron emission tomography and single photon computed emission tomography.^[13]

2. Acetylcholinesterase and Butyrylcholinesterase in the Brains of Patients with Alzheimer's Disease

Human brain cholinesterases can be divided into acetylcholinesterases and butyrylcholinesterases and these are expressed in at least 6 different molecular forms: globular monomers (G1), dimers (G2) and tetramers (G4) of catalytic subunits and asymmetric molecules with 1, 2 or 3 tetramers (A4, A8, A12) coupled to a 3-stranded collagen-like coiled structure.^[14,15] The most abundant form of acetylcholinesterase is the extracellular G4 molecular form but the cytosolic G1 form is also present in a smaller amount in the brain.^[16] Acetylcholinesterase has also been found in erythrocytes while high levels of butyrylcholinesterase, also known as pseudo or nonspecific cholinesterase, is found in serum.

The activity of acetylcholinesterase, and especially of the G4 form, has been reported to be decreased in the brains of patients with Alzheimer's disease.^[17,18] Acetylcholinesterase has also been detected in senile plaques and neurofibrillary tan-

gles in the brains of patients with Alzheimer's disease. The G4 form of acetylcholinesterase has been suggested to be of the asymmetric type and may accelerate β -amyloid formation.^[15,16] The activity of butyrylcholinesterase has been reported to be increased in the brains of patients with Alzheimer's disease^[17] as a consequence of reactive gliosis and accumulation of butyrylcholinesterase on neuritic plaques.^[20]

Acetylcholinesterase levels in the ventricular or lumbar cerebrospinal fluid (CSF) are lower in patients with Alzheimer's disease compared with age-matched controls.^[21,22] An anomalous molecular form of acetylcholinesterase has been found in the CSF of patients with Alzheimer's disease which is a possible indication of changes in acetylcholinesterase at the molecular level.^[23] Since the CSF anomalous acetylcholinesterase has also been found in individuals without dementia, it has been speculated that this molecular form of acetylcholinesterase may be present in CSF before clinical signs of dementia are observed.^[24] This finding may also explain the overlap in acetylcholinesterase activity in CSF seen between individuals with and without dementia.^[25]

Recently, attempts have been made to visualise acetylcholinesterase activity *in vivo* using imaging techniques. Pappata et al.^[26] using ¹¹C-physostigmine and positron emission tomography, showed a regional distribution of acetylcholinesterase in the human brain. Recently, by using ¹¹C-N-methyl-4-piperidyl acetate, Iyo et al.^[27] demonstrated reduced acetylcholinesterase activity *in vivo* in patients with Alzheimer's disease, especially in cortical brain regions, compared with control individuals.

3. Molecular and Functional Properties of Cholinesterase Inhibitors

The different molecular structures of various cholinesterase inhibitors (Fig. 1) make them differently selective for acetylcholinesterase and butyrylcholinesterase. Tacrine and physostigmine have demonstrated reasonably equal potency for inhibiting acetylcholinesterase compared with in-

hibiting butyrylcholinesterase and are therefore considered as rather unselective cholinesterase inhibitors. Other cholinesterase inhibitors, including donepezil and rivastigmine, appear to be more selective for acetylcholinesterase compared with butyrylcholinesterase (table I). The cholinesterase inhibitors can also be characterised as reversible, e.g. donepezil, tacrine and galantamine, or irreversible, e.g. metrifonate, as well as competitive, e.g. galantamine, or noncompetitive, e.g. tacrine and donepezil, in nature.

The strategy behind using cholinesterase inhibitors for Alzheimer's disease is to improve cholinergic synaptic function by elevating the acetylcholine content of the synaptic cleft and thereby augmenting the function of the cholinergic receptors. *In vitro* studies have indicated that cholinesterase inhibitors such as physostigmine and tacrine can enhance the potassium-induced acetylcholine release from cortical tissue slices taken at autopsy from patients who had had Alzheimer's disease.^[28] Interestingly, the release of acetylcholine was decreased in autopsy brain tissue from patients without Alzheimer's disease in the presence of similar concentrations of the cholinesterase inhibitors.^[28] This finding illustrates that the effect of cholinesterase inhibitors can be different in the brains of healthy individuals and patients with Alzheimer's disease.

Depending on the amount of acetylcholine in the synaptic cleft, an increase or decrease of the level of the transmitter can be obtained in the presence of cholinesterase inhibitors.^[29] Low levels of acetylcholine present in the synaptic cleft (as is the case in patients with Alzheimer's disease) trigger the facilitatory presynaptic muscarinic M₁ receptors to increase the release of acetylcholine into the synaptic cleft.^[29]

Tacrine has been shown to have a variety of pharmacological actions including inhibition of the uptake as well as increase in the release of several neurotransmitters, increase in the synthesis of acetylcholine and directly binds to muscarinic and nicotinic receptors and ion channels.^[30] Whether these various pharmacological effects are exerted

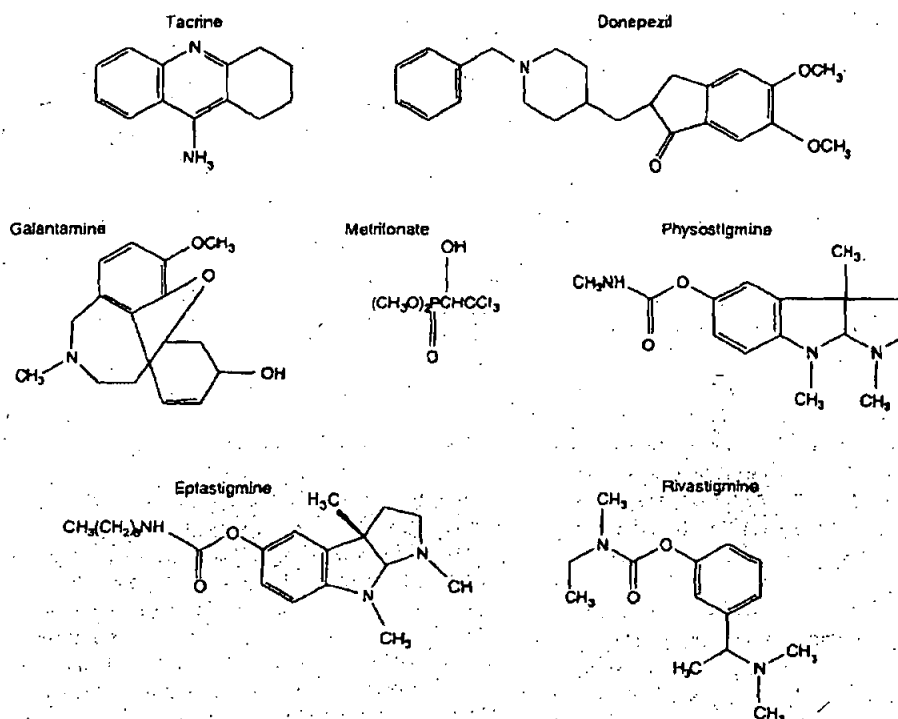


Fig. 1. Chemical structures of cholinesterase inhibitors tacrine, donepezil, galantamine (galanthamine), metrifonate, physostigmine, eptastigmine and rivastigmine.

by other cholinesterase inhibitors has not been explored extensively. Physostigmine has demonstrated less affinity for muscarinic and nicotinic receptors than tacrine.^[28] Interestingly, several cholinesterase inhibitors, including tacrine, galantamine and donepezil, have been shown to bind to an allosteric site on the nicotinic acetylcholine receptor and this may be of importance for clinical efficacy.^[31-33]

Increasing levels of acetylcholine due to cholinesterase inhibition may regulate in the formation of amyloid precursor proteins. Studies in animals and cell lines indicate that treatment with different cholinesterase inhibitors including tacrine, physostigmine, eptastigmine and metrifonate can enhance the release of non-amyloidogenic deriva-

tives of amyloid precursor protein and prevent β -amyloid accumulation.^[34-38] Both tacrine and donepezil have been found to attenuate β -amyloid neurotoxicity in cell lines.^[38]

4. Tacrine

Tacrine causes an allosteric reversible inhibition of acetylcholinesterase and butyrylcholinesterase by interacting with a hydrophobic region near the anionic α and γ site of the enzyme.^[39] A 60% inhibition of acetylcholinesterase in red blood cells and a 40% inhibition of cholinesterase in plasma were measured in patients receiving tacrine 160 mg/day,^[40] the highest recommended clinical daily dose.

4.1 Pharmacokinetics

The pharmacokinetic properties of tacrine have been studied following the administration of a single dose and after long term treatment.^[40-48] Inter-individual variations in tacrine pharmacokinetic parameters have been reported.^[30] The bioavailability of tacrine has been found to range from 17 to 37%^[41,43,45,48] (table II). Time to reach maximal plasma concentration (t_{max}) in the blood was 1 to 2 hours following oral administration of tacrine 10 to 50mg to patients with Alzheimer's disease.^[40,43-46] The absorption is decreased by concomitant intake of food. The elimination half-life for tacrine is 1.3 to 7 hours in patients with Alzheimer's disease.^[40,41,43,45]

A positive correlation has been observed between tacrine concentration and cholinesterase inhibition in plasma.^[40] The therapeutic window for tacrine has been suggested to range between 7.5 and 20 µg/L.^[49] Tacrine has been shown to be 75% bound to plasma albumin. It is metabolised in the liver by the cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP1D6 and 5 metabolites have been found in serum and urine.^[30,50] The major metabolite is 1-hydroxy-tacrine, which is present in plasma and CSF at a concentration that is 10 times higher than that of tacrine.^[9] This metabolite can inhibit cholinesterase and exerts clinical effects on its own.^[51]

Higher plasma concentrations of tacrine have been reported in women^[49] compared with men. This difference might be due to the lower activity of the CYP1A2 isoenzyme in women. A lower tacrine concentration has been reported in smokers compared with nonsmokers and this might be explained by the fact that smoking induces CYP1A2 activity.^[50]

4.2 Administration Regimens

Tacrine is usually administered 4 times daily starting at an initial dosage of 40 mg/day and increased every 6 weeks up to a maximal dosage of 160 mg/day. New labelling for the agent indicates that the dosage of tacrine can be increased after 4 weeks at each dosage level. Since some patients may not be able to tolerate the highest dosage of tacrine, titration to their maximum tolerated dosage is recommended.^[50,52]

4.3 Interactions

Theophylline is metabolised via CYP1A2 and concomitant administration of tacrine and theophylline results in a 2-fold increase in theophylline concentration.^[30,50] Cimetidine inhibits the metabolism of tacrine in the elderly and increases the plasma concentration of tacrine.^[30,50]

Table I. A comparison of cholinesterase inhibition and percent of cholinergic adverse events between different cholinesterase inhibitors (see sections 3 to 11 for details and references)

Cholinesterase inhibitors	Cholinesterase inhibition (AChE vs BuChE)	Maximal inhibition of RBC AChE (%)	RBC AChE inhibition (%) achieved with therapeutic dosages	Administration (times/day)	Cholinergic adverse events (% of treated patients)
Tacrine	BuChE > AChE	60	30	4	10-30
Donepezil	AChE >> BuChE	90	64	1	10
Gаланthamine	AChE > BuChE	30-60		3	4-20
Metrifonate	AChE = BuChE	62-72	50-70	1	7-18
Physostigmine	AChE > BuChE	70		2	7-40
Eptastigmine	BuChE = AChE	18-44	38	2 or 3	34
Rivastigmine	AChE > BuChE	40 ^a		21	<20

a 62% CSF AChE inhibition.

AChE = acetylcholinesterase; BuChE = butyrylcholinesterase; RBC = red blood cell, = = equal inhibition; > = stronger inhibition; >> = much stronger inhibition.

Table II. Pharmacokinetic profile of different cholinesterase inhibitors in patients with Alzheimer's disease (see sections 2 to 11 for details and references)

Cholinesterase inhibitor	Bioavailability (%)	t_{max} (h)	Elimination $t_{1/2}$ (h)	Effect of food	Metabolism	Excreted via urine (%)
Tacrine	17-37	1-2	1.3-7	Yes	CYP1A2, CYP2D6 (5 metabolites, 1 of which is active)	<3
Donepezil	100	3-5	70-80	None	CYP2D6, CYP3A4	17
Galantamine (galanthamine)	85	1	6	NDA	CYP2D6 (4 metabolites, 1 of which is active)	50 ^a
Metrifonate	NDA	0.5	2.3	NDA	Not via CYP450	80
Physostigmine ^b	3-8	0.8	0.3	NDA	Not via CYP450	NDA
Eptastigmine	NDA	1-1.4	12.1	NDA	NDA	NDA
Rivastigmine	40	0.5-2	0.8-2	Yes	Not via CYP450 (1 metabolite)	Mainly (via the metabolite NAP 228-90)

a 25% unchanged and 25% metabolised.

b Healthy volunteers; no data available for patients with Alzheimer's disease.

CYP = cytochrome P450; NDA = no data available; t_{max} = time to reach maximum concentration; $t_{1/2}$ = half-life.

4.4 Adverse Effects

4.4.1 Liver Toxicity

The most important adverse effect of tacrine is liver toxicity. The hepatotoxic effects of tacrine have been reviewed by Watkins et al.^[53] who summarised data from 6 multicentre trials involving 2446 patients. Increases in serum alanine aminotransferase (ALT) levels occurred in 49% of patients with Alzheimer's disease treated with tacrine.^[53] The ALT level increased to 3 times the upper limit of normal in 25% of the patients; 8% of the patients had ALT values that were 10 or more times the upper limit of normal. However, this increase in ALT level is mainly asymptomatic, although fatigue, fever and eosinophilia occurred more frequently in patients with ALT levels 10 or more times the upper level of normal. Three patients underwent liver biopsies, which showed lobular hepatitis. The mean interval from initiation of tacrine treatment to ALT level elevations to 3 times the upper limit of normal was 50 days and the ALT levels increased mainly during the first 12 weeks of treatment. When patients were rechallenged with tacrine, 30% of them experienced another increase in ALT levels.^[53] 72% of patients who did not experience an elevation in ALT levels following rechallenge were found to be able to tolerate higher dosages than those that caused the initial increase in ALT levels.^[53]

4.4.2 Other Adverse Effects

Relatively higher plasma concentrations of tacrine have been reported in patients developing adverse effects related to tacrine.^[49] The most common adverse events experienced by patients with Alzheimer's disease receiving tacrine relate to the gastrointestinal system. In a randomised, controlled trial of tacrine in patients with 410 Alzheimer's disease, nausea and vomiting were experienced by 35% of patients, diarrhoea by 18%, anorexia by 12%, dyspepsia by 11% and abdominal pain by 9%, following 30 weeks of treatment with tacrine 80 to 160 mg/day.^[52] Of the patients, 16% withdrew from the study because of gastrointestinal complaints.^[52] The gastrointestinal adverse effects of tacrine can be somewhat diminished by concomitant administration of food.

The safety of tacrine, as observed in 2706 patients with Alzheimer's disease in clinical trials and 9861 patients with Alzheimer's disease in a treatment investigational new drug (TIND) programme, was recently overviewed.^[54] 398/2706 (15%) patients who had been treated with tacrine experienced an adverse effect that was classified as serious. 461 (17%) patients were withdrawn from treatment due to adverse effects and transaminase level elevations accounted for almost half of these withdrawals. 24% of the patients (2404 patients) in the TIND programme were withdrawn from treatment. 10% of the TIND patients were withdrawn

from treatment due to elevations in ALT levels, 6% for symptoms due to involvement of digestive systems and 6% related to CNS effects including agitation, confusion, hallucinations. 3% of patients (81 patients) in the TIND programme died, but only 2 of the 81 deaths were considered possibly related to tacrine treatment.

5. Donepezil

Donepezil is a reversible specific piperidine acetylcholinesterase inhibitor that primarily has a noncompetitive inhibitory action but also has some competitive characteristics (mixed inhibitor).^[55,56]

5.1 Pharmacokinetics

The pharmacokinetic properties of donepezil have been studied following administration of a single dose and t_{max} was found to be 3 to 5 hours (table II).^[57,58] Maximal plasma concentrations of 9.1 and 25.6 µg/L were obtained following administration of single oral doses of donepezil 5 and 10 mg, respectively. Steady-state concentrations were obtained following 15 days of treatment.^[59] When donepezil was administered in dosages of 3 or 5 mg once daily for 21 days the plasma concentrations were 18.2 and 30.2 µg/L, respectively.^[57,59]

The inhibition of red blood cell acetylcholinesterase by 64% was reported following 6 weeks treatment with donepezil 5 mg/day while the corresponding inhibition with 10 mg/day was 77%.^[60] During long term treatment with donepezil for 192 weeks, acetylcholinesterase inhibition up to 90% was measured at a plasma concentration of 75 µg/L.^[61] following administration of donepezil 10 mg/day.

The elimination half-life of donepezil has been estimated to be 70 to 80 hours^[59] and the mean apparent plasma clearance has been estimated at 0.13 L/h/kg. A longer half-life of donepezil has been observed in the elderly compared with young adults although no difference in pharmacokinetics was observed between healthy older volunteers and patients with Alzheimer's disease.^[58,59,62]

Donepezil is extensively bound to proteins (96%) with 75% bound to albumin and 21% bound to α_1 -acid glycoproteins.^[58] Donepezil is metabolised by CYP2D6 and CYP3A4 and glucuronidised with about 17% of the dose excreted unchanged in the urine.^[58]

5.2 Administration Regimens

Donepezil is recommended to be given once daily, initially at a dose of 5 mg for at least 4 to 6 weeks. Thereafter, the dosage can be increased to 10 mg/day.

5.3 Interactions

No effect of food on the absorption of donepezil has been reported. Administration of cimetidine, digoxin, theophylline or warfarin has not been found to significantly change the pharmacokinetics of donepezil.^[59] Donepezil 0.3 to 10 mg/L has not been found to influence the *in vitro* binding of furosemide (frusemide) 5 mg/L, digoxin 2 µg/L or warfarin 3 mg/L, to albumin. It is possible that inducers of CYP2D6 and CYP3A4, for example phenytoin, carbamazepine, dexamethasone, rifampicin and phenobarbital (phenobarbitone), may potentially increase the elimination of donepezil, but more studies need to be performed to clarify this issue.^[58] The outcome of donepezil treatment in patients with deficiencies of the isoenzymes CYP2D6 and CYP3A4 is unknown.

5.4 Adverse Effects

Donepezil shows cholinergic adverse effects and the most frequent adverse effects related to donepezil are gastrointestinal adverse effects and dizziness. No liver toxicity has been reported following up to 192 weeks of donepezil treatment.^[61] The most common adverse events seen in a 24-week, double-blind, placebo-controlled trial of donepezil 10 mg/day in 316 patients with Alzheimer's disease were nausea (experienced by 17% of donepezil recipients versus 4% of placebo recipients), diarrhoea (17 versus 7%); gastric upset (10 versus 2%), dizziness (8 versus 4%), muscle

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cramps (8 versus 1%).^[60] The frequency of adverse effects of donepezil was generally lower at the 5 mg/day dosage (diarrhoea 9%, nausea 4%, vomiting 3%, dizziness 10%, muscle cramps 6%). In an open study of donepezil up to 10 mg/day in 133 patients with mild to moderate Alzheimer's disease administered for 192 weeks, 83% of the patients experienced adverse events that were mainly of a mild and transient nature on at least one occasion.^[61] However, 79% of these events were considered not to be related to donepezil but to be related to the patient's underlying Alzheimer's disease.

6. Galantamine (Galanthamine)

Galantamine is a phenanthrene alkaloid similar to codeine which was isolated from the European daffodil or common snowdrop, *Galanthus nivalis*. Galantamine is a reversible inhibitor of acetylcholinesterase with a competitive action. This means that the degree of inhibition caused by galantamine does not depend on the absolute concentration of the agent but more on the relationship between the inhibitor and the substrate concentration. 30 to 60% inhibition of red blood cell acetylcholinesterase is obtained 30 to 45 minutes following oral doses of galantamine, and the inhibitory effect of galantamine on red blood cell acetylcholinesterase is greater than its effect on butyrylcholinesterase (table I).^[63]

6.1 Pharmacokinetics and Dosage

Galantamine is readily absorbed after oral administration with a bioavailability of 85% (table II). Following oral administration, t_{max} is 52 minutes with a plasma elimination half-life of 5.7 hours and a total plasma clearance of 0.34 L/h/kg in young healthy volunteers.^[64] A 30% lower plasma half-life and clearance was observed in patients with Alzheimer's disease.^[64] A positive correlation has been observed between the concentration of galantamine in red blood cells and acetylcholinesterase inhibition.^[63] Galantamine does not bind to plasma proteins.^[64]

Sanguinine (*O* demethyl-galantamine) is a metabolite of galantamine formed by CYP2D6 and it can account for up to 20% of administered galantamine.^[64] Interestingly, sanguinine has been reported to be 3 times more potent than galantamine as an acetylcholinesterase inhibitor.^[63] 50% of the administered dose of galantamine has been found in urine 72 hours after administration; 25% is excreted unchanged and 25% is metabolised (table II).^[64]

A galantamine dosage of 10mg 3 times daily is recommended.

6.2 Adverse Effects

No liver toxicity has been reported with galantamine. Nausea was reported to occur in 21, 29 and 63% of 141 patients with Alzheimer's disease who were receiving galantamine 29.4, 34.7 and 37.9 mg/day for 13 weeks, respectively.^[65] Other symptoms such as diarrhoea, abdominal cramp and anorexia were observed in less than 4% of the patients.^[65]

7. Metrifonate

Metrifonate is a prodrug of dichlorvos (2,2-dichlorovinyl dimethyl-phosphate or DVVP) and undergoes spontaneous dehydrochlorination.^[66] Metrifonate is an irreversible acetylcholinesterase inhibitor with a biphasic effect. Initially, it interacts competitively with the enzyme and then this changes to noncompetitive inhibition with progressive phosphorylation of the enzyme catalytic site.^[67] Metrifonate can be characterised as a pseudoirreversible cholinesterase inhibitor. It inhibits both acetylcholinesterase and butyrylcholinesterase^[68] to a similar extent.^[69]

7.1 Pharmacokinetics and Dosage

Metrifonate is readily absorbed after oral administration. Following administration of a single dose of 7.5 mg/kg to patients with Alzheimer's disease, t_{max} was 26 minutes.^[70] An elimination half-life of 2.3 hours with an apparent oral clearance of 0.34 L/h/kg has been obtained for metrifonate in

healthy volunteers, with similar estimations in patients with Alzheimer's disease.^[70,71] It is estimated that 2% of metrifonate reaches the brain as dichlorvos.^[71] Red blood cell acetylcholinesterase was inhibited by 62 to 72% following 28 days of treatment with metrifonate at a maintenance dosage of 0.4 to 0.7 mg/day in patients with Alzheimer's disease.^[68] Recently Becker et al.^[69] reported a 60% inhibition of red blood cell acetylcholinesterase and plasma butyrylcholinesterase following 6 months' treatment with metrifonate. Acetylcholinesterase in CSF was reported to be inhibited by 37 and 47% in 2 patients with Alzheimer's disease following administration of metrifonate 5 mg/kg/week.^[72] Metrifonate is mainly eliminated via the urine (80%).^[68]

Metrifonate is given orally once daily. The maintenance dosage has been estimated to be 0.64 mg/kg/day.^[68]

7.2 Adverse Effects

Metrifonate is hydrolysed to an active compound and has been shown to interact with the CYP system. No liver function abnormalities have been reported for metrifonate.

Nausea, vomiting, abdominal discomfort, diarrhoea, weakness and leg cramps have been reported following treatment with metrifonate.^[68] In a double-blind, placebo-controlled study, involving 273 patients treated with metrifonate 0.65 mg/kg/day and 135 placebo patients treated for 26 weeks, 12% of metrifonate-treated patients discontinued treatment because of adverse effects compared with 4% of placebo-treated patients.^[73] Adverse effects following metrifonate treatment were considered mild to moderate in intensity and the occurrence of adverse events was 7 to 18% in the metrifonate-treated group compared with 1 to 8% in the placebo-treated group.^[73] No correlation has been observed between adverse events and acetylcholinesterase inhibition.^[68]

Diarrhoea was the most common adverse effect (experienced by 18% of metrifonate recipients) and this effect was assumed to be caused by overstimulation of the intestinal muscarinic receptors.

Leg cramps were experienced by 9% of metrifonate recipients and they were assumed to occur because of excessive activation of nicotinic receptors at the neuromuscular junction.^[73] Interestingly, polyneuropathy has been reported in patients after exposure to large doses of metrifonate taken accidentally or intentionally.^[74] An experimental study with cholinesterase inhibitor intoxication has indicated that the contractions of the trachea requires inhibition of both acetylcholinesterase and butyrylcholinesterase.^[75] Since some patients in clinical trials with metrifonate have experienced muscle weakness, the manufacturer of metrifonate, Bayer, has recently suspended phase III trials of this agent.^[76]

8. Physostigmine

Physostigmine is a tertiary amine with lipophilic properties which acts as a reversible inhibitor of both acetylcholinesterase and butyrylcholinesterase.

8.1 Pharmacokinetics and Administration

The pharmacokinetic properties of physostigmine following oral administration are characterised by high first-pass metabolism and a short elimination half-life which restricts its therapeutic use.^[77] Physostigmine is available as controlled-release tablets and transdermal systems have been developed.^[78,79] Following the intravenous infusion of physostigmine salicylate 2mg to healthy young volunteers t_{max} was 4.2 hours, plasma half-life was 0.5 hours and elimination clearance was 5.7 L/min.^[79] Corresponding values for oral solution and transdermal patches (containing physostigmine 30mg base) were t_{max} 0.6 and 14.1 hours, and plasma half life of 0.3 and 4.9 hours, respectively.^[79]

Physostigmine has been reported to cause an inhibition of acetylcholinesterase of up to 70% in red blood cells.^[80] Physostigmine is known to be rapidly metabolised by nonspecific esterases in blood^[81] and the absolute bioavailability has been estimated to be 3 to 8%.^[79,82]

Controlled-release physostigmine salicylate 12mg is given orally twice daily.^[78]

8.2 Adverse Effects

Physostigmine has not been reported to produce hepatotoxicity.^[78] Nausea and vomiting was reported in 40% of 183 patients with Alzheimer's disease treated with physostigmine salicylate 10 to 30mg for 10 weeks in a double-blind, placebo-controlled study.^[78] Other adverse events experienced by physostigmine-treated patients in this study were diarrhoea (12.6% of patients), anorexia (10.9%) and dizziness (10.9%); these effects occurred in 1 to 4% of placebo-treated patients.

9. Eptastigmine

Eptastigmine (heptylphysostigmine) is a carbamate derivative of physostigmine which reversibly inhibits acetylcholinesterase and butyrylcholinesterase (table 1).

9.1 Pharmacokinetics and Administration

The plasma concentration of eptastigmine increased in a dose-related manner following administration of single doses of eptastigmine 10 to 30mg.^[83] Following administration of a single dose of eptastigmine t_{max} was found to be 1 to 1.4 hours and the peak concentration was 0.86 µg/L.^[83,84] The distribution half-life was 0.44 hours in elderly volunteers receiving an oral dose of eptastigmine 30mg and the elimination half-life was found to be 12.1 hours.^[84]

Peak enzyme inhibition of acetylcholinesterase in red blood cells (15 to 35%) was obtained 3 to 3.6 hours after oral administration of a single dose of eptastigmine 10 to 30mg.^[85] Oral administration of eptastigmine 12 to 28mg 3 times daily for 14 days resulted in a 18 to 44% inhibition of acetylcholinesterase.^[86] Plasma concentration of eptastigmine was found to be inversely correlated to the acetylcholinesterase activity in red blood cells but not to butyrylcholinesterase activity in the plasma.^[84]

In clinical trials, eptastigmine has been administered orally at a dosage of 30 to 60 mg/day given in 2 or 3 divided doses.

9.2 Adverse Effects

No hepatotoxicity is known to occur with eptastigmine. 34% of patients with Alzheimer's disease treated with eptastigmine 40 or 60 mg/day for 4 weeks reported adverse events mainly of a cholinergic nature such as nausea, vomiting, bradycardia and ventricular extrasystoles.^[87] In these patients, the inhibition of acetylcholinesterase in red blood cells at steady state was high (70%).^[87]

A decrease in the number of neutrophils in peripheral blood was reported in 10 patients treated with eptastigmine 30 to 45 mg/day for 25 weeks compared with 1 patient in the placebo group.^[83]

Recently, the manufacturer of eptastigmine suspended all clinical development studies involving this agent because 2 patients in a clinical trial involving 2000 patients developed aplastic anaemia.^[88]

10. Rivastigmine

Rivastigmine is considered a 'pseudoirreversible' acetylcholinesterase inhibitor that forms a carbamoylated complex with the enzyme.^[89] Rivastigmine has been reported to selectively inhibit acetylcholinesterase rather than butyrylcholinesterase in the brain.^[89] Recently, Cutler et al.^[90] observed that rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase in the CSF to a similar extent.

10.1 Pharmacokinetics and Administration

Rivastigmine is rapidly absorbed following oral administration with a t_{max} of 0.5 to 2 hours.^[91] Rivastigmine is 40% bound to plasma proteins and rapidly eliminated (elimination half-life 0.6 to 2 hours).^[90,91] Administration of the drug after intake of food has been reported to reduce t_{max} by 30%.^[92] Medication given concomitantly to patients with Alzheimer's disease including antacids,

β -blockers, calcium antagonists, estrogens, anti-anginals, benzodiazepines and antidiabetics have not shown any interactions with rivastigmine. Rivastigmine has been reported to selectively inhibit the G1 isozyme of acetylcholinesterase in brain.^[91] An oral dose of rivastigmine 3mg was observed to inhibit acetylcholinesterase in CSF by 40% with minimal effect on cholinesterase in the plasma.^[94] Rivastigmine is rapidly metabolised and one metabolite, named NAP 226-90, has been found in the CSF, plasma and urine.^[95] As the metabolite of rivastigmine appears to be reduced in patients with renal and mild to moderate hepatic impairment, dosage recommendations to titrate according to individual tolerability should be closely followed in these patients.^[95] Rivastigmine is inactivated by cleavage to a phenolic product during the process of inhibiting acetylcholinesterase and is excreted via the kidneys.^[92]

Clinical studies have shown that the best maintenance dose for rivastigmine is 6 to 12 mg/day given as 2 divided doses.^[91]

10.2 Adverse Effects

Rivastigmine is not metabolised via the CYP system and to date no hepatotoxicity has been observed. Treatment with the maximal dosage of rivastigmine of 12 mg/day to 235 patients with Alzheimer's disease for 26 weeks resulted in adverse events in <20% of patients. Those that were observed were nausea (20%), vomiting (16%), dizziness (14%) and dyspepsia (5%).^[96] When the data from 3006 patients treated with rivastigmine and 985 patients treated with placebo were summarised regarding adverse effects, it was observed that the most common adverse effect was nausea (40% in the treatment group versus 10% in the placebo group) followed by vomiting (24 versus 7%), dizziness (20 versus 10%).^[95] The cholinergic adverse effects correlated better to the metabolite NAP-226-90 than to the mother compound. Similarly the area under the curve (AUC) of acetylcholinesterase activity was most closely correlated with the CSF AUC of the metabolite. When the dose titration is

performed slowly and the drug is given together with food, less adverse effects are observed.^[95]

11. Clinical Efficacy of Cholinesterase Inhibitors in Alzheimer's Disease

The clinical efficacy of the different cholinesterase inhibitors in Alzheimer's disease cannot be compared directly across trials since each trial used slightly different entry criteria and different populations, were performed at different centres and sometimes also used different outcome assessments. Thus, a direct comparison of the efficacy of the different cholinesterase inhibitors is impossible except in head to head clinical trials.

The cholinesterase inhibitors generally appear to produce symptomatic effects in patients with Alzheimer's disease following different lengths of treatment (table III). The clinical efficacy in drug trials has revealed an improvement in the Alzheimer's Disease Assessment Scale - Cognitive Subscale score (ADAS-cog) varying between 1.8 to 4.9 points compared with placebo (table III). The cholinesterase inhibitors appear to have effect on cognition but also beneficial effects on behavioural abnormalities, including apathy, anxiety and delusions.^[97]

A significant correlation has been reported between change in ADAS-cog and acetylcholinesterase inhibition in red blood cells.^[62] The maximal inhibition of acetylcholinesterase for various cholinesterase inhibitors ranges between 40 to 90% (table I). Cholinesterase inhibitors causing mild peripheral cholinergic adverse effects are used in therapeutic dosages that cause greater acetylcholinesterase inhibition in red blood cells (50 to 70%) than those with pronounced peripheral adverse effects (30%). For some of the cholinesterase inhibitors, e.g. physostigmine, eptastigmine and metrifonate an inverse U-shaped relationship between acetylcholinesterase inhibition and cognitive effect has been reported.^[98] Thus eptastigmine has been shown to have maximal clinical efficacy at 40% red blood cell acetylcholinesterase inhibition.^[99] In preclinical studies, tacrine also has been shown to have a U-shaped dose-response.^[99,100]

Table III. A comparison of the clinical efficacy of different cholinesterase inhibitors in patients with Alzheimer's disease (Intention-to-treat/evaluable patient analysis results)

Cholinesterase inhibitor	Daily dose	Length of treatment	ADAS-cog points difference from placebo	Reference
Tacrine	80mg	12 wks	3.8	54
	160mg	30 wks	4.1	52
Donepezil	5mg	24 wks	2.5	60
	10mg		2.9	60
Galantamine (galanthamine)	20-50mg	13 wks	3.1	65
Malrifonate	0.65 mg/kg	26 wks	2.9	73
Physostigmine	18-30mg	8 wks	1.8	78
Eptastigmine	40-60mg	25 wks	2.0	83
Rivastigmine	1-4mg	28 wks	1.9	86

ADAS-cog = Alzheimer's Disease Assessment Scale - Cognitive Subscale score

which may be difficult to observe clinically since the peripheral adverse effects limit the use of higher doses.

There is support for existence of persistent long term effects of cholinesterase inhibitors and that treatment with cholinesterase inhibitors may delay nursing home placement.^{14,611} The outcome of treatment may have significant importance for both patient and care-giver. However, additional long term studies need to be performed using several cholinesterase inhibitors and focusing on both clinical effects and tolerability aspects in patients with Alzheimer's disease. Of interest for future study are additional indications for the use of cholinesterase inhibitors, for example the possible treatment of acute confusion in elderly.

12. Conclusions

Three cholinesterase inhibitors, tacrine, donepezil and rivastigmine, have been approved for use in Alzheimer's disease in Europe and two, tacrine and donepezil have been approved in the US. They differ in their risk of liver toxicity and peripheral adverse effects while the clinical efficacy has been found to be similar. Some other cholinesterase inhibitors are presently undergoing clinical evaluation and probably 2 to 3 additional agents will soon come into clinical use in the treatment of Alzheimer's disease.

It is reasonable to assume that cholinesterase inhibitors with few adverse effects and long half-lives, allowing once or twice daily administration, will be preferred in the future by the clinicians. So far, the different cholinesterase inhibitors appear rather consistent regarding effect size on cognitive measures. It has been noted that the degree of cholinesterase inhibition is not always directly correlated to the outcome treatment effect. The possibility of tolerance phenomena regarding cholinesterase inhibition following longer term treatment (i.e. in the order of years) has yet to be evaluated. Signs of upregulation of the acetylcholinesterase enzyme after long term cholinesterase inhibitor treatment have been observed in patients with Alzheimer's disease treated with tacrine (A. Nordberg, unpublished observations). The enhanced acetylcholinesterase activity in the CSF of patients with Alzheimer's disease after 12 months of tacrine treatment is supported by experimental data suggesting that exposure to cholinesterase inhibitors increases acetylcholinesterase gene expression.^{1100,1011}

Drug monitoring, including measurements of plasma levels and cholinesterase inhibition in blood and possibly the CSF, as well as the risk of drug interactions have to be further investigated. These factors may play an important role when choosing between cholinesterase inhibitors.

The prospects for new treatment strategies in Alzheimer's disease have brightened considerably during the recent years. Although existing therapy is still mainly considered as a symptomatic therapy with palliative effects on existing cognitive disturbances it might also have some effects on progression of the disease. Before a curative or preventive treatment strategy is available for Alzheimer's disease the development of cholinesterase inhibitors with optimal efficacy and tolerability must be encouraged.

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