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No. 06-017219-00006-0000

Fecha: 2009-09-28 17:24:35 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve. 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 3

Ref: EXPEDIENTE N° 06-017219

Solicitud de Patente a nombre de

ALLERGAN, INC

Me refiero al Oficio N° 5704 y al concepto técnico N° 01333 notificado en el asunto de la referencia.

Los solicitantes hacen las siguientes observaciones en cuanto al concepto técnico se refiere.

"A pesar de lo afirmado por el Examinador, ni la anterioridad D1 o D2 describen el compuesto sometido a estudio, dentro de las reivindicaciones 1 a 6 de la presente invención.

El análisis del Examinador sobre los documentos D1, D2 es una inapropiada apreciación.

En realidad, el examinador no ha proveído ningún razonamiento valedero acerca del porqué una persona con pericia ordinaria en el arte podría modificar los compuestos expuestos en D1 al mirar a los compuestos determinados en D2. Los compuestos de D2 son cardiotónicos. Con todo el debido respeto, una propiedad

biológica de un grupo de compuestos no es una sugerencia para modificar la estructura ni una sugerencia acerca de cual se supondría que la modificación estructural debería ser. Por lo tanto, el examinador no ha provisto una sugerencia o motivación para modificar D1 para obtener el compuesto determinado en la presente solicitud.

Es mas, cuando todas las variaciones en las revelaciones de D1 y D2 son consideradas, existen de manera literal, billones de compuestos sugeridos mediante la combinación D1 y D2. Claramente, con ausencia de las enseñanzas o instrucciones de la presente solicitud, una persona con pericia dentro del arte **no podría** dirigirse hacia el compuestos expuesto en la presente reivindicación 1.

Realmente, el análisis del examinador es imperfecto, pues falla en considerar los billones de posibles compuestos cubiertos por las referencias reveladas. Y es aún mayor el fallo porque el examinador utilizo una "apreciación impermisible" para determinar que enseña la referencia mientras ignora el número sustancial de selecciones y modificaciones que deben ser hechas a las referencias para obtener la estructura de la reivindicación 1.

Finalmente, no existe de manera apropiada el rechazo "prima facie" por la falta de nivel inventivo pues no existe la motivación para combinar las referencias y tales referencias no enseñan o sugieren el compuesto determinado en la reivindicación 1. Por lo tanto, el compuesto de la reivindicación 1 no es obvio sobre el arte anterior.

PCT

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146
D1 145

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/415		A1	(11) International Publication Number: WO 97/15302 (43) International Publication Date: 1 May 1997 (01.05.97)
(21) International Application Number: PCT/FI96/00560 (22) International Filing Date: 23 October 1996 (23.10.96) (30) Priority Data: 9521680.0 23 October 1995 (23.10.95) GB (71) Applicant (for all designated States except US): ORION-YHTYMÄ OY [FI/FI]; Orionintie 1, FIN-02200 Espoo (FI). (71)(72) Applicants and Inventors: ÄKERMÄN, Karl, E., O. [FI/FI]; Virmuntie 14, FIN-20540 Turku (FI). JANSSEN, Christian [FI/FI]; Välskärinkatu 41 B 7, FIN-20570 Turku (FI). KUKKONEN, Jyrki [FI/FI]; Itäinen Pitkätie 16 B, FIN-20520 Turku (FI). (72) Inventors; and (73) Inventors/Applicants (for US only): SAVOLA, Juha-Matti [FI/FI]; Siutlankatu 8, FIN-20380 Turku (FI). WURSTER, Siegfried [DE/FI]; Uudenmaantie 70 A 19, FIN-20720 Turku (FI). COCKCROFT, Victor [GB/FI]; Yliopistonkatu 5 A 9, FIN-20110 Turku (FI). (74) Agent: ORION CORPORATION; Orion Pharma, Patent Service, P.O. Box 65, FIN-02101 Espoo (FI).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: PHARMACEUTICAL COMPOSITIONS OF LEVO-ENANTIOMERS OF MEDETOMIDINE DERIVATIVES AND THEIR USE			
(57) Abstract The levo-isomers of certain imidazole derivatives, particularly medetomidine, have been found to be inverse agonists of adrenergic α -2 receptors and are therefore useful in the prevention or treatment of conditions associated with overexpression or hypersensitization of adrenergic α -2 receptors such as obesity, a withdrawal symptom to an adrenergic α -2 receptor agonist, a neurological disorder, multiple system atrophy, diabetes mellitus, benign prostatic hyperplasia and drug-induced sensitization of adrenergic α -2 receptors. The pharmaceutical composition is preferably transdermal.			

146 D2
147

①
 **Europäisches Patentamt**
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⑪ Publication number:

0 302 603
A1

⑫

EUROPEAN PATENT APPLICATION

⑰ Application number: **88306292.9**

⑱ Int. Cl.⁴: **C07D 233/04 , C07C 97/10 ,**
A61K 31/415

⑳ Date of filing: **08.07.88**

Claims for the following Contracting States: ES
+ GR.

㉑ Priority: **09.07.87 US 71515**

㉒ Date of publication of application:
08.02.89 Bulletin 89/06

㉓ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

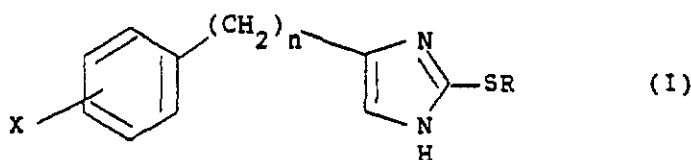
㉔ Applicant: **SMITHKLINE BECKMAN**
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Smith Kline & French Laboratories Ltd.
Corporate Patents Mundells
Welwyn Garden City Hertfordshire AL7
1EY(GB)

㉗ **Dopamine-beta-hydroxylase inhibitors.**

㉘ Compounds of formula (I):



in which X is H, F, Cl, Br, C₁₋₄alkyl, CN, NO₂, SO₂NH₂, COOH, OH, CHO, C₁₋₄alkoxy, CH₂OH, CH₂OC₁₋₄alkyl, CF₃, C₂F₅, C₃F₇, SO₂CH₃, SO₂CF₃, or CO₂C_aH_{2a+1} wherein a is 1-5, or any accessible combination thereof of up to 5 substituents; R is H or C₁₋₄alkyl; and n is 0-5; and salts thereof, processes for their preparation, pharmaceutical compositions containing them and their use in therapy as inhibitors of dopamine-β-hydroxylase activity.

EP 0 302 603 A1

Journal of Ocular Pharmacology and Therapeutics

Ocular Hypotensive Effects of Medetomidine and Its Analogs

To cite this article:

YING JIN, SIMEONA WILSON, EDWARD E. ELKO, THOMAS YORIO. Journal of Ocular Pharmacology and Therapeutics. Winter 1991, 7(4): 285-296. doi:10.1089/jop.1991.7.285.

Published in Volume: 7 Issue 4: March 18, 2009

Full Text: • [PDF for printing](#) (1,126.6 KB) • [PDF w/ links](#) (451 KB)

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THOMAS YORIO

ABSTRACT

The ocular hypotensive effects of medetomidine, a relatively selective α_2 agonist, and its analogs were tested in rabbits and cats and their inhibition of adenylate cyclase in the isolated bovine ciliary process was also studied. It was found that topical unilateral administration of medetomidine (0.5-2.0%) to the normotensive rabbits produced a dose-dependent bilateral decrease in IOP with peak reduction in IOP at 2 hr in the treated eye and 1 hr in the untreated eye. A dose-dependent mydriasis was also observed in the treated eye. The dose-response curves of medetomidine and its analogs showed that the ranked order of intrinsic activity at lowering IOP was medetomidine $\geq$ MPV-1440 > detomidine > MPV-1441 and MPV-305 BII. At concentrations lower than those used in rabbits, topical application of medetomidine to the normotensive cats lowered IOP in both treated and untreated eyes. Medetomidine and detomidine caused a dose-dependent inhibition of isoproterenol-stimulated adenylate cyclase activity. Detomidine was found to be a partial agonist producing about 43% of maximum inhibition obtained by medetomidine. The IOP efficacy of these α_2 -agonists paralleled their effects on adenylate cyclase activity. The results demonstrated that these imidazoline derivatives are effective ocular hypotensive agents which may be useful in understanding the contribution of α_2 -receptors to the regulation of IOP.

Ocular Hypotensive Effects of Medetomidine and Its Analogs

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Department of Pharmacology, Texas College of Osteopathic Medicine, Fort Worth, Texas

ABSTRACT

The ocular hypotensive effects of medetomidine, a relatively selective α_2 -agonist, and its analogs were tested in rabbits and cats and their inhibition of adenylate cyclase in the isolated bovine ciliary process was also studied. It was found that topical unilateral administration of medetomidine (0.5-2.0%) to the normotensive rabbits produced a dose-dependent bilateral decrease in IOP with peak reduction in IOP at 2 hr in the treated eye and 1 hr in the untreated eye. A dose-dependent mydriasis was also observed in the treated eye. The dose-response curves of medetomidine and its analogs showed that the ranked order of intrinsic activity at lowering IOP was medetomidine $\geq$ MPV-1440 > detomidine > MPV-1441 and MPV-305 BII. At concentrations lower than those used in rabbits, topical application of medetomidine to the normotensive cats lowered IOP in both treated and untreated eyes. Medetomidine and detomidine caused a dose-dependent inhibition of isoproterenol stimulated adenylate cyclase activity. Detomidine was found to be a partial agonist producing about 43% of maximum inhibition obtained by medetomidine. The IOP efficacy of these α_2 -agonists paralleled their effects on adenylate cyclase activity. The results demonstrated that these imidazoline derivatives are effective ocular hypotensive agents which may be useful in understanding the contribution of α_2 -receptors to the regulation of IOP.

INTRODUCTION

Selective α_2 -adrenergic agonists decrease the intraocular pressure (IOP) in ocular normotensive animals when applied to cats (1), monkeys (2,3) and rabbits (4-6). In humans, several α_2 -agonists have been shown to reduce IOP in glaucoma patients (7) and the α_2 -agonist, apraclonidine (p-amino-clonidine), has recently been approved for the treatment of acute elevation of IOP following laser surgery. Therefore, the α_2 -adrenoceptor agonists represent potentially useful ocular hypotensive agents. However, the underlying mechanisms of their IOP lowering effects are not clear. Experimental evidence has suggested that α_2 -adrenergic receptors in rabbit iris-ciliary body (ICB) are negatively coupled to adenylate cyclase (8-10). Observations from our laboratory presented evidence for the existence of α_2 -adrenergic receptors inhibitory to adenylate cyclase both in bovine ciliary process and in rabbit ICB. Moreover, the results demonstrated that the inhibition of



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European Journal of Pharmacology
Volume 339, Issues 2-3, 27 November 1997, Pages 113-119

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doi:10.1016/S0014-2999(97)01375-7

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α ₂-Adrenergic control of dopamine overflow and metabolism in mouse striatum

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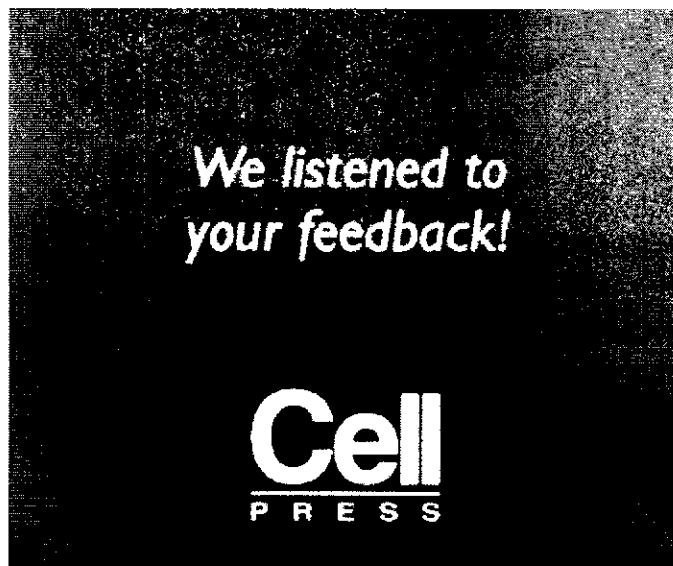
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Received 22 May 1997; revised 24 September
1997; accepted 26 September 1997. Available
online 13 January 1998.

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Abstract

The effects of the α_2 -adrenoceptor drugs, medetomidine and atipamezole, on dopamine overflow evoked by low (6 Hz–10 s) and high (50 Hz–4 s) frequency electrical stimulation of the median forebrain bundle were studied in striatum of BALB/C mice anaesthetized with chloral hydrate with fast in vivo voltammetry techniques. The effects of these drugs on the basal concentrations of dopamine metabolites were also investigated by means of differential pulse voltammetry. Medetomidine dose dependently decreased dopamine overflow in nucleus accumbens in the dose range 5–100 $\mu\text{g/kg}$, s.c. This effect was seen only at low frequency stimulation and reached 85% at a dose of 100 $\mu\text{g/kg}$. Medetomidine also decreased the basal concentration of striatal homovanillic acid. This effect did not exceed 35%. Atipamezole antagonized the inhibitory effects of medetomidine on the dopamine overflow, but showed no effect itself. We suggest that α_2 -adrenoceptors in dopaminergic terminal fields in the mouse striatum are involved in the regulation of dopamine release at physiological stimulation frequencies.

Author Keywords: Atipamezole; Medetomidine; Dopamine overflow; Dopamine metabolisms; Voltammetry, in vivo; Mouse

Article Outline

1. Introduction
2. Methods
 - 2.1. Preparation of animals
 - 2.2. Electrical stimulation
 - 2.3. Electrochemical technique
 - 2.4. Data presentation and statistics
3. Results
4. Discussion

Acknowledgements

References

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Contrasting effects of the imidazol(in)e α_2 -adrenoceptor agonists, medetomidine, clonidine and UK 14,304 on extraneuronal levels of noradrenaline in the rat frontal cortex: evaluation using *in vivo* microdialysis and synaptosomal uptake studies

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1 *In vivo* microdialysis in halothane-anaesthetized rats and synaptosomal [³H]-noradrenaline uptake studies *in vitro* were used to evaluate the effects of imidazole (medetomidine) and imidazoline (clonidine and UK 14,304) α_2 -adrenoceptor agonists on extraneuronal levels of noradrenaline in the frontal cortex.

2 Levels of noradrenaline in the dialysate were increased by a depolarizing concentration of K⁺ (60 mM for 20 min) and substantially attenuated by reducing Ca²⁺ supply in the perfusate. These results suggest that spontaneous efflux of noradrenaline in the cortex is regulated predominantly by cation-dependent exocytotic mechanisms.

3 At a low perfusion concentration (0.5 μ M), medetomidine, clonidine and UK 14,304 all reduced the level of noradrenaline in cortical dialysates. Continuous perfusion of the selective α_2 -adrenoceptor antagonist, atipamezole (0.5 μ M) caused a sustained increase in noradrenaline efflux and reversed the inhibitory effects of medetomidine. All these changes are consistent with drug actions at presynaptic α_2 -adrenoceptors.

4 Higher concentrations of medetomidine (5–50 μ M), but not clonidine or UK 14,304, evoked a non-desensitizing increase in noradrenaline efflux. This effect was not antagonized by 0.5 μ M atipamezole.

5 The tricyclic noradrenaline reuptake inhibitor, desmethylinipramine (0.5–50 μ M), increased noradrenaline efflux in a concentration-dependent manner.

6 The specific uptake of [³H]-noradrenaline into cortical synaptosomes was inhibited by medetomidine and desmethylinipramine with IC₅₀ values of approximately 7 μ M and 8 μ M respectively. Neither clonidine nor UK 14,304 inhibited [³H]-noradrenaline uptake.

7 These results indicate that micromolar concentrations of the selective α_2 -adrenoceptor agonist, medetomidine, can augment extraneuronal levels of noradrenaline in the rat frontal cortex; this effect seems to involve an inhibition of noradrenaline reuptake rather than an action at α_2 -adrenoceptors.

Keywords: Atipamezole; clonidine; cortical synaptosomes; desmethylinipramine; frontal cortex; medetomidine; microdialysis; UK 14,304

Introduction

It is widely accepted that presynaptic α_2 -adrenoceptors modulate noradrenaline release in the brain. Evidence to support this view stems from experiments *in vitro* studying transmitter release from synaptosomes (de Langen *et al.*, 1979; Maura *et al.*, 1992) and brain slices (Reichenbacher *et al.*, 1982; Raiteri *et al.*, 1992), and from experiments using *in vivo* microdialysis (L'Heureux *et al.*, 1986; Thomas & Holman, 1991; van Veldhuizen *et al.*, 1993). In all of these studies, noradrenaline efflux was reduced by α_2 -adrenoceptor agonists and increased by α_2 -adrenoceptor antagonists.

The imidazole derivative, ($\pm$)-4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole (medetomidine), is a potent α_2 -adrenoceptor agonist with an α_2/α_1 selectivity ratio of over 1600 (Virtanen *et al.*, 1988). In recent experiments, we used *in vivo* microdialysis to test the effects of this compound on noradrenaline efflux in the rat frontal cortex. The drug was administered directly into the terminal field *via* the dialysis probe. We found that the effects of medetomidine were strongly concentration-dependent. At a low perfusion concentration (0.5 μ M), medetomidine reduced noradrenaline

levels in the dialysate but higher concentrations evoked a non-desensitizing increase in noradrenaline efflux. These preliminary findings have been reported to the British Pharmacological Society (Dalley & Stanford, 1994). The aim of the present study was to eliminate the possibility that this increase in noradrenaline efflux involves α_2 -adrenoceptors. To achieve this, we first tested whether the increase could be prevented by the selective α_2 -adrenoceptor antagonist, atipamezole. In further studies the effects of medetomidine on noradrenaline efflux were compared with those of the imidazoline α_2 -adrenoceptor agonists, clonidine and 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine (UK 14,304).

One limitation of *in vivo* microdialysis is that levels of noradrenaline in the dialysate reflect the net influence of both neurotransmitter release from the nerve terminals and its neuronal and non-neuronal reuptake from the extracellular fluid. Spontaneous changes in noradrenaline efflux are highly Ca²⁺-dependent (L'Heureux *et al.*, 1986; van Veldhuizen *et al.*, 1990), suggesting that it is mainly transmitter release which determines the levels of noradrenaline in the dialysate under basal conditions. However, drug-induced changes in noradrenaline efflux could reflect changes in release and/or

¹ Author for correspondence.

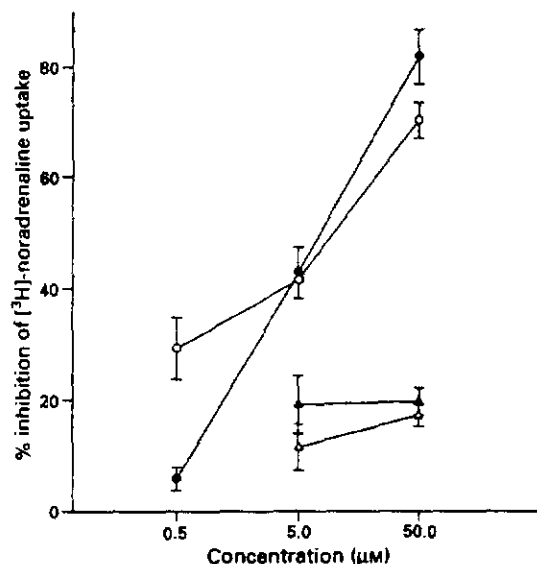


Figure 5 Concentration-dependent inhibition of [^{3} H]-noradrenaline uptake into cortical synaptosomes by medetomidine (●) and desmethylinipramine (○). Clonidine (▲) and UK 14,304 (Δ) were also tested. Each data point represents mean $\pm$ s.e. mean % inhibition of specific [^{3} H]-noradrenaline uptake ($n = 6-9$). Statistical analyses of the raw data are described in the text.

0.5 μ M atipamezole alone ($F = 11.92$; d.f. 1,8; $P = 0.009$). In contrast, noradrenaline efflux during perfusion of 50 μ M medetomidine was significantly greater than that in equivalent samples collected with atipamezole alone ($F = 13.64$; d.f. 1,8; $P = 0.006$).

Atipamezole (0.5 μ M) was then co-administered with medetomidine (5–50 μ M). When compared with medetomidine alone there was no main effect of drug ($F = 0.22$; d.f. 1,8; $P = 0.065$) over all samples, but there was a main effect of concentration ($F = 93.62$; d.f. 3,24; $P < 0.001$) and a significant drug $\times$ concentration interaction ($F = 3.39$; d.f. 3,24; $P = 0.034$) (Figure 4). Noradrenaline efflux was therefore compared between specific drug treatments. Comparison of noradrenaline efflux with 0.5 μ M medetomidine and 0.5 μ M medetomidine plus 0.5 μ M atipamezole failed to expose a main effect of drug ($F = 2.21$; d.f. 1,8; $P = 0.175$). Multivariate tests also failed to show any drug treatment $\times$ time interaction ($P = 0.129$). Since comparison of medetomidine alone and atipamezole alone did expose a drug $\times$ time interaction (see above), it seems that changes in noradrenaline efflux induced by 0.5 μ M medetomidine or 0.5 μ M atipamezole are diminished when these drugs are given in combination. This suggests an additive interaction between these drugs at these concentrations. In contrast, there was no effect of atipamezole on noradrenaline efflux when this was co-administered with either 5.0 μ M ($F = 4.44$; d.f. 1,8; $P = 0.068$) or 50 μ M medetomidine ($F = 0.65$; d.f. 1,8; $P = 0.444$ cf. medetomidine alone).

Effects of medetomidine, UK 14,304, clonidine and desmethylinipramine on uptake of (–)-[^{3} H]-noradrenaline by cortical synaptosomes in vitro

Specific synaptosomal uptake of [^{3} H]-noradrenaline at 37°C was 1.02 ± 0.10 pmol mg^{-1} protein ($n = 9$). This uptake was inhibited by medetomidine with an IC_{50} of approximately 7 μ M ($F = 11.15$; d.f. 3,35; $P < 0.001$) (Figure 5). Compared with the uptake in the absence of drug, *post hoc* tests exposed

significant uptake inhibition at both 5 and 50 μ M drug concentrations. Similar results were obtained with desmethylinipramine: this produced a significant, concentration-dependent reduction in synaptosomal uptake ($F = 6.52$; d.f. 3,42; $P = 0.01$) with *post hoc* tests exposing significant inhibition at both 5 and 50 μ M concentrations. The IC_{50} for uptake inhibition was approximately 8 μ M. In contrast, neither clonidine ($F = 0.11$; d.f. 2,11; $P = 0.896$) nor UK 14,304 ($F = 0.04$; d.f. 2,11; $P = 0.954$) produced any changes in synaptosomal uptake of [^{3} H]-noradrenaline.

Discussion

Systemic administration of medetomidine produces sedation, hypotension (Savola & Virtanen, 1991), antinociception (reviewed by Pertovaara, 1993), hypothermia (MacDonald *et al.*, 1988) and a reduction in general anaesthetic requirement (Bloor *et al.*, 1992). These effects have been attributed to activation of α_2 -adrenoceptors since they are shared by other α_2 -adrenoceptor agonists and are prevented by α_2 -adrenoceptor antagonists. This is consistent with evidence from binding studies *in vitro* showing that medetomidine has a greater selectivity for α_2 - versus α_1 -adrenoceptors, and a higher affinity for binding to α_2 -adrenoceptors than either clonidine or UK 14,304 (Virtanen *et al.*, 1988). In view of this binding profile, systemic administration of medetomidine should reduce noradrenaline release in the brain by activating both somatodendritic α_2 -autoreceptors in the locus coeruleus and presynaptic α_2 -adrenoceptors in the terminal field. Attenuated release of noradrenaline is suggested by a decline in brain levels of the noradrenaline metabolite, 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) after systemic administration of a low dose of medetomidine (MacDonald *et al.*, 1991). Also, in the present study, a low micromolar concentration of medetomidine reduced noradrenaline efflux, whereas the α_2 -adrenoceptor antagonist, atipamezole, increased it.

Despite this receptor selectivity, the main finding of the present study was that, at higher concentrations (5–50 μ M), medetomidine markedly increased the levels of noradrenaline in cortical dialysates. Although unlikely to contribute to its clinical actions, this effect could be relevant to published reports that medetomidine has a biphasic effect on brain MHPG content: after an initial reduction, MHPG levels show a dose-dependent recovery (MacDonald *et al.*, 1991). It might also explain the reversal of sedation as the drug dose is increased beyond that recommended in anaesthesia (Doze *et al.*, 1989). It is also unlikely that the increase in noradrenaline efflux induced by medetomidine is related to its agonist action at α_2 -adrenoceptors. This is because both clonidine and UK 14,304 were devoid of this effect, yet both these compounds are regarded as relatively potent and selective α_2 -adrenoceptor agonists. More importantly, the increase in noradrenaline efflux was not prevented by co-administration of the α_2 -adrenoceptor antagonist, atipamezole.

Attenuation of noradrenaline efflux by low, and increased efflux at high, drug concentrations could suggest that medetomidine has a lower efficacy at presynaptic α_2 -adrenoceptors than noradrenaline. There are several reasons for discounting this possibility. First, the large increase in efflux caused by 50 μ M medetomidine would indicate that α_2 -adrenoceptors experience considerable tonic activation by spontaneously released noradrenaline. Yet, this is at variance with our results: the increase was no greater after treatment with atipamezole, either alone or in conjunction with medetomidine, than after medetomidine alone. Others have shown that, even high concentrations (100 μ M) of selective α_2 -antagonists, piperoxan and yohimbine, have little or no effect on noradrenaline levels in dialysates of the rat frontoparietal cortex (van Veldhuizen *et al.*, 1993). Interestingly, the imidazoline α_2 -adrenoceptor antagonist, idazoxan

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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	Actuación	430
	Oficio	470
	Folios	13

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/US2004/027134
Fecha de Presentación Internal. 30 de Agosto de 2004

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

1. Documentos estudiados

Descripción: Folios: 17 a 54 como se radicó inicialmente

Reivindicaciones: Folios 55 a 56 como se radicó inicialmente

Dibujos: Folios 57 a 58

Prioridad: Folios: 1
12/09/2003, US, 60/502,562
151/07/2004, US, 10/891.953

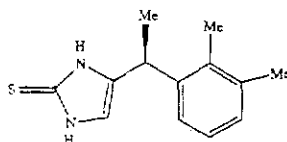
Respuesta del solicitante: Folios 143 a 145

2. Análisis de la Prioridad

La fecha de prioridad del 12 de Septiembre de 2003 y su correspondiente documento, son aceptados para el estudio de patentabilidad

receptor α -2A adrenérgico comparado con el receptor α -1A adrenérgico

Solución: Un agonista selectivo α -2A/ α -1A, representado por:



IPC: A61K 31/4164, C07D 233/84

3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

Las reivindicaciones 2 y 5 se encuentran caracterizadas por el resultado a alcanzar.
(Actividad farmacológica)

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de presentación de la solicitud prioritaria: 12 de Septiembre de 2003

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: **12/09/2003** se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
D1	WO 97/15302	Pharmaceutical compositions of levo-enantiomers of medetomidina derivatives and their use	01/05/1997
D2	EP 0302603	Dopamine-beta-hydroxylase inhibitors	08/02/89

5. Análisis de Patentabilidad (Art 14 D486)

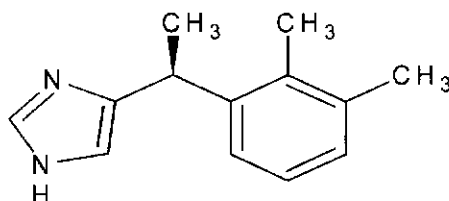
Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en:

"Un agonista selectivo α -2A/ α -1A, que comprende un compuesto representado por:"



El Estado de la Técnica más cercano es **D1**, que da a conocer derivados de medetomidina y su uso como agonista del receptor α -2 con fórmula I y sus composiciones (Ver resumen) y que al realizar los reemplazos sugeridos para R^1 como C_1 - C_2 -alquilo, R_2 , R_3 , R_4 los cuales son lo mismo o diferente y son independientemente de hidrógeno, C_1 - C_2 -alquilo entre otros, en la reivindicación 1 se obtiene el compuesto (Ver página 8, líneas 9-10)

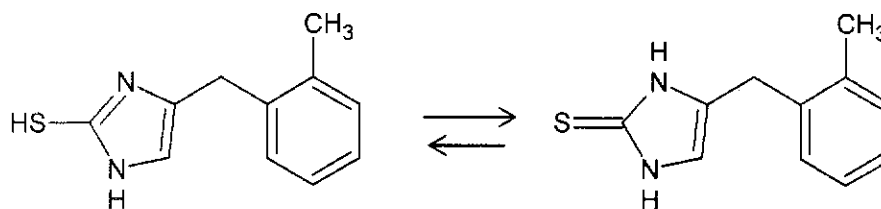


El compuesto objeto de esta solicitud se diferencia de los compuestos de **D1**, en que el anillo de imidazol presenta la función tiona.

El hecho de incluir la función tiona en el anillo del imidazol en los compuestos que se daban a conocer en **D1**, causaría que los compuestos sean selectivos sobre los receptores α -2A comparado con el receptor α -1A adrenérgico.

El Problema Técnico Objetivo era "cómo obtener compuestos útiles como agonistas selectivos α -2A/ α -1A".

D2 describe una manera de solucionar el problema técnico, mediante la adición de la función tiona en el anillo de imidazol, en compuestos inhibidores de la dopamina-beta-hidroxilasa, donde al realizar los reemplazos en la estructura de fórmula I, cuando X es C_{1-4} alquilo, R es H, y n es 1-5; se obtiene la siguiente estructura química con su correspondiente tautómero:



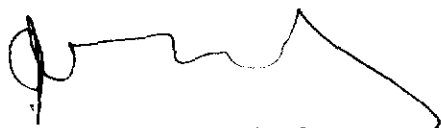
La reivindicación es obvia, porque el Experto en la Materia enfrentado al problema de "obtener agonistas selectivos α -2A/ α -1A" incluiría "la función tiona en el anillo de imidazol" que se revela en **D2**, en la estructura química de la medetomidina que se enseña en **D1**, logrando de esta forma el compuesto objeto de esta solicitud. Por tanto, la reivindicación 1 no tiene Nivel Inventivo. Las reivindicaciones dependientes 2- 6, no mencionan alguna característica que haga inventivo al compuesto de la reivindicación 1, por lo cual se considera que no tienen nivel inventivo.

6. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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



JESÚS FERNEL GARCÍA GARCÍA
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha

CONCEPTO TÉCNICO No. 04233	EXAMINADOR TÉCNICO Código No. 202070
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