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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011 Evento : 379 Actuación : 444

Referencia : Expediente No. 04039958
Asunto : REGISTRO - PATENTE PCT PHENYL-PIPERAZINE
DERIVATIVES AS SEROTONIN REUPTAKE
INHIBITORS
Solicitante : H. LUNDBECK A/S
Clase : A61K 031/044, A61K 31/4965, A61P 025/000, C07D
211/020, C07D 211/070, C07D 241/004, C07D 243/008, C07D 295/096

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. 857 notificado por fijación en lista del 25 de Enero de 2008.

2. Mediante el Oficio No. 857 se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la siguiente manera:

3. Evaluación de los requisitos de patentabilidad:

Su Despacho concluye que el nivel inventivo de las reivindicaciones 1 a 4 y la novedad de la reivindicación 5 de

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la presente solicitud de patente, se ven afectadas por el documento WO0149678 (D1).

3.1 Novedad.

Su Despacho enuncia:

"Como se observa, el elemento característico del compuesto reivindicado (reivindicación 5) era conocido en D1 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de novedad".

Con respecto a que el documento D1 afecta la novedad de la reivindicación 5 de la presente solicitud, mi representada desea respetuosamente señalar lo siguiente:

Todos los compuestos divulgados en la reivindicación 5 son compuestos fenilsulfanil, y en D1 ningún compuesto fenilsulfanil es revelado. Todos los compuestos específicamente descritos en D1 son compuestos fenoxi, por tanto D1 no afecta la novedad de la reivindicación 5 y esta objeción debe tenerse por superada.

3.2 Nivel inventivo.

Su Despacho enuncia:

" El experto en la materia, en vista del Estado de la Técnica en su totalidad, es decir en vista de D1, hubiera sugerido sin mucho esfuerzo de su parte, modificar los grupos característicos de los compuestos de las composiciones farmacéuticas de D1, y así lograr las composiciones farmacéuticas (caracterizadas por un compuesto de formula

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general I) reivindicadas que no parecen tener un efecto superior como inhibidores de la reabsorción de la serotonina".

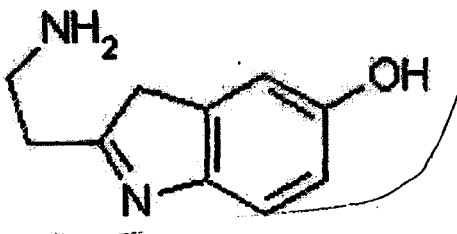
Con respecto a que el documento D1 afecta el nivel inventivo de las reivindicaciones 1 a 4 de la presente solicitud, mi representada respetuosamente no comparte la posición del examinador. Al respecto desea señalar lo siguiente:

La posición del Señor Examinador para objetar la falta de nivel inventivo de las reivindicaciones 1 a 4, es que es evidente para una persona versada en el tema remover un indol-alquil de los compuestos de D1 y por ende obtener los compuestos de la presente invención.

Sin embargo, partiendo de D1, una persona versada distinguiría que los compuestos divulgados en este son ligandos 5-HT1a. Igualmente notaría que **algunos** de los compuestos divulgados en D1 también exhiben actividad farmacológica adicional, por ejemplo la inhibición de reabsorción de serotonina y/o la actividad ligante de D3/D4. Adicionalmente, a partir de la tabla 1 que se muestra en D1 una persona versada se percataría de que ciertos compuestos fenoxi exhiben la inhibición de la reabsorción de serotonina. No obstante, a partir de este documento no se conoce nada sobre las propiedades de inhibición del transporte de serotonina de los compuestos fenilsulfanil.

Por tanto, no es evidente para una persona versada remover la fracción de indol con el fin de obtener los compuestos de la presente invención. Cualquier químico farmacéutico al observar la estructura de los compuestos en D1 asumiría que el indol es esencial para cualquier actividad de inhibición de la reabsorción de serotonina que los compuestos puedan presentar.

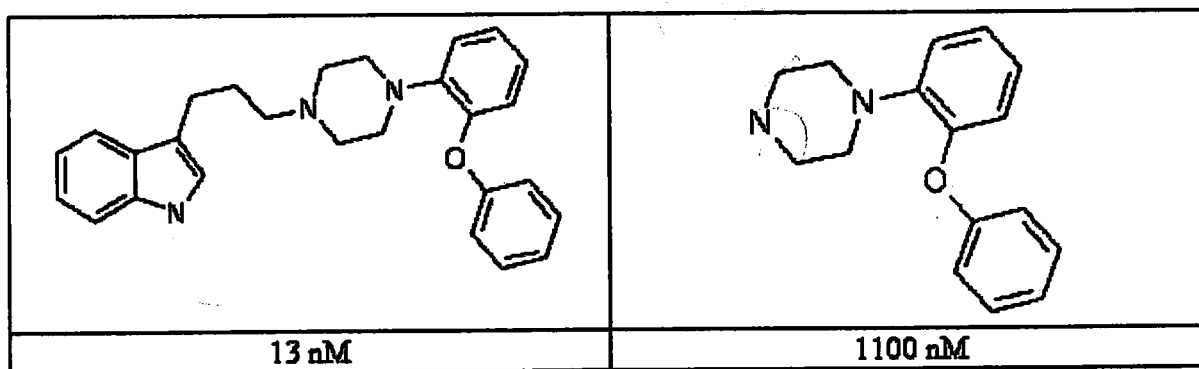
De hecho, la serotonina en sí es un derivado indol y un ligando transportador de serotonina.



Así entonces, estudiando los compuestos de D1 la persona versada en el tema asumiría que el grupo indol de las moléculas es responsable de que este se enlace (ligue) al transportador de serotonina. Adicionalmente a los argumentos anteriores, respetuosamente solicito al Señor Examinador tener en cuenta el estudio publicado por Matzen (*J.Med.Chem*, 43, 1149, 2000), el cual se encuentra anexo en el presente memorial, donde al grupo funcional indol y a un grupo funcional de anilina se les realizaron pruebas con el fin de medir su habilidad de inhibir la reabsorción de serotonina. El grupo indol por si solo es un inhibidor de la reabsorción de serotonina, mientras que la fracción de anilina no lo es. Las moléculas combinadas todavía presentan inhibidores de reabsorción de serotonina que permanecen en estas, a partir de lo cual la persona versada en la materia concluiría que el grupo indol es fundamental para la actividad de inhibición de la reabsorción de serotonina. Los autores del artículo que se encuentra anexo llegan a esta conclusión (página 1153).

Adicionalmente, en el ejemplo 5e del documento referenciado D1 se muestra un IC50 para el transportador de serotonina de 13 nM. En contraste, el compuesto correspondiente donde el grupo funcional

indolalquil ha sido removido tiene un IC50 de 1100 nM (con baja o ninguna actividad inhibitoria de reabsorción de serotonina).



Los datos anteriores claramente muestran que al remover el grupo indol de los compuestos D1 se podrían obtener compuestos sin actividad inhibitoria de la serotonina. Lo cual demuestra a partir de datos experimentales, que el grupo indol es fundamental para la inhibición de la reabsorción de la serotonina de una molécula.

Por lo tanto no se considera que para una persona versada en la materia correspondiente, los compuestos reivindicados con actividad inhibitoria de la reabsorción de serotonina en la presente invención, se deriven de manera evidente del documento referenciado en el estado de la técnica debido a que nada en el estado de la técnica o en D1 por si solo alentaría a la persona versada en el tema a sustituir el oxigeno en la fracción fenoxi por un azufre para obtener compuestos sulfanilfenil.

Por el contrario, es claro que el documento referenciado antes que tener una enseñanza o sugerencia que permitiera a un técnico medio obtener la presente invención, lo alejaría de la misma ya que la persona versada seria desalentada a remover el grupo indol

al asumir que esto seria perjudicial para la inhibición de reabsorción de serotonina.

Teniendo en cuenta los argumentos a favor del nivel inventivo se puede concluir que la presente invención es inventiva frente al documento D1 citado por su Despacho, porque la referencia citada no enseña los compuestos reivindicados en la presente solicitud y el estado del arte no dirige a una persona versada en el tema a cambiar las referencias de tal forma que se obtengan los compuestos reivindicados. Por consiguiente, no resulta obvia la invención y no se deriva de manera evidente del estado de la técnica ya que un técnico medio que realiza el examen debe partir del conocimiento general que se tiene sobre el estado de la técnica y determinar si con tales conocimientos técnicos ya existentes se puede producir tal invención y este no es el caso.

Por las anteriores razones, se debe tener por superadas las objeciones formuladas por novedad a la reivindicación 5 y por nivel inventivo a las reivindicaciones 1 - 4.

Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación.

6. Anexos:

- MATZEN Lisa, etal. 5-HT Reuptake Inhibitors with 5-HT_{1B/1D} Antagonistic Activity: A new Approach toward Efficient Antidepressants. J.Med.Chem, 43, páginas 1149-1157, 2000.

5-HT Reuptake Inhibitors with 5-HT_{1B/1D} Antagonistic Activity: A New Approach toward Efficient Antidepressants

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As part of our research program toward new, potential antidepressants, a series of unsymmetrical ureas has been prepared and evaluated as 5-HT reuptake inhibitors with 5-HT_{1B/1D} antagonistic activities. The design of these compounds was based on coupling of various indole derivatives, previously shown to inhibit 5-HT reuptake, to three different aniline moieties, which are part of known 5-HT_{1B/1D} ligands. Binding experiments in rat frontal cortex using [¹²⁵I]iodocyanopindolol, in calf striatum using [³H]5-HT, and in rat hippocampus using [³H]8-OH-DPAT as radioligands, respectively, revealed significantly higher affinity at the 5-HT_{1B} receptor as compared to the affinities for the 5-HT_{1A} and 5-HT_{1D} receptors for a number of compounds, among them 4-(5-fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide (**5**), the corresponding 4-fluoro-1*H*-indol-3-yl analogue **21a**, and the corresponding 6-fluoro-1*H*-indol-3-yl analogue **21b**. Conformational restriction of the aniline moiety in **5** only slightly enhanced the 5-HT_{1B} affinity, whereas introduction of an aniline moiety with higher conformational flexibility resulted in a less potent 5-HT_{1B} receptor ligand as compared to **5**. The functional 5-HT_{1B/1D} antagonistic activity was investigated using the rabbit saphenous vein model as well as the [³H]5-HT release from guinea pig cortical slices. All new compounds tested in the rabbit saphenous vein model were shown to antagonize the sumatriptan-evoked contractile responses with pA₂ values ranging from 7.3 to 8.7. These observations were consistent with the results of the cortical slice model, in which the ureas were found to block the sumatriptan-induced inhibition of potassium-evoked [³H]5-HT release. The 5-HT reuptake inhibition of the ureas determined in rat brain synaptosomes was found to be either increased or decreased as compared to the uncoupled indole derivatives indicating that the reuptake inhibition shown by the ureas is not only due to the indole part but also affected by the aniline moiety of the molecule. Among this series of compounds described the ureas **5**, **21a**, and **21b** seem to be the most interesting candidates showing both 5-HT reuptake inhibition and 5-HT_{1B/1D} antagonism in vitro. This dual pharmacological profile should in theory lead to a pronounced enhancement in serotonergic neurotransmission and consequently to a more efficient treatment of depression.

Introduction

Serotonin (5-HT, **1**; Chart 1), a biogenic amine neurotransmitter with diverse physiological actions in both the central and peripheral nervous systems, operates through various distinct membrane receptors.^{1–4} Disturbances in the central serotonin system have been associated with the pathogenesis of depression, and the antidepressant effect of the selective 5-HT reuptake inhibitors (SSRIs) is believed to be due to an enhancement of postsynaptic 5-HT levels.^{5–11} Although SSRIs are effective in the treatment of depression, clinical improvement is first obtained after several weeks. Thus, the delayed onset of therapeutic action of SSRIs needs to be improved.¹²

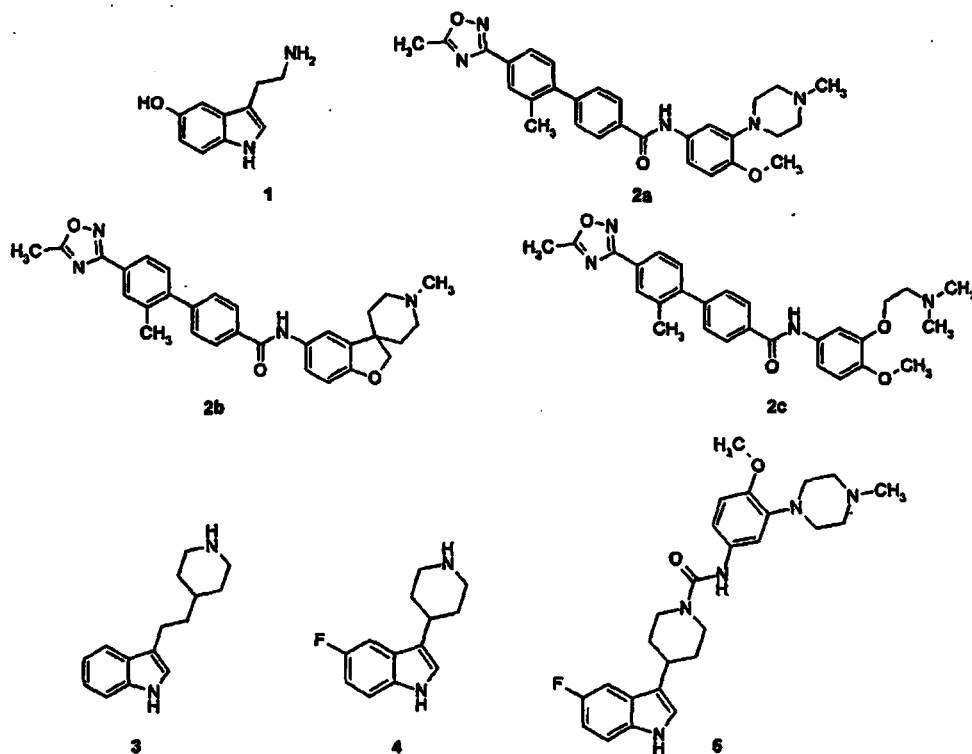
One of the hypotheses proposed to explain the delayed onset of the antidepressant action of SSRIs is the time required for desensitization of somatodendritic 5-HT_{1A} receptors and terminal 5-HT_{1B/1D} autoreceptors.^{8,9,11} The terminal 5-HT_{1B/1D} autoreceptors modulate the 5-HT release and are inhibitory such that agonists decrease

extracellular 5-HT.^{13,14} SSRIs lead to an increase in 5-HT levels, and the extracellular 5-HT counteracts the desired increase by activation of terminal 5-HT_{1B/1D} receptors resulting in a decreased 5-HT release. Thus, the therapeutic action of SSRIs is believed to set in after desensitization of the terminal 5-HT_{1B/1D} receptors. However, blockade of terminal 5-HT_{1B/1D} receptors by selective antagonists would in theory prevent the initial decrease in 5-HT release.^{12,15} It is therefore anticipated that coadministration of a SSRI and a 5-HT_{1B/1D} antagonist would lead to a potentiation of the SSRI effect and produce a large increase in extracellular 5-HT concentrations. As a consequence, the time of onset of therapeutic action would be diminished and the clinical efficacy in the treatment of depressive disorders improved.^{12,14} However the role of 5-HT_{1B/1D} receptors in depression is still not clear and needs further evaluation.

GR 127935 (**2a**; Chart 1) has been reported as the first example of a selective 5-HT_{1D/1B} antagonist.¹⁶ However, later investigations have shown that **2a** acts as a partial agonist at human 5-HT_{1B} and 5-HT_{1D} receptors.¹⁷

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Chart 1. Chemical Structures of Serotonin (1), the Partial 5-HT_{1B/1D} Agonist GR 127935 (2a), the Inverse 5-HT_{1B} Agonist 2b, the Partial 5-HT_{1B} Agonist 2c, the 5-HT Reuptake Inhibitors Indalpine (3) and 4, and the Lead Structure 5



Interestingly, two structurally closely related analogues of **2a**, **2b** and **2c** (Chart 1), have recently been identified as an inverse agonist and a partial agonist for the 5-HT_{1B} receptor, respectively, both with significant selectivity over the 5-HT_{1D} receptor.¹⁸

Microdialysis data published for 2a have been controversial. Thus, local perfusion of 2a into the guinea pig frontal cortex increased 5-HT levels whereas 5-HT levels were decreased after ip administration.¹⁹ In a microdialysis study performed by Rollema et al.,¹⁴ combined sc administration of 2a and the SSRI sertraline resulted in a pronounced, long-lasting increase in 5-HT levels in guinea pig hypothalamus indicating that 2a potentiates the effects of SSRIs on terminal 5-HT levels and enhances extracellular 5-HT concentration more effectively when 5-HT tone is increased.¹⁴ Instead of combining a SSRI with a 5-HT_{1B/1D} antagonist to potentiate the postsynaptic 5-HT level, our research program directed toward new, efficient, and fast-acting antidepressive drugs has aimed at compounds with a dual pharmacological profile showing both 5-HT reuptake inhibition and 5-HT_{1B/1D} antagonism within a single molecule.

Many compounds of various structures have been described as selective inhibitors of 5-HT reuptake, among them 3-(alkylpiperidin-4-yl)indoles (e.g. indalpine, **3**; Chart 1).²⁰ In connection with our previous work in the field of antidepressants we have identified a number of substituted 4-(indol-3-yl)piperidines such as **4** (Chart 1), which were shown to act as potent inhibitors of 5-HT reuptake.

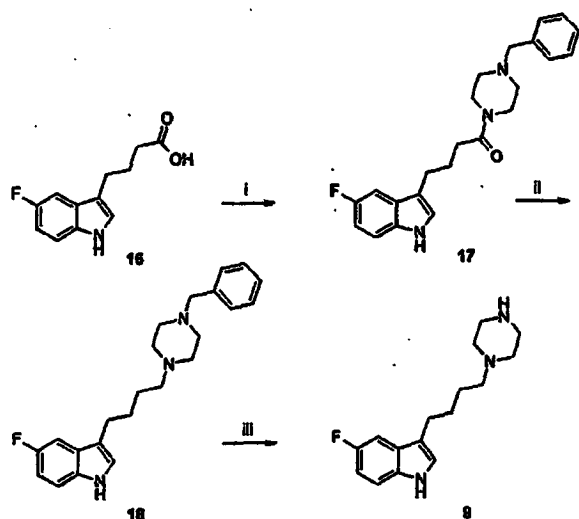
Aiming at compounds with a mixed pharmacological profile containing both 5-HT reuptake inhibition and

5-HT_{1B/1D} antagonistic properties, we have coupled structural moieties believed to induce 5-HT_{1B/1D} antagonism to the above-mentioned 4-(indol-3-yl)piperidines, inhibiting 5-HT reuptake. Coupling of 4-(5-fluoro-1*H*-indol-3-yl)piperidine (4) to the arylpiperazine moiety of 2a resulted in the urea 5 (Chart 1) which was found to inhibit [³H]5-HT uptake in rat brain synaptosomes and to have affinity for the 5-HT_{1B} receptor (Table 2). Using 5 as a lead structure this publication reports on the synthesis and the in vitro pharmacology of a series of new indole derivatives. Similar ureas have been reported earlier.³⁴ The pharmacological characterization includes binding studies at the 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1A} receptor sites – in rat frontal cortex using [¹²⁵I]-iodocyanopindolol, in calf striatum using [³H]5-HT, and in rat hippocampus using [³H]8-OH-DPAT as radioligands, respectively. [³H]5-HT release experiments in guinea pig cortex slices as well as the determination of the effect on sumatriptan-induced contractile responses in rabbit saphenous vein were performed to study the 5-HT_{1B/1D} antagonistic activity in vitro. The [³H]5-HT reuptake inhibition was determined in rat brain synaptosomes.

Results and Discussion

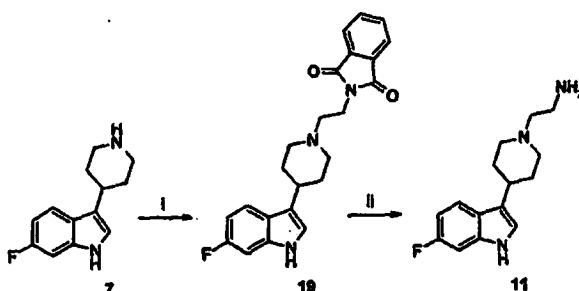
Chemistry. The 4-(indol-3-yl)piperidines (**4**, **6**, **7**, **13–15**) and the 3-(indol-3-yl)pyrrolidine (**10**) (Table 1) were obtained according to a published method by condensation of the respective indole with 1-benzyl-4-piperidone or 1-benzyl-3-pyrrolidone in alkaline medium, followed by hydrogenation and *N*-debenzylation.²¹ The carboline derivative **12**,²² indalpine (**3**),²⁰ and tryptamine (**8**)³² were prepared as described before.

Scheme 1^a



^a (i) 1-Benzylpiperazine, CDI; (ii) sodium bis(2-methoxyethoxy)-aluminum dihydride; (iii) H₂, Pd-C 5%.

Scheme 2^a



^a (i) N-(2-Bromoethyl)phthalimide; (ii) hydrazine hydrate.

The piperazine analogue 9 was prepared from 16²³ by acylation with 1-benzylpiperazine using 1,1'-carbonyldiimidazole (CDI) as a coupling reagent to give the amide 17 in 60% yield (Scheme 1). Reduction of the amide by treatment with sodium bis(2-methoxyethoxy)-aluminum dihydride resulted in 85% of 18, which was N-debenzylated to give 9 in 73% yield.

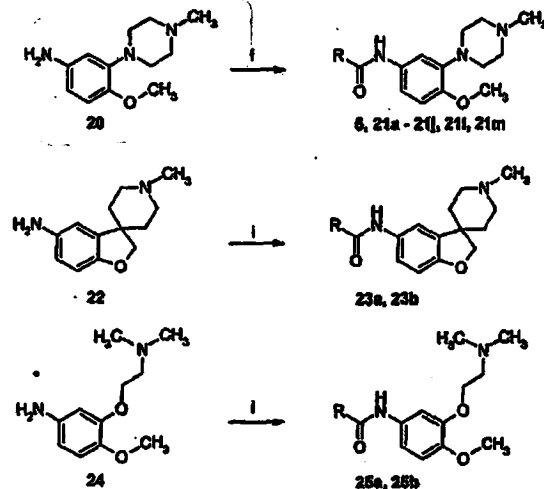
The piperidine analogue 11 was synthesized by alkylation of 7 with commercially available N-(2-bromoethyl)phthalimide to give 19 in 80% yield. Treatment of 19 with hydrazine resulted in 92% of 11 (Scheme 2).

The arylpiperazine moiety 20 of GR 127935 (2a)²⁴ as well as the conformationally restricted analogue 22¹⁸ and the aniline 24¹⁸ were synthesized as described before.

The unsymmetrical ureas 5, 21a–21j, 21m, 23a, 23b, 25a, and 25b were prepared by treatment of the anilines 20, 22, and 24, respectively, with CDI in the presence of triethylamine (TEA) to give an intermediate which upon addition of the respective indole (Table 1) gave the ureas in moderate to good yields (Scheme 3 and Table 2). Compound 21l was obtained after hydrogenation of the respective benzyl derivative 21k.

Biology. The binding affinities for the 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1A} receptor sites were determined in rat frontal cortex using [¹²⁵I]iodocyanopindolol,²⁵ in calf striatum using [³H]5-HT,²⁶ and in rat hippocampus using [³H]8-

Scheme 3^a



^a (i) (1) CDI, TEA, (2) 3–15 and 5-benzoyloxytryptamine, TEA.

Table 1. 5-HT RUI in Rat Brain Synaptosomes

Compd	Structure	5-HT RUI ^a IC ₅₀ (nM)	Compd	Structure	5-HT RUI ^a IC ₅₀ (nM)
3		1 ± 0.04	11		11 ± 2
4		55 ± 8	12		> 100
6		60 ± 6	13		68 ± 2
7		20 ± 0.3	14		60 ± 10
8		130 ± 4	16		> 100
9		0.15 ± 0.05	20		> 1000
			22		> 1000
10		45 ± 2	24		> 1000

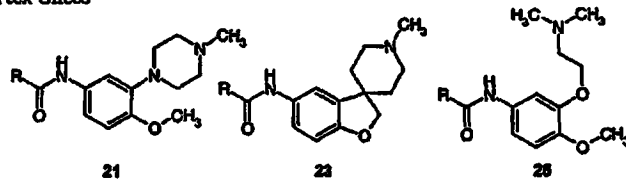
^a n = 2–3.

OH-DPAT²⁷ as radioligands, respectively (Table 2). The 5-HT_{1B/1D} antagonist potency was evaluated in vitro by measuring the effect on the sumatriptan-induced contractile response of rabbit saphenous vein (RSV)²⁸ and by determining the extent of antagonism against sumatriptan-induced inhibition of potassium-evoked [³H]5-HT release in slices of guinea pig cortex (Table 2).²⁹ The in vitro inhibitory effects of the new compounds on 5-HT reuptake were measured using rat brain synaptosomes (Tables 1 and 2).³⁰

Receptor Binding. The indole analogues 3–4 and 6–15 (Table 1) were inactive in the 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1A} receptor binding assays (results not shown). The affinities for the 5-HT_{1B} receptor of the ureas 5, 21a–21j, 21l, 21m, 23a, 23b, 25a, and 25b ranged from low to modest affinities, none of the new compounds being more potent than 2a and 2b (Table 2). In the series of

Matzen et al.

Table 2. Receptor Binding Affinities at 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1A} Receptors, 5-HT RUI in Rat Brain Synaptosomes, Inhibitory Activities on Sumatriptan-Induced Contractile Responses in RSV, and Antagonism of Sumatriptan-Induced Inhibition of K⁺-Evoked [³H]5-HT Release in Guinea Pig Cortex Slices



Compd	R	Receptor Binding IC ₅₀ (nM) ^a			5-HT RUI ^b IC ₅₀ (nM)	RSV app. pA ₅₀	Release ^c % (300 nM)
		5-HT _{1B}	5-HT _{1D}	5-HT _{1A}			
2a		63 ± 24	1.8 ± 0.7	360 ± 76	1000	8.4 ^c	114 ± 12
2b		>1000	2.1 ± 1.1	>1000	>1000	N.T.	134 ± 14
8		233 ± 33	86 ± 12	367 ± 67	21 ± 5	7.8	151 ± 18
21a		300 ± 0	60 ± 6	300 ± 68	65 ± 4	8.7	145 ± 36
21b		200 ± 0	80 ± 12	667 ± 145	49 ± 1	7.6	169 ± 8
21c		167 ± 33	63 ± 20	27 ± 9	367 ± 6	7.7	134 ± 36
21d		367 ± 67	77 ± 15	50 ± 10	0.7 ± 0.05	7.7	120 ± 15
21e		233 ± 33	233 ± 33	100 ± 0	106 ± 6	N.T.	N.T.
21f		200 ± 0	233 ± 33	160 ± 40	1.9 ± 0.3	N.T.	N.T.
21g		667 ± 120	667 ± 13	>800	469 ± 16	N.T.	N.T.
21h		400 ± 0	267 ± 88	233 ± 67	1.9 ± 0.08	8.0	167 ± 15
21i		233 ± 33	50 ± 12	400 ± 100	200 ± 11	7.7	127 ± 4
21j		200 ± 0	120 ± 40	>300	10 ± 10.8	7.7	121 ± 5
21l		200 ± 0	467 ± 33	57 ± 3	314 ± 54	N.T.	N.T.
21m		100 ± 0	113 ± 43	17 ± 3	472 ± 14	7.8	217 ± 18
23a		900	23 ± 3	>200	0.2 ± 0.05	7.3	125 ± 11
23b		900	300 ± 58	700 ± 115	2.2 ± 0.25	N.T.	N.T.
26a		>1000	633 ± 145	>500	4.0 ± 0.49	N.T.	N.T.
26b		433 ± 33	133 ± 33	233 ± 33	1.2 ± 0.2	N.T.	N.T.

^a n = 3–5. ^b n = 3–4. N.T. = not tested.

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ureas containing the arylpiperazine **20**, the compounds **5**, **21a–21d**, **21i**, **21j**, and **21m** were shown to have IC₅₀ values of 50–120 nM in the 5-HT_{1B} binding assay. The substitution pattern of the indole in **5**, **21a**, and **21b** did not seem to play a role in the 5-HT_{1B} affinity. However, replacement of the 5-fluoro substituent in **5** by a cyano group lowered the 5-HT_{1B} receptor affinity of **21h**, whereas replacement by a carboxamido group to give **21m** decreased selectivity versus the 5-HT_{1A} receptor. Replacement of the piperidine of **5** by pyrrolidine to give **21e** led to a decrease in 5-HT_{1B} affinity. A similar effect was observed upon conformational restriction of the 4-(5-fluoro-1*H*-indol-3-yl)piperidine ring system of **5** resulting in **21g**. Decreasing the conformational flexibility of the arylpiperazine moiety **20** did not change or only slightly improved the 5-HT_{1B} affinity (compare **21f/23b** and **5/23a**, respectively). Replacement of **20** by **24** resulted in a less potent 5-HT_{1B} ligand and a ligand with slightly higher 5-HT_{1B} affinity (compare **5/25a** and **21f/25b**, respectively). None of the compounds tested displayed significant affinity for the 5-HT_{1D} receptor. On the other hand, the tryptamines **21c** and **21i** as well as the piperazine **21d** and the piperidine **21m** turned out to be quite potent ligands for the 5-HT_{1A} receptor sites, although attempts to determine any agonistic or antagonistic activity of **21m** in a functional 5-HT_{1A} system³³ (data not shown) failed. The most promising compounds with both high affinity at the 5-HT_{1B} receptor and some selectivity over the 5-HT_{1A} and 5-HT_{1D} receptors were **5**, **21a**, **21b**, **21i**, **21j**, and **23a**.

Rabbit Saphenous Vein (RSV). The results of the RSV model are shown in Table 2. All ureas tested antagonized the contractile responses evoked by sumatriptan although with lower potency than **2a**. The level of 5-HT_{1B/1D} antagonistic activity displayed by the new compounds was shown to be modest but significant, the apparent pA₂ values ranging from 7.3 to 8.7. None of the new compounds showed intrinsic activity in this model, neither did **2a** nor **2b**.

[³H]5-HT Release Test. The results displayed in Table 2 demonstrate that all compounds tested in this model were able to antagonize the sumatriptan-induced inhibition of potassium-evoked [³H]5-HT release from guinea pig cortex slices. The fluoro analogues **5**, **21a**, and **21b**, the 5-cyano analogue **21h**, and the carboxamide analogue **21m** turned out to be the most potent antagonists enhancing the 5-HT release by 145–217% as compared to the release observed with sumatriptan in the absence of test compound. Interestingly, all ureas tested in the release model showed equal or better potency than the reference compounds **2a** and **2b**. The new compounds displayed no intrinsic activity on potassium-induced [³H]5-HT release in the absence of sumatriptan (results not shown), which is consistent with the results obtained from the RSV model.

[³H]5-HT Reuptake Inhibition (5-HT RUI). The results of the rat brain synaptosomes experiments are summarized in Tables 1 and 2. In the series of the substituted 4-(indol-3-yl)piperidines, **4**, **6**, **7**, **13**, **14**, and the pyrrolidine derivative **10** were equally potent in inhibiting the reuptake of 5-HT (Table 1). However, the carboxamido-substituted compound **15** as well as the anilines **20**, **22**, and **24** were found to be inactive in this test.

It is obvious from the results obtained that the distance between the indole moiety and the basic nitrogen atom is critical to the activity as a 5-HT reuptake inhibitor. Thus, the compounds **3** and **9** displayed improved 5-HT inhibitory activity as compared to the 3-(piperidin-4-yl)indoles. Conformational restriction of **4** resulted in a decrease of 5-HT reuptake inhibition, as demonstrated by **12**.

Coupling of the indole moieties **3**, **4**, and **6–15** to **20** led to an increased activity as 5-HT reuptake inhibitors for the compounds **5**, **21f**, and **21h** as compared to the corresponding indoles (Tables 1 and 2). In contrast, the compounds **21a–21c**, **21e**, **21i**, and **21j** were shown to be weaker 5-HT reuptake inhibitors than the corresponding indoles.

Compounds in which the arylpiperazine moiety **20** was replaced by **22** and **24**, respectively, displayed higher potency as compared to the uncoupled indoles (Tables 1 and 2). In addition, the compounds **23a** and **25a** turned out to be more potent 5-HT reuptake inhibitors than the analogue **5**, whereas **23b** and **25b** were equipotent to **21f**.

These observations indicate that the indole part of the molecule may not be sufficient to account for the 5-HT reuptake inhibition and that the mode of interaction of the indole part with the 5-HT reuptake site probably is modulated by the nature of the aniline moiety.

Conclusion

As mentioned in the Introduction coadministration of a SSRI and a 5-HT_{1B/1D} receptor antagonist should in theory immediately increase serotonergic neurotransmission avoiding the time required for desensitization of the terminal 5-HT_{1B/1D} autoreceptors and so decreasing the time of onset of antidepressive action. Instead of coadministration of two separate molecules to improve the delayed onset of therapeutic action, this new approach describes the development of a series of novel compounds with mixed pharmacological profiles showing both 5-HT reuptake inhibition and 5-HT_{1B/1D} receptor antagonism within a single molecule. The new compounds contain various indole moieties shown to inhibit 5-HT reuptake and the aniline part of **2a**, **2b**, and **2c** (**20**, **22**, and **24**, respectively) believed to introduce 5-HT_{1A/1D} receptor activity. Coupling of the indole moieties **3**, **4**, and **6–15** to the anilines **20**, **22**, and **24**, respectively, resulted in an increased or decreased 5-HT reuptake inhibition indicating that the 5-HT reuptake inhibitory activity is not only due to the indole part of the molecule but also modulated by the aniline moieties **20**, **22**, and **24**, although they were not inhibitory by themselves (Table 1). On the other hand, combination of the different indole moieties with the anilines **20**, **22**, and **24** diminished the activity in the 5-HT_{1B} binding assay in all cases as compared to **2a** and **2b**. However, the ureas **5**, **21a**, **21b**, **21i**, **21j**, and **23a** still maintained a significant affinity for the 5-HT_{1B} receptor and showed some selectivity versus the 5-HT_{1A} and 5-HT_{1D} receptors.

In the RSV test the new compounds inhibited the constrictor effects of sumatriptan indicating 5-HT_{1B/1D} receptor antagonistic properties. In guinea pig cortical slices all ureas tested were found to block the sumatriptan-induced inhibition of [³H]5-HT release.

The 5-HT_{1B} receptor binding affinities do not always correlate to the results obtained in the rabbit saphenous vein preparation and in the [³H]5-HT release model. The differences between the function of the 5-HT_{1B/1D} receptors in rat frontal cortex, rabbit saphenous vein, and guinea pig cortex still need to be evaluated. In addition the affinity to other 5-HT receptor subtypes such as 5-HT_{1F} and 5-HT₂ (not tested) could disturb the correlation of the results obtained in the functional models and the binding data.

Interestingly, the ureas antagonized the inhibition of [³H]5-HT release with equal or better potency than 2a or 2b, although having weaker affinity to the 5-HT_{1B} receptor. This may be due to the additional 5-HT reuptake inhibition of these compounds. The high potency of 21m in the release model may be due to the combination of 5-HT_{1B} and 5-HT_{1A} effects, but this still has to be evaluated further.

Among the new compounds presented the ureas 5, 21a, and 21b appear to be the most promising new 5-HT reuptake inhibitors with 5-HT_{1B/1D} antagonistic activity. To our knowledge, this is the first report describing compounds which contain these activities within a single molecule. Their mixed profile should facilitate serotonergic transmission, and their further pharmacological characterization will be of primary importance to evaluate the antidepressive potential of these novel compounds.

Experimental Section

Chemistry. General Procedures. Melting points were determined in capillary tubes and are uncorrected. Elemental analyses are within $\pm 0.4\%$ of the calculated values, unless otherwise stated. Analytical HPLC was conducted on a Li-Chrospher RP Select B column 5 μ m (4 mm i.d. $\times$ 250 mm) using a gradient of water (with 0.1% TFA) and acetonitrile (with 0.08% TFA) for elution, with UV monitoring at 220 nm. ¹H NMR spectra were recorded on a Bruker AMX 300 spectrometer at 300 MHz using DMSO-*d*₆ as solvent. Unless otherwise stated, chemical shift values (δ) are expressed in ppm relative to TMS. The following abbreviations are used for multiplicity of NMR signals: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet. Mass spectra were obtained on a VG-70 SE spectrometer from VG-Instruments to get molecular weight information ($(M + H)^+$) for FAB-MS and on a 70-70E spectrometer from VG-Instruments to get molecular weight information ($(M)^+$) for EI-MS. Drying of organic phases was performed using Na₂SO₄. Column chromatography (CC) and TLC were performed on silica gel 60 (70–230 mesh, Merck) and silica gel F₂₅₄ plates (Merck), respectively.

1-(4-Benzylpiperazin-1-yl)-4-(5-fluoro-1*H*-indol-3-yl)-butan-1-one (17). A solution of 4-(5-fluoro-1*H*-indol-3-yl)-butyric acid (16)²³ (20.0 g, 90.0 mmol) and carbonyldiimidazole (CDI) (14.6 g, 90 mmol) in THF (100 mL) was stirred for 1 h at room temperature. A solution of 1-benzylpiperazine (15.9 g, 90 mmol) in THF (50 mL) was added and stirring was continued for 12 h. The reaction mixture was evaporated to dryness, the residue was dissolved in EtOAc (100 mL), washed with H₂O (2 $\times$ 100 mL), dried and evaporated. CC [eluent: EtOAc] gave 17 (20.4 g, 60%): mp 85–87 °C; ¹H NMR (DMSO-*d*₆) δ 10.81 (s, 1 H), 7.28 (m, 7 H), 7.16 (d, 1 H, *J* = 2.2 Hz), 7.86 (dt, 1 H, *J* = 8.8 Hz and *J* = 1.3 Hz), 3.49 (s, 2 H), 3.42 (d, 4 H, *J* = 12.0 Hz), 2.65 (t, 2 H, *J* = 8.0 Hz), 2.31 (m, 6 H), 1.87 (quintet, 2 H, *J* = 6.8 Hz); EI-MS (M)⁺ *m/z* 380.

3-[4-(Benzylpiperazin-1-yl)butyl]-5-fluoro-1*H*-indole Dihydrochloride (18). To a solution of 17 (20.0 g, 53.0 mmol) in THF (350 mL) was added a 65% solution of sodium bis(2-methoxyethoxy)aluminum dihydride in toluene (43.0 mL, 132 mmol) dropwise at 5–10 °C in N₂ atmosphere. After stirring

for 4 h at room temperature H₂O (40 mL) was added. The reaction mixture was filtered, evaporated, dissolved in EtOAc (300 mL), washed with H₂O (2 $\times$ 200 mL), dried and evaporated. Dissolution of the residue in acetone and addition of 1 M HCl in EtOH resulted in a precipitate which was collected and dried to give 18 (23.2 g, 85%): mp 233–235 °C; ¹H NMR (DMSO-*d*₆) δ 10.90 (s, 1 H), 7.65 (br s, 2 H), 7.44 (br s, 3 H), 7.29 (m, 3 H), 6.86 (dt, 1 H, *J* = 8.8 Hz and *J* = 2.0 Hz), 4.37 (br s, 2 H), 3.79–3.30 (m, 8 H), 3.17 (br s, 2 H), 2.69 (t, 2 H, *J* = 6.6 Hz), 1.72 (m, 4 H); FAB-MS ($(M + H)^+$) *m/z* 366.

5-Fluoro-3-(4-piperazin-1-ylbutyl)-1*H*-indole Oxalate (9). A solution of 18 (19.7 g, 44.9 mmol) in MeOH (300 mL) was hydrogenated using Pd–C 5% (3.5 g) as catalyst. Filtration, evaporation and CC [eluent: CH₂Cl₂–MeOH (9:1)] gave an oily residue. Upon dissolution in acetone and addition of a solution of oxalic acid in acetone a precipitate formed. The precipitate was collected and dried to give 9 (12.0 g, 73%): mp 175–176 °C; ¹H NMR (DMSO-*d*₆) δ 10.84 (s, 1 H), 8.75 (br s, 1 H), 7.29 (dd, 1 H, *J* = 11.0 Hz and *J* = 2.4 Hz), 7.21 (dd, 1 H, *J* = 11.0 Hz and *J* = 2.2 Hz), 7.12 (d, 1 H, *J* = 1.5 Hz), 6.87 (dt, 1 H, *J* = 8.8 Hz and *J* = 2.0 Hz), 3.16 (m, 4 H), 2.78 (m, 4 H), 2.66 (t, 2 H, *J* = 6.6 Hz), 2.59 (t, 2 H, *J* = 6.6 Hz), 1.61 (m, 4 H); EI-MS (M)⁺ *m/z* 275.

2-[2-[4-(6-Fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethyl]-isoindole-1,3-dione Hydrobromide (19). A mixture of 4-(6-fluoro-1*H*-indol-3-yl)piperidine (7) (21.8 g, 100 mmol) and *N*-(2-bromoethyl)phthalimide (25.4 g, 100 mmol; purchased from Merck #820178) in 500 mL acetonitrile was stirred under reflux for 48 h. The crystalline precipitate formed was collected and dried to give 19 (33.2 g, 80%): ¹H NMR (DMSO-*d*₆) δ 10.81 (s, 1 H), 7.85 (d, 1 H, *J* = 8.8 Hz), 7.56 (m, 3 H), 7.33 (br s, 1 H), 7.06 (m, 2 H), 6.82 (t, 1 H, *J* = 8.7 Hz), 4.64 (br s, 1 H), 4.35 (t, 2 H, *J* = 7.5 Hz), 3.98 (t, 2 H, *J* = 7.5 Hz), 3.20–2.65 (m, 5 H), 1.68 (br s, 3 H); FAB-MS ($(M + H)^+$) *m/z* 393.

2-[4-(6-Fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethylamine (11). A mixture of 19 (33.2 g, 70 mmol) and hydrazine hydrate (5.0 mL, 100 mmol) in MeOH (500 mL) was stirred under reflux for 2 h. After cooling the reaction mixture was filtered and evaporated. Dissolution of the residue in 1 M NaOH (300 mL), extraction with EtOAc (3 $\times$ 300 mL), drying and evaporation gave 11 (16.8 g, 92%): mp 165–166 °C; ¹H NMR (DMSO-*d*₆) δ 10.91 (s, 1 H), 7.52 (dd, 1 H, *J* = 7.0 Hz and *J* = 3.5 Hz), 7.11 (m, 2 H), 6.82 (m, 1 H), 2.93 (d, 2 H, *J* = 13.7 Hz), 2.66 (t, 2 H, *J* = 7.0 Hz), 2.35 (t, 2 H, *J* = 7.0 Hz), 1.50–2.12 (m, 9 H); FAB-MS ($(M + H)^+$) *m/z* 262.

General Method for the Synthesis of Unsymmetrical Ureas. **4-(5-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide Hydrochloride Hydrate (5).** A solution of 4-methoxy-3-(4-methylpiperazin-1-yl)aniline dihydrochloride (20)²⁴ (2.7 g, 9.2 mmol), TEA (4.6 mL, 32.2 mmol) and CDI (1.6 g, 10.1 mmol) in acetonitrile (100 mL) was stirred at room temperature for 4 h. A suspension of 4-(5-fluoro-1*H*-indol-3-yl)piperidine (4) (2.0 g, 9.2 mmol) and TEA (1.3 mL, 9.2 mmol) in acetonitrile (100 mL) was added and stirring was continued for 12 h. The reaction mixture was evaporated to dryness, the residue was dissolved in EtOAc (100 mL), washed with H₂O (2 $\times$ 100 mL), dried and evaporated. The residue was dissolved in acetone (100 mL) and stirred with 1 M HCl. Collection of the precipitate followed by recrystallization (EtOH–Et₂O) gave 5 (2.2 g, 35%): mp 230–231 °C; ¹H NMR (DMSO-*d*₆) δ 11.18 (s, 1 H), 10.93 (s, 1 H), 8.35 (s, 1 H), 7.30 (d, 1 H, *J* = 9.0 Hz), 7.24 (d, 1 H, *J* = 10.0 Hz), 7.21 (d, 1 H, *J* = 2.1 Hz), 7.17 (1 H, s), 6.90 (d, 1 H, *J* = 9.0 Hz), 6.85 (d, 1 H, *J* = 10.0 Hz), 4.26 (d, 2 H, *J* = 12.0 Hz), 3.74 (s, 3 H), 3.55 (m, 4 H), 3.55–2.85 (m, 7 H), 2.78 (s, 3 H), 1.95 (d, 2 H, *J* = 12.1 Hz), 1.57 (m, 2 H); FAB-MS ($(M + H)^+$) *m/z* 466. Anal. (C₂₄H₂₂FN₅O₂·HCl·H₂O) C, H, N; Cl: calcd, 6.82%; found, 7.45%.

4-(4-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide Dihydrochloride (21a). Compound 21a was synthesized as described for 5 using 20²⁴ (1.2 g, 4.1 mmol), TEA (2.7 mL, 18.5 mmol), CDI (730 mg, 4.5 mmol) and 4-(4-fluoro-1*H*-indol-3-yl)piperidine (6) (895 mg, 4.1 mmol) in acetonitrile (75 mL).

172
150
179

CC [eluent: toluene-MeOH-TEA (7:2:1)] and preparation of the dihydrochloride followed by recrystallization (2-propanol-light petroleum) gave 21a (640 mg, 30%): mp 205 °C dec; ¹H NMR (DMSO-*d*₆) δ 11.68 (s, 1 H), 11.11 (s, 1 H), 8.33 (s, 1 H), 7.17 (m, 3 H), 7.05 (m, 1 H), 6.60 (d, 1 H, *J* = 8.8 Hz), 6.67 (dd, 1 H, *J* = 12.0 Hz and *J* = 9.0 Hz), 4.25 (d, 2 H, *J* = 12.0 Hz), 3.73 (s, 3 H), 3.45 (d, 4 H, *J* = 11.0 Hz), 3.39–2.85 (m, 7 H), 2.55 (s, 3 H), 1.96 (d, 2 H, *J* = 11.1 Hz), 1.57 (m, 2 H); FAB-MS (*M* + *H*)⁺ *m/z* 466. Anal. (C₂₈H₃₂FN₅O₂·2HCl) C, H, N; Cl: calcd, 13.17%; found, 12.30%.

4-(6-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide Dihydrate (21b). Compound 21b was synthesized as described for 5 using 20²⁴ (588 mg, 2.0 mmol), TEA (1.3 mL, 9 mmol), CDI (357 mg, 2.2 mmol) and 4-(6-fluoro-1*H*-indol-3-yl)piperidine (7) (437 mg, 2.0 mmol) in acetonitrile (50 mL). CC [eluent: toluene-MeOH-TEA (7:2:1)] followed by recrystallization (EtOAc-light petroleum) gave 21b (126 mg, 14%): mp 135–137 °C; ¹H NMR (DMSO-*d*₆) δ 10.85 (s, 1 H), 8.23 (s, 1 H), 7.55 (m, 1 H), 7.10 (m, 3 H), 7.03 (s, 1 H), 6.83 (d, 1 H, *J* = 8.3 Hz), 6.72 (d, 1 H, *J* = 9.0 Hz), 4.25 (d, 2 H, *J* = 12.1 Hz), 3.72 (s, 3 H), 2.92 (m, 7 H), 2.38 (br s, 4 H), 2.20 (s, 3 H), 1.92 (d, 2 H, *J* = 11.3 Hz), 1.57 (m, 2 H); FAB-MS (*M* + *H*)⁺ *m/z* 466. Anal. (C₂₈H₃₂FN₅O₂·2H₂O) C, H, N: calcd, 14.22%; found, 13.70%.

1-[2-(5-Fluoro-1*H*-indol-3-yl)ethyl]-3-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]urea Hemihydrate (21c). Compound 21c was synthesized as described for 5 using 20²⁴ (1.2 g, 4.1 mmol), TEA (3.3 mL, 22.6 mmol), CDI (730 mg, 4.5 mmol) and 5-fluorotryptamine hydrochloride (8)³² (880 mg, 4.1 mmol) in acetonitrile (75 mL). Recrystallization (EtOAc-light petroleum) gave 21c (1.27 g, 75%): mp 97–98 °C; ¹H NMR (DMSO-*d*₆) δ 10.91 (s, 1 H), 8.22 (s, 1 H), 7.32 (m, 2 H), 7.23 (d, 1 H, *J* = 2.2 Hz), 6.92 (m, 3 H), 6.75 (d, 1 H, *J* = 8.8 Hz), 5.95 (t, 1 H, *J* = 6.6 Hz), 3.69 (s, 3 H), 3.40 (t, 2 H, *J* = 6.6 Hz), 2.94 (br s, 4 H), 2.80 (t, 2 H, *J* = 6.6 Hz), 2.43 (br s, 4 H), 2.20 (s, 3 H); FAB-MS (*M* + *H*)⁺ *m/z* 426. Anal. (C₂₃H₂₈FN₅O₂·0.5H₂O) C, H, N: calcd, 16.12%; found, 14.28%.

4-[4-(5-Fluoro-1*H*-indol-3-yl)butyl]piperazine-1-carboxylic Acid [4-Methoxy-3-(4-methyl-1-piperazin-1-yl)phenyl]amide Dihydrochloride Hydrate (21d). Compound 21d was synthesized as described for 5 using 20²⁴ (1.2 g, 4.1 mmol), TEA (3.9 mL, 26.7 mmol), CDI (730 mg, 4.5 mmol) and 5-fluoro-3-(4-piperazin-1-yl)butyl-1*H*-indole oxalate (9) (1.5 g, 4.1 mmol) in acetonitrile (75 mL). Preparation of the dihydrochloride followed by recrystallization (EtOH-Et₂O) gave 21d (1.0 g, 42%): mp 220 °C dec; ¹H NMR (DMSO-*d*₆) δ 10.90 (s, 1 H), 8.59 (s, 1 H), 7.32 (m, 2 H), 7.25 (br s, 1 H), 7.14 (m, 2 H), 6.82 (d, 2 H, *J* = 8.2 Hz), 4.23 (br s, 6 H), 3.75 (s, 3 H), 3.46 (br, 2 H), 3.40–2.93 (m, 10 H), 2.81 (s, 3 H), 2.70 (t, 2 H, *J* = 5.1 Hz), 1.88–1.60 (m, 4 H); FAB-MS (*M* + *H*)⁺ *m/z* 523. Anal. (C₂₈H₃₈FN₆O₂·2HCl·H₂O) H, Cl; C: calcd, 56.76%; found, 56.24%; N: calcd, 13.96%; found, 13.13%.

3-(5-Fluoro-1*H*-indol-3-yl)pyrrolidine-1-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide (21e). Compound 21e was synthesized as described for 5 using 20²⁴ (1.2 g, 4.1 mmol), TEA (3.3 mL, 23.1 mmol), CDI (730 mg, 4.5 mmol) and (*R,S*)-3-(5-fluoro-1*H*-indol-3-yl)pyrrolidine (10) (987 mg, 4.1 mmol) in acetonitrile (75 mL). CC [eluent: EtOAc-MeOH-TEA (5:2:1)] followed by recrystallization (EtOAc-light petroleum) gave 21e (1.0 g, 30%): mp 210–213 °C; ¹H NMR (DMSO-*d*₆) δ 10.97 (s, 1 H), 7.88 (s, 1 H), 7.35 (m, 2 H), 7.28 (d, 1 H, *J* = 2.2 Hz), 7.14 (m, 2 H), 6.91 (dt, 1 H, *J* = 8.8 Hz and *J* = 2.2 Hz), 6.76 (d, 1 H, *J* = 8.8 Hz), 3.93 (t, 1 H, *J* = 6.6 Hz), 3.73 (s, 3 H), 3.62 (m, 2 H), 3.55–3.25 (m, 2 H), 2.93 (br s, 4 H), 2.45 (br s, 4 H), 2.30 (m, 1 H), 2.23 (s, 3 H), 2.10 (m, 1 H); FAB-MS (*M* + *H*)⁺ *m/z* 452. Anal. (C₂₅H₃₀FN₅O₂) C, H, N.

1-[2-[4-(6-Fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethyl]-3-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]urea Dihydrochloride Hydrate (21f). Compound 21f was synthesized as described for 5 using 20²⁴ (1.2 g, 4.1 mmol), TEA (2.7 mL, 18.6 mmol), CDI (730 mg, 4.5 mmol) and 2-[4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethylamine (11) (1.1 g, 4.1 mmol) in

acetonitrile (75 mL). Collection of the precipitate, dissolution in acetone and preparation of the dihydrochloride gave 21f (1.5 g, 61%): mp 189–192 °C; ¹H NMR (DMSO-*d*₆) δ 10.82 (s, 1 H), 8.39 (s, 1 H), 7.52 (t, 1 H, *J* = 6.6 Hz), 7.10 (d, 1 H, *J* = 8.8 Hz), 7.05 (s, 1 H), 6.98 (s, 1 H), 6.92 (d, 1 H, *J* = 8.8 Hz), 6.75 (m, 2 H), 5.93 (br s, 1 H), 3.70 (s, 3 H), 3.29 (br s, 2 H), 3.22 (m, 2 H), 2.95 (br s, 6 H), 2.74 (m, 1 H), 2.44 (br s, 4 H), 2.21 (s, 3 H), 2.12 (t, 2 H, *J* = 9.3 Hz), 1.95 (m, 2 H), 1.72 (m, 2 H); FAB-MS (*M* + *H*)⁺ *m/z* 509. Anal. (C₂₈H₃₇FN₆O₂·2HCl·H₂O) C, H, Cl; N: calcd, 14.02%; found, 13.35%.

8-Fluoro-1,3,4,5-tetrahydropyrido[4,3-*b*]indole-2-carboxylic Acid [4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide (21g). Compound 21g was synthesized as described for 5 using 20²⁴ (1.2 g, 4.1 mmol), TEA (2.7 mL, 18.5 mmol), CDI (730 mg, 4.5 mmol) and 8-fluoro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (12)²² (780 mg, 4.1 mmol) in acetonitrile (75 mL). CC [eluent: EtOAc-MeOH-TEA (5:2:1)] followed by recrystallization (EtOAc) gave 21g (1.1 g, 61%): mp 243–245 °C; ¹H NMR (DMSO-*d*₆) δ 10.97 (s, 1 H), 8.60 (s, 1 H), 7.28 (dd, 1 H, *J* = 8.5 Hz and *H* = 4.4 Hz), 7.09 (m, 3 H), 6.86 (dt, 1 H, *J* = 8.8 Hz and *J* = 2.2 Hz), 6.77 (d, 1 H, *J* = 8.8 Hz), 4.60 (s, 2 H), 3.81 (t, 2 H, *J* = 6.6 Hz), 3.73 (s, 3 H), 2.95 (br s, 4 H), 2.64 (m, 2 H), 2.45 (br s, 4 H), 2.23 (s, 3 H); FAB-MS (*M* + *H*)⁺ *m/z* 438. Anal. (C₂₄H₂₈FN₅O₂) C, H, N.

4-(5-Cyano-1*H*-indol-3-yl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide-0.25H₂O (21h). Compound 21h was synthesized as described for 5 using 20²⁴ (647 mg, 2.2 mmol), TEA (1.4 mL, 9.9 mmol), CDI (392 mg, 2.4 mmol) and 4-(5-cyano-1*H*-indol-3-yl)piperidine (13) (496 mg, 2.2 mmol) in acetonitrile (50 mL). CC [eluent: toluene-MeOH-TEA (7:2:1)] followed by recrystallization (acetonitrile-Et₂O) gave 21h (100 mg, 10%): mp 194–196 °C; ¹H NMR (DMSO-*d*₆) δ 11.44 (s, 1 H), 8.23 (s, 1 H), 8.15 (s, 1 H), 7.49 (d, 1 H, *J* = 8.8 Hz), 7.38 (d, 1 H, *J* = 8.8 Hz), 7.33 (br s, 1 H), 7.05 (m, 2 H), 6.72 (d, 1 H, *J* = 9.0 Hz), 4.26 (d, 2 H, *J* = 12.5 Hz), 3.70 (s, 3 H), 3.32 (m, 3 H), 2.95 (m, 8 H), 2.20 (s, 3 H), 1.97 (m, 2 H), 1.55 (m, 2 H); FAB-MS (*M* + *H*)⁺ *m/z* 489. Anal. (C₂₇H₃₂N₆O₂·0.25H₂O) C, H, N: calcd, 17.62%; found, 17.09%.

4-(3-Indolyl)-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide Dihydrochloride (21i). Compound 21i was synthesized as described for 5 using 20²⁴ (1.8 g, 6.1 mmol), TEA (4.0 mL, 27.5 mmol), CDI (1.1 g, 6.7 mmol) and 4-(1*H*-indol-3-yl)piperidine (14) (1.2 g, 4.1 mmol) in acetonitrile (100 mL). CC [eluent: EtOAc-MeOH-TEA (5:2:1)] followed by preparation of the dihydrochloride gave 21i (1.4 g, 44%): mp 203–205 °C; ¹H NMR (DMSO-*d*₆) δ 10.79 (s, 1 H), 8.35 (s, 1 H), 7.57 (d, 1 H, *J* = 8.8 Hz), 7.29 (d, 1 H, *J* = 8.8 Hz), 7.18 (m, 2 H), 7.11 (d, 1 H, *J* = 3.0 Hz), 7.06 (t, 1 H, *J* = 8.2 Hz), 6.97 (t, 1 H, *J* = 89.2 Hz), 6.85 (d, 1 H, *J* = 8.8 Hz), 4.24 (d, 2 H, *J* = 13.2 Hz), 3.75 (s, 3 H), 3.44 (d, 4 H, *J* = 13.2 Hz), 3.17 (q, 2 H, *J* = 9.0 Hz), 2.99 (m, 5 H), 2.75 (s, 3 H), 1.99 (d, 2 H, 13.2 Hz), 1.59 (m, 2 H); FAB-MS (*M* + *H*)⁺ *m/z* 448. Anal. (C₂₆H₃₃N₅O₂·2HCl) C, H, N; Cl: calcd, 13.45%; found, 12.34%.

4-[2-(3-Indolyl)ethyl]-*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]piperidine-1-carboxamide (21j). Compound 21j was synthesized as described for 5 using 20²⁴ (588 mg, 2.0 mmol), TEA (1.3 mL, 9.0 mmol), CDI (357 mg, 2.2 mmol) and indalpine (3)²⁰ (457 mg, 2.0 mmol) in acetonitrile (50 mL). Recrystallization (acetonitrile) gave 21j (700 mg, 76%): mp 200–202 °C; ¹H NMR (DMSO-*d*₆) δ 10.68 (s, 1 H), 8.16 (s, 1 H), 7.50 (d, 1 H, *J* = 7.7 Hz), 7.33 (d, 1 H, *J* = 7.7 Hz), 7.07 (m, 4 H), 6.95 (t, 1 H, *J* = 7.8 Hz), 6.76 (d, 1 H, *J* = 8.8 Hz), 4.09 (d, 2 H, *J* = 13.2 Hz), 3.71 (s, 3 H), 2.94 (br s, 4 H), 2.74 (m, 4 H), 2.45 (br s, 4 H), 2.20 (s, 3 H), 1.76 (d, 2 H, *J* = 13.2 Hz), 1.67 (m, 2 H), 1.50 (m, 1 H), 1.10 (m, 2 H); FAB-MS (*M* + *H*)⁺ *m/z* 476. Anal. (C₂₈H₃₇N₆O₂) C, H, N: calcd, 14.72%; found, 15.35%.

1-(2-(5-Benzyloxy-1*H*-indol-3-yl)ethyl)-3-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]urea-0.25H₂O (21k). Compound 21k was synthesized as described for 5 using 20²⁴ (1.8 g, 6.1 mmol), TEA (4.9 mL, 33.6 mmol), CDI (1.1 g, 6.7 mmol) and 5-benzyloxytryptamine (1.8 g, 6.1 mmol) in acetonitrile

(100 mL). CC [eluent: toluene-MeOH-TEA (7:2:1)] followed by recrystallization (EtOAc-light petroleum) gave 21k (2.4 g, 77%); mp 153–154 °C; ^1H NMR (DMSO- d_6) δ 10.70 (s, 1 H), 8.24 (s, 1 H), 7.42 (m, 2 H), 7.38 (t, 2 H, $J = 6.0$ Hz), 7.30 (t, 1 H, $J = 6.1$ Hz), 7.20 (d, 1 H, $J = 9.0$ Hz), 7.15 (s, 1 H), 7.09 (s, 1 H), 6.99 (s, 1 H), 6.86 (d, 1 H, $J = 8.8$ Hz), 6.75 (m, 2 H), 5.92 (t, 1 H, $J = 5.0$ Hz), 5.05 (s, 2 H), 3.67 (s, 3 H), 3.42 (m, 3 H), 2.91 (s, 4 H), 2.80 (t, 2 H, $J = 7.0$ Hz), 2.39 (br s, 3 H), 2.15 (s, 3 H); MS (M^+) m/z 513. Anal. ($\text{C}_{30}\text{H}_{33}\text{N}_5\text{O}_3 \cdot 0.25\text{H}_2\text{O}$) C, H, N.

1-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-3-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]urea Hemihydrate (21l). A solution of 21k (1.1 g, 21 mmol) in MeOH (100 mL) was hydrogenated using Pd-C 5% (1.0 g) as catalyst. Filtration, CC [EtOAc-MeOH-TEA (5:2:1)] gave 21l (200 mg, 25%); mp 140–142 °C; ^1H NMR (DMSO- d_6) δ 10.46 (s, 1 H), 8.55 (s, 1 H), 8.19 (s, 1 H), 7.12 (d, 1 H, $J = 8.8$ Hz), 7.05 (d, 1 H, $J = 3.0$ Hz), 6.97 (d, 1 H, $J = 3.0$ Hz), 6.91 (dd, 1 H, $J = 8.9$ Hz and $J = 3.1$ Hz), 6.87 (d, 1 H, $J = 3.0$ Hz), 6.78 (d, 1 H, $J = 8.9$ Hz), 6.57 (dd, 1 H, $J = 8.7$ Hz and $J = 3.3$ Hz), 5.93 (t, 1 H, $J = 6.6$ Hz), 3.70 (s, 3 H), 3.43 (d, 4 H, $J = 13.2$ Hz), 2.91 (br s, 4 H), 2.75 (t, 2 H, $J = 6.7$ Hz), 2.40 (m, 2 H), 2.25 (s, 3 H); FAB-MS ($(M + H)^+$) m/z 424. Anal. ($\text{C}_{23}\text{H}_{28}\text{N}_5\text{O}_3 \cdot 0.5\text{H}_2\text{O}$) C, H, N: calcd, 6.99%; found, 8.19%. N: calcd, 16.19%; found, 15.37%.

3-[1-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenylamino]carbonyl]-4-piperidyl]indole-5-carboxamide Hydrate (21m). Compound 21m was synthesized as described for 5 using 20²¹ (1.2 g, 4.1 mmol), TEA (2.7 mL, 18.5 mmol), CDI (730 mg, 4.5 mmol) and 4-(5-carboxamido-1*H*-indol-3-yl)-piperidine monohydrate (15) (1.1 g, 4.1 mmol) in acetonitrile (75 mL). CC [eluent: toluene-MeOH-TEA (7:2:1)] followed by recrystallization (acetonitrile) gave 21m (241 mg, 12%); mp 179 °C dec; ^1H NMR (DMSO- d_6) δ 11.00 (s, 1 H), 8.29 (s, 1 H), 8.22 (s, 1 H), 7.80 (br s, 1 H), 7.63 (d, 1 H, $J = 8.8$ Hz), 7.33 (d, 1 H, $J = 8.8$ Hz), 7.20 (d, 1 H, $J = 2.2$ Hz), 7.11 (m, 2 H), 7.02 (br s, 1 H), 6.79 (d, 1 H, $J = 8.8$ Hz), 4.26 (d, 2 H, $J = 12.8$ Hz), 3.72 (s, 3 H), 3.05 (m, 7 H), 2.66 (br s, 4 H), 2.35 (s, 3 H), 2.03 (d, 2 H, $J = 13.0$ Hz), 1.60 (m, 2 H); FAB-MS ($(M + H)^+$) m/z 491. Anal. ($\text{C}_{27}\text{H}_{34}\text{N}_6\text{O}_3 \cdot \text{H}_2\text{O}$) C, H, N.

4-(5-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid [2,3-Dihydro-1'-methylspiro(benzofuran-3,4'-piperidine)]-amide Hemihydrate (23a). Compound 23a was synthesized as described for 5 using 5-amino-2,3-dihydro-1'-methylspiro(benzofuran-3,4'-piperidine) (22)¹⁸ (300 mg, 1.4 mmol), TEA (0.5 mL, 3.5 mmol), CDI (243 mg, 1.5 mmol) and 4-(5-fluoro-1*H*-indol-3-yl)piperidine (4) (306 mg, 1.4 mmol) in acetonitrile (50 mL). CC [toluene-MeOH-TEA (7:2:1)] followed by recrystallization (EE-light petroleum) gave 23a (300 mg, 47%); mp 213–215 °C; ^1H NMR (DMSO- d_6) δ 10.85 (s, 1 H), 8.27 (s, 1 H), 7.32 (dd, 1 H, $J = 9.7$ Hz and $J = 2.2$ Hz), 7.25 (d, 1 H, $J = 2.2$ Hz), 7.19 (dd, 1 H, $J = 9.7$ Hz and $J = 2.2$ Hz), 7.13 (m, 2 H), 6.81 (dt, 1 H, $J = 9.8$ Hz and $J = 2.2$ Hz), 6.62 (d, 1 H, $J = 8.8$ Hz), 4.55 (s, 2 H), 4.44 (d, 2 H, $J = 11.9$ Hz), 2.97 (m, 3 H), 2.73 (d, 2 H, $J = 11.9$ Hz), 2.42 (s, 3 H), 1.95 (m, 4 H), 1.80 (dt, 2 H, $J = 12.5$ Hz and $J = 4.4$ Hz), 1.60 (m, 4 H); FAB-MS ($(M + H)^+$) m/z 463. Anal. ($\text{C}_{27}\text{H}_{31}\text{FN}_4\text{O}_2 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

1-[2-[4-(6-Fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethyl]-[2,3-dihydro-1'-methylspiro(benzofuran-3,4'-piperidine)]-amide (23b). Compound 23b was synthesized as described for 5 using 22¹⁸ (349 mg, 1.6 mmol), TEA (0.58 mL, 4.0 mmol), CDI (292 mg, 1.8 mmol) and 2-[4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethylamine (11) (418 mg, 1.6 mmol) in acetonitrile (50 mL). Recrystallization (EE-light petroleum) gave 23b (170 mg, 21%); mp 237–239 °C; ^1H NMR (DMSO- d_6) δ 10.30 (s, 1 H), 8.37 (s, 1 H), 7.52 (dd, 1 H, $J = 8.8$ Hz and $J = 4.4$ Hz), 7.23 (d, 1 H, $J = 3.0$ Hz), 7.07 (m, 3 H), 6.80 (dt, 1 H, $J = 8.7$ Hz and $J = 3.0$ Hz), 6.60 (d, 1 H, $J = 8.9$ Hz), 5.91 (t, 1 H, $J = 7.0$ Hz), 4.29 (s, 2 H), 3.21 (m, 2 H), 2.99 (d, 2 H, $J = 11.0$ Hz), 2.69 (d, 3 H, $J = 10.09$ Hz), 2.43 (t, 2 H, $J = 6.6$ Hz), 2.17 (s, 3 H), 2.11 (m, 2 H), 1.98–1.55 (m, 10 H); FAB-MS ($(M + H)^+$) m/z 506. Anal. ($\text{C}_{28}\text{H}_{36}\text{FN}_5\text{O}_2$) C, H, N.

4-(5-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid

[3-(2-(Dimethylamino)ethoxy)-4-methoxyphenyl]amide Hydrochloride (25a). Compound 25a was synthesized as described for 5 using 3-(2-(dimethylamino)ethoxy)-4-methoxyaniline (24)¹⁸ (631 mg, 3.0 mmol), TEA (1.1 mL, 8.0 mmol), CDI (535 mg, 3.3 mmol) and 4-(5-fluoro-1*H*-indol-3-yl)piperidine (4) (655 mg, 3.0 mmol) in acetonitrile (75 mL). CC [eluent: EtOAc-MeOH-TEA (5:2:1)] and preparation of the dihydrochloride gave 25a (900 mg, 61%); mp 210–211 °C; ^1H NMR (DMSO- d_6) δ 10.90 (s, 1 H), 8.41 (s, 1 H), 7.33 (m, 2 H), 7.19 (d, 1 H, $J = 2.2$ Hz), 7.08 (dd, 1 H, $J = 11.0$ Hz and $J = 2.2$ Hz), 6.90 (m, 3 H), 4.30 (m, 4 H), 3.75 (s, 3 H), 3.49 (t, 2 H, $J = 5.3$ Hz), 3.02 (m, 3 H), 2.90 (6 H, s), 1.95 (d, 2 H, $J = 11.9$ Hz), 1.55 (m, 2 H); FAB-MS ($(M + H)^+$) m/z 455. Anal. ($\text{C}_{25}\text{H}_{31}\text{N}_4\text{O}_3 \cdot \text{HCl}$) C, H, Cl: calcd, 7.22%; found, 7.88%. N: calcd, 11.41%; found, 11.88%.

1-[3-(2-(Dimethylamino)ethoxy)-4-methoxyphenyl]-3-[2-[4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethyl]urea Dihydrochloride Hydrate (25b). Compound 25b was synthesized as described for 5 using 24¹⁸ (631 mg, 3.0 mmol), TEA (1.1 mL, 8.0 mmol), CDI (535 mg, 3.3 mmol) and 2-[4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethylamine (11)²⁴ (758 mg, 2.9 mmol) in acetonitrile (75 mL). CC [eluent: EE-MeOH-TEA (5:2:1)] followed by preparation of the dihydrochloride gave 25b (850 mg, 52%); mp 130–131 °C; ^1H NMR (DMSO- d_6) δ 10.95 (s, 1 H), 8.91 (s, 1 H), 7.68 (m, 1 H), 7.50 (d, 1 H, $J = 2.2$ Hz), 7.14 (2H, m), 6.45–7.00 (4 H, m), 4.42 (t, 2 H, $J = 6.0$ Hz), 3.75 (s, 3 H), 3.70–3.40 (m, 6 H), 2.76 (m, 5 H), 2.82 (6H, s), 2.12 (br s, 4 H); FAB-MS ($(M + H)^+$) m/z 498. Anal. ($\text{C}_{27}\text{H}_{32}\text{N}_6\text{O}_3 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$) C, H, Cl, N.

Receptor Binding Assays. Affinities for 5-HT_{1B} receptors were determined in rat frontal cortex using [¹²⁵I]iodocyanopindolol as radioligand, final concentration 0.1 nM.²⁵ The 5-HT_{1D} assays were performed according to Peroutka et al.²⁶ using membranes prepared from calf striatum and 1.7 nM [³H]-serotonin in the presence of 100 nM 8-OH-DPAT and 100 nM mesulergine to mask 5-HT_{1A} and 5-HT_{2C} binding sites. Non-specific binding was determined in the presence of 10 μM serotonin. Inhibition by drugs of the binding of 0.5 nM [³H]-8-OH-DPAT to 5-HT_{1A} receptors in membranes from rat hippocampus was determined according to the reported method.²⁷

Rabbit Saphenous Vein (RSV). The inhibition of the contractile responses elicited by sumatriptan in rabbit saphenous vein was determined according to a published method.²⁸ For determining of 5-HT_{1B/1D} antagonistic activity, segments of isolated rabbit saphenous veins were suspended in organ baths and subjected to two concentration-response curves to sumatriptan, the second challenge being performed in the presence of the antagonist or control vehicle (incubated for 60 min). Apparent pA_2 values were calculated using a single antagonist concentration in at least 3 preparations.

[³H]5-HT Release. The effect on the sumatriptan-induced inhibition of potassium-evoked [³H]5-HT release from guinea pig cortex slices was determined according to a method published by Ormandy.²⁹ Cerebral cortices were removed from male Dunkin-Hartley guinea pigs, cross-chopped into slices, and then incubated 30 min with [³H]5-HT. Slices were placed into chambers of a superfusion apparatus and superfused with oxygenated Krebs's solution. Superfusate was collected in 4-min periods beginning 60 min after the slices were placed in the chambers. The slices were exposed to two periods (4 min) of 30 mM K⁺ at 68- and 108-min superfusion (S1 and S2, respectively). Sumatriptan at a concentration of 3 μM (controls) and sumatriptan plus test compounds (30 nM, 300 nM, and 3 μM , respectively) were superfused prior to and during the S2 stimulation period. Released radioactivity in each sample was measured, and after basal release was subtracted, the S2/S1 ratio was calculated. Results represent the mean ($\pm$ SEM) of 3–4 determinations. The effects of drugs were expressed as a percent of control, i.e. purely sumatriptan perfused S2/S1 ratio.

[³H]5-HT Reuptake Inhibition. Crude synaptosomal fraction (P₂ fraction) of rat cerebral tissue was prepared according to Whittaker³¹ giving a suspension enriched in synaptosomes of 3 mg protein/mL. The synaptosomal uptake was performed

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LXI
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5-HT Reuptake Inhibitors with 5-HT_{1B/1D} Activity

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in a total volume of 570 μ L, which contained 12 nM [^{3} H]5-HT. Incubation was performed at 37 $^{\circ}$ C for 4 min in Krebs-Ringer buffer (126 mM NaCl, 1.4 mM MgCl₂, 4.8 mM KCl, 15.8 mM Na₂HPO₄, 11 mM glucose, 0.9 mM CaCl₂, pH 7.4, 346 mOsm).³⁰

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HT_{1A} receptors (40 µg of cell homogenate) were incubated for 15 minutes at 37 °C in 50 mM Tris buffer at pH 7.7 in the presence of ³H-5-CT. Non-specific binding was determined by including 10 µM of metergoline. The reaction was terminated by rapid filtration through Unifilter GF/B filters on a Tomtec Cell Harvester. Filters were counted in a Packard Top 5 Counter. The results obtained are presented in table 1 below.

Inhibition of ³H-5-HT Uptake Into Rat Brain Synaptosomes

- 10 Using this method, the ability of drugs to inhibit the accumulation of ³H-5-HT into whole rat brain synaptosomes is determined *in vitro*. The assay was performed as described by Hyttel, J., *Psychopharmacology* 1978, 60, 13. The results obtained are presented in table 1:

Table 1:

Compound No.	column 1 Inhibition of ³ H-5-CT Binding IC ₅₀ (nM)	column 2 Inhibition of ³ H-5-HT Uptake IC ₅₀ (nM)
1b	7.8	130
2b	16	2.8
3c	16	27% inhibition at 100nM
3e	24	40% inhibition at 100 nM
5a	19	14
5e	10	13
5f	10	4.8
5h	10	55% inhibition at 100nM
5i	10	46 % inhibition at 100nM
5l	13	4.7
5x	18	33
5ae	26	42% inhibition at 100nM
5ag	26	23
5ai	28	34% inhibition at 100nM

153 176
154

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

Radicación No. 04039958

**Clasificación Internacional(IPC): A61K31/44, A61K31/4965, A61P25/00
,C07D295/06, C07D241/04, C07D243/08, C07D211/20, C07D211/70.**

Patente de Invención

☒

Patente de Modelo de Utilidad

☐

Vía Nacional

☐

Vía PCT (fase nacional)

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Cap.I

☐

Cap. II

☒

No. Sol. Internacional

PCT/DK02/010659

Fecha de Presentación Internal.

02 de Octubre de 2002

Como resultado del examen definitivo, realizado con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción:

Folios: 34 a 64 como se radicó inicialmente.

1.2. Reivindicaciones:

Folios: 65 a 68 como se radicó inicialmente

Folios : 120 a 122 (Modificado.)

1.3. Prioridad:

Folio : 2 (04 de Octubre de 2001,DK PA2001 01466).

1.4. Comunicación del solicitante

Folios: 115 a 118 (primera comunicación).

Folios. 136 a 151 (segunda comunicación).

2. Objeto de la invención

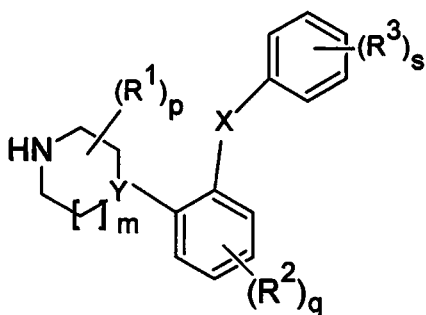
- Título de la solicitud: Derivados de fenilpiperazina como inhidores de la reabsorción de la serotonina.

El objeto de la presente solicitud de patente de invención consiste en:
Compuestos derivados de fenil-piperazina.

Reivindicación 1-4

: Composición farmacéutica caracterizada por un compuesto de la fórmula (I):

177
155



Reivindicaciòn 5 : Compuesto de formula I.

El problema planteado en esta solicitud es la necesidad de composiciones farmacèuticas caracterizadas por compuestos que son inhibidores de la reabsorciòn de la serotonina para el tratamiento por ejemplo de la depresiòn, los trastornos del pánico, trastorno compulsivo, ansiedad, entre otros.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos de fórmula (I), procedimientos para su preparaciòn y composiciones farmacèuticas que emplean dichos compuestos.

El objeto de la invenciòn definido anteriormente se clasificó de acuerdo con la Clasificaciòn Internacional de Patentes (IPC) : A61K31/44, A61K31/4965, A61P25/00 ,C07D295/06, C07D241/04, C07D243/08, C07D211/20, C07D211/70.

3. Determinaciòn del Estado de la Técnica

Considerando que la fecha de presentaciòn de la primera solicitud de patente de la cual se reivindica prioridad es 4 de Octubre de 2001, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicaciòn anterior y se encontraron los siguientes documentos que anticipan el objetó de esta solicitud :

Nº	Documento	Título	Fecha de Publicaciòn*
D1	WO0149678	SUBSTITUTED PHENYL-PIPERAZINE DERIVATES, THEIR PREPARATION AN USE.	12 de Julio del 2001.

4. Análisis de patentabilidad (artículo 14 D486)

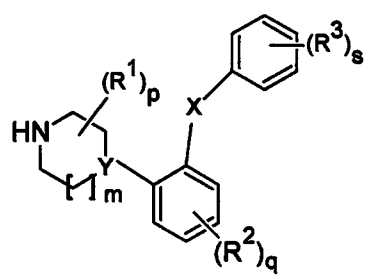
4.1. Novedad (artículo 16 D486)

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

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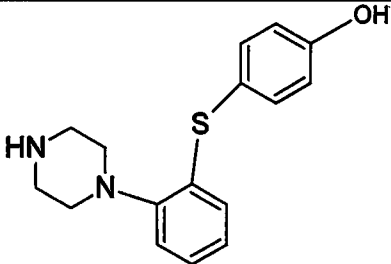
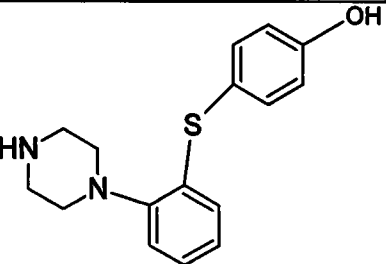
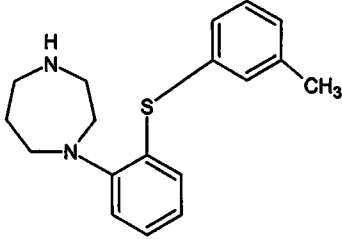
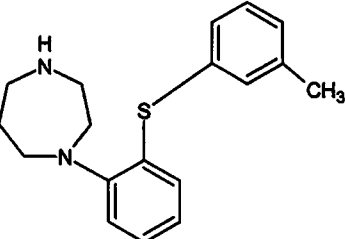
Para la reivindicación 5 :

La presente Solicitud de Patente Colombiana No. 04039958, se refiere a:
Compuesto de fórmula I



D1 (Folios 105-109) enseña compuestos derivados de fenil-piperazina utilizados para el tratamiento de la depresión y la psicosis. , caracterizados por unirse a los receptores 5HT_{1A} con altas afinidades, potente actividad de la inhibición de la reabsorción de la serotonina y/o afinidad por el receptor D4y/o el D3.

SOLICITUD	DOCUMENTO D1
En donde: m es 1 ; p = 0 ; q es 0 ; X es S ; s es 1 R3 es halògeno (Bromo) ; Y es N. 1-[2-(4-(Bromofenilsulfanil)fenil]piperazina)	No hay enlace. R⁶ y R^{6'} son hidrógeno ; m es 2 . Y es N ; X es S R3 es halògeno (Bromo) R1 , R2, R4 y R5 son hidrógeno 1-[2-(4-(Bromofenilsulfanil)fenil]piperazina

 En donde: m es 1 ; $p = 0$; q es 0 ; X es S ; s es 1 R^3 es hidroxilo ; Y es N. 1-[2-(4-hidroxifenilsulfanil)fenil]piperazina.	 No hay enlace. R^6 y $R^{6'}$ son hidrógeno ; m es 2 . Y es N ; X es S R^3 es hidroxilo. R^1 , R^2 , R^4 y R^5 son hidrógeno 1-[2-(4-hidroxifenilsulfanil)fenil]piperazina
 En donde: m es 2 ; $p = 0$; q es 0 ; X es S ; s es 1 R^3 es alquilo C_{1-6} ; Y es N. 1-[2-(3-metilfenilsulfanil)fenil][1,4]diazepan.	 No hay enlace. R^6 y $R^{6'}$ son hidrógeno ; m es 3 . Y es N ; X es S R^2 es alquilo C_{1-6}. R^1 , R^3 , R^4 y R^5 son hidrógeno 1-[2-(3-metilfenilsulfanil)fenil][1,4]diazepan.

Estos compuestos específicos de la anterioridad D1 (Folio 106 líneas 17-27 y Folio 109 líneas 1-3 que son intermediarios de síntesis) son iguales a los compuestos de la presente solicitud, tras hacer los reemplazos respectivos de sustituyentes.

Como se observa, el elemento característico del compuesto reivindicado (reivindicación 5) era conocido en D1 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

4.2 Nivel inventivo (artículo 18 D486)

Para las reivindicaciones 1-4.

El documento del estado de la técnica más cercano es D1 (Folios 105-109) que enseña composiciones farmacéuticas de compuestos derivados de fenilpiperazinas caracterizadas por unirse a los receptores $5HT_{1A}$ con altas afinidades, ser potentes inhibidores de la reabsorción de la serotonina y/ o los ligandos D3 y D4, útiles en tratamiento de la depresión , ansiedad, pánico, desórdenes compulsivos, fobia social, desórdenes alimenticios, psicosis y desórdenes neurológicos como isquemia y demencia senil .

La diferencia con D1 es que en esta solicitud las composiciones farmacéuticas se caracterizan por tener compuestos derivados de fenilpiperazinas no sustituidas en el nitrógeno de la piperazina y en la anterioridad son composiciones farmacéuticas

de compuestos derivados de fenilpiperazinas sustituidas en el nitrógeno de la piperazina por un grupo indoil (folio 106 , líneas 7-10).

Esta diferencia no parece conceder un efecto técnico inesperado o una ventaja a las composiciones reivindicadas en comparación con las composiciones del Estado de la Técnica más cercano; porque estas composiciones **no presentan un efecto superior como inhibidores de la reabsorción de la serotonina (Ver folio 64 y Folios 123-125) .**

Así que el Problema Técnico planteado en esta solicitud que consiste la necesidad de composiciones farmacéuticas caracterizadas por compuestos que son inhibidores de la reabsorción de la serotonina para el tratamiento por ejemplo de la depresión, los trastornos del pánico, trastorno compulsivo, ansiedad, entre otros, se había solucionado previamente mediante las composiciones farmacéuticas de compuestos derivados de fenil- piperazinas que se encuentran sustituidas en el nitrógeno de la piperazina por un grupo indoil. De manera que los nuevas composiciones **son una alternativa a los composiciones conocidas porque no presentan un efecto superior como inhibidores de la reabsorción de la serotonina.**

El experto en la materia, en vista del Estado de la Técnica en su totalidad, es decir en vista de D1 , hubiera sugerido sin mucho esfuerzo de su parte, remover el grupo indoil por mecanismos de retrosíntesis de los compuestos que caracterizan las composiciones farmacéuticas de D1 (Folio 106 , líneas 7-10) , y así lograr los composiciones farmacéuticas (caracterizadas por un compuesto de fórmula general I) reivindicadas (Folio 108 , líneas 1-5) que no parecen tener **un efecto superior como inhibidores de la reabsorción de la serotonina**

Por lo cual se consideran obvios para el experto en la materia. En consecuencia, carecen de nivel inventivo.

5. Respuesta a los argumentos del solicitante:

En cuanto a los argumentos enunciados en forma general en cuanto a la novedad de la actual solicitud por el solicitante "**Todos los compuestos divulgados en la reivindicación 5 son compuestos de fenilsulfanil, y en D1 ningún compuesto fenilsulfanil es revelado. Todos los compuestos específicamente descritos en D1 son compuestos fenoxi, por tanto D1 no afecta la novedad de la reivindicación 5**".

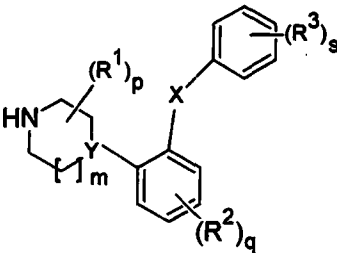
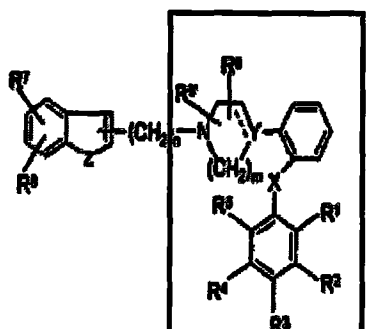
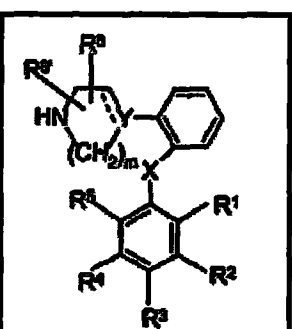
Como es declarado por la decisión 486 ,el documento D1 según el análisis de patentabilidad realizado muestra claramente que dicho documento si afecta la novedad de la presente solicitud . El solicitante basa la novedad en que en D1 solo están descritos de manera específica los compuestos fenoxi . Sin embargo esto no es correcto ya que como se puede observar claramente en la estructura III de la página 11 folio 108 y página 13 folio 109 ,corresponde a la estructura reclamada en la actual solicitud. Además si bien es cierto que los compuestos mencionados como ejemplos de D1 corresponden a fenoxi., según la decisión 486 en su artículo 16 el acceso de un documento no se limita a los compuestos específicos de los ejemplos sino incluye toda enseñanza técnica que haya sido accesible al público y que pueda ser derivable de la descripción escrita u oral contenida en el documento. Asimismo la actual reivindicación 5 , se mira como selección de la estructura III de D1 y dicha selección no es nueva No hay una nueva enseñanza (estructural) técnica evidente que le confiera novedad y el

sustituyente definido como X=S se divulga específicamente en D1. Por consiguiente hay que tenerse en cuenta que los ejemplos son ilustrativos para la una invención más no son restrictivos para esta.

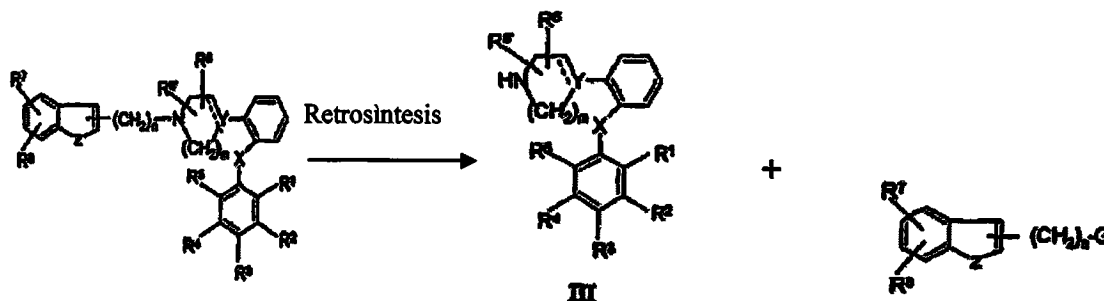
Como se observa en el análisis de novedad, los compuestos reivindicados son conocidos en el estado del arte como compuestos intermediarios de los derivados de fenilpiperazinas, sustituidas en el nitrógeno de la piperazina por un grupo indol y si afecta la novedad. El hecho de que a estos se les determine otro tipo de uso o función no les confiere NOVEDAD.

Ahora en cuanto a los argumentos enunciados en forma general en cuanto al nivel inventivo de la actual solicitud por el solicitante "Partiendo de D1 una persona versada distinguiría que los compuestos divulgados en este son ligandos 5HT1a. Igualmente notaría que algunos de los compuestos divulgados en D1 también exhiben actividad farmacológica adicional, como por ejemplo de reabsorción de serotonina y/ actividad ligante de D3 y D4. No obstante, a partir de este documento no se conoce nada sobre las propiedades de inhibición de transporte de serotonina de los compuestos de fenilsulfanil. Por lo tanto no es evidente para una persona versada remover la fracción de indol con el fin de obtener los compuestos de la presente invención., ya que al observar la estructura de los compuestos de D1, el indol es esencial para cualquier actividad de inhibición de la reabsorción de serotonina que los compuestos puedan presentar. Adicionalmente el estudio publicado por Matzen (J.MED.CHEM,43,1149, 2000). concluye que el grupo indol por si solo es un inhibidor de la reabsorción de la serotonina, mientras que la fracción de la anilina no lo es. Por lo tanto el grupo indol es fundamental en la actividad de la inhibición de la reabsorción de la serotonina.

Se encuentra lo siguiente al realizar el siguiente cuadro comparativo:

SOLICITUD	COMPUESTOS DE LA ANTERIORIDAD D1	COMPUESTOS INTERMEDIARIOS DE LA ANTERIORIDAD D1.
 Teniendo en cuenta la reivindicación 1. En donde : Y es N, X es S. m es 1 o 2. p es 0 q es 0 s es 0,1,2 R3 es halógeno Alquilo, alquilo, alquilsulfanilo, alquilo, haloalquilo, hidroxialquilo,	 Teniendo en cuenta la reivindicación 1. En donde . Y es N. X es O o S. m es 2 o 3. R6 y R6`son hidrógeno. R1 ,R2, y R3 R4 y R5 son hidrógeno , halógeno., alquilo, hidroxialquilo, alquilsulfanilo,	 Teniendo en cuenta la reivindicación 1. En donde : Y es N. X es O o S. m es 2 o 3. R6 y R6`son hidrógeno. R1 ,R2, y R3 R4 y R5 son hidrógeno , halógeno., alquilo, hidroxialquilo, alquilsulfanilo,

En cuanto al nivel inventivo, una persona versada en la materia se puede ver motivada a determinar la actividad farmacológica de los compuestos intermediarios los cuales pueden ser obtenidos de manera evidente por mecanismos de retrosíntesis, tal como lo describe la reacción divulgada en D1.:



con el fin de observar si tiene la misma o una actividad superior ya que el grupo fármacofórico (en el recuadro) que corresponde a los compuestos reivindicados es el mismo.

Ahora en cuanto lo reseñado por el señor solicitante, en relación a que D1 por si solo no alentaría a la persona versada en la materia a sustituir un oxígeno en la fracción fenoxi por un azufre para obtener los compuestos sulfanilfenil, reivindicados, esta oficina difiere ya que claramente a la luz de la reivindicación 1 y el aparte descriptivo de D1, X puede ser S ò O (folio 106, línea 20.) por lo que se concluye que D1 si divulga que se puede sustituir el oxígeno por el azufre y que al variar de heteroátomo la actividad farmacológica no se ve afectada.

Esto también se hace evidente cuando al mirar la actual solicitud en su aparte descriptivo, ya que en los ejemplos observados en el folio 40 se encuentran compuestos de fenil sulfanil y fenoxi, como preferidos de la invención. Y adicionalmente cuando observamos el primer capítulo reivindicatorio (folio 65) en la reivindicación 1 encontramos que X puede ser O o S, por lo que también se puede concluir que la variación del heteroátomo tampoco influye en la actividad farmacológica.. El simple hecho de restringir los compuestos tal como se ve en el segundo capítulo reivindicatorio, no le confiere novedad ni nivel inventivo según lo sustentado en el aparte descriptivo.

Aunque los compuestos presentan actividad como inhibidores de la serotonina, si comparamos con los datos del aparte descriptivo (Folio 64) en los que se encuentra que el IC50 es menor de 200nM, más preferiblemente es menor de 100nM, más preferiblemente por debajo de 50 nM y los de interés particular el IC50 es menor de 10nm y los anexados por el solicitante (folios 123-124) ya de manera específica en donde los compuestos varían en un IC50 entre 2.4 y 120nM, no se observa una ventaja sorprendente o inesperada sobre los compuestos del estado de la técnica más cercano (Folio 152) ya que estos últimos además de presentar una potente actividad de inhibición de la recaptación de la serotonina (Columna 2), también presentan una afinidad por los receptores 5 HT1A (Columna 1) y adicionalmente son afines por el receptor D4 y/o D3. Por tal motivo estas actividades combinadas les confiere una mayor ventaja sobre los de la actual solicitud. en el tratamiento de múltiples patologías.

En cuanto al documento anexado por el señor solicitante en el que se demuestra que por la remoción del grupo indoil hay una reducción del efecto de absorción de serotonina y que dicho grupo indoil es fundamental para la reabsorción de esta, por lo cual la persona versada sería desalentada al remover el grupo indoil al asumir que esto sería perjudicial para la inhibición de la reabsorción de la serotonina se aclara lo siguiente: