

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señora

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Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. _____ S. _____ D. _____

Referencia: Expediente No. 06.019.948

Solicitud de Patente de Invención titulada: "Derivado de (TIO)
carbamoilciclohexano como antagonista de los receptores D3/D2"

Solicitante: Richter Gedeon Vegyészeti RT.

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 14
DEL 22 DE ENERO DE 2010, OFICIO NO. 551 (SOLICITUD DE SUMINISTRO DE
INFORMACIÓN DE ACUERDO CON EL ART. 46)

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término legal:

De acuerdo con su solicitud presento copia simple del documento: GLASE S.A. *et. al.*: 4-bromo-1-metoxi-N-[2-(4-aryl-1-piperazinyl) ethyl]-2-naphtalenecarboxamides: selective dopamine D3 receptor partial agonists. BIOORGANIC & MEDICINAL CHEMISTRY



Pergamon

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4-BROMO-1-METHOXY-N-[2-(4-ARYL-1-PIPERAZINYL)ETHYL]-2-NAPHTHALENECARBOXAMIDES: SELECTIVE DOPAMINE D₃ RECEPTOR PARTIAL AGONISTS

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Robert G. MacKenzie, Peter J. Manley, Thomas A. Pugsley, Jon L. Wright, and Lawrence D. Wise

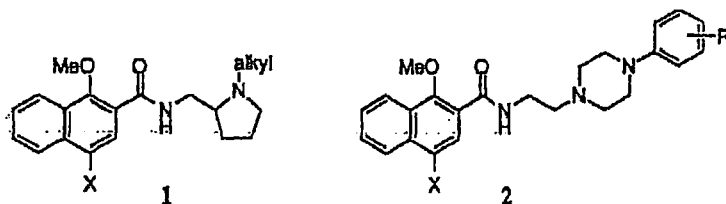
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Abstract: A series of 4-bromo-1-methoxy-N-[2-(4-aryl-1-piperazinyl)ethyl]-2-naphthalenecarboxamide dopamine (DA) D₃ receptor agonists has been identified. These compounds were found to be selective for DA D₃ over D₂ receptors and were shown to be partial to full agonists as measured by stimulation of mitogenesis in D₃-transfected CHO p-5 cells. Copyright © 1996 Elsevier Science Ltd

Introduction

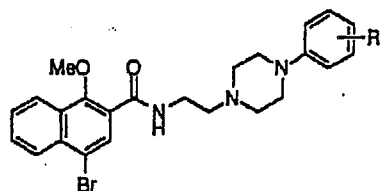
Most marketed antipsychotics exert their effects through antagonist activity at the dopamine (DA) D₂ receptors. High levels of D₂ receptor expression in the striatal as well as limbic regions of the brain may be responsible for adverse motor effects such as extrapyramidal syndrome (EPS) and tardive dyskinesia that are attributed to DA blockade. The recently cloned DA D₃ receptor was found to have a much more restricted distribution with expression predominantly localized to the limbic region which is responsible for cognitive and emotional functions. Atypical antipsychotics (i. e. drugs which are known to cause fewer neurological side effects) have high affinity for the DA D₃ as well as the DA D₂ receptor.¹ This led to the hypothesis that a selective DA D₃ antagonist may provide a novel antipsychotic agent with little or no EPS side effects.

Initial studies by Sokoloff et al.² indicated that methoxy naphthalene amides with a general structure 1 are DA D₃ selective antagonists. We were interested in expanding the scope of this work by synthesizing and testing the aryl piperazine analogs 2.



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Table 1: Effects of phenyl piperazine substitution on DA receptor binding

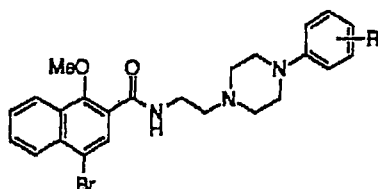


Compound	R	hD ₃ binding ^a (K _i nM)	hD ₂ binding ^a (K _i nM)
3	H	24	1892
4	2-Me	66	484
5	3-Me	339	1207
6	4-Me	260	996
7	2,3-diMe	50	1173
8	2-Cl	39	517
9	3-Cl	40	703
10	4-Cl	132	35% @ 10μM
11	2,3-diCl	8	35% @ 10μM
12	2-OMe	76	303
13	3-OMe	652	1288
14	4-OMe	731	5692
15	2-NO ₂	24	151
16	3-NO ₂	652	1288
17	4-NO ₂	731	5692

^a[³H]spiperone in rat striatum; K_i values were obtained from 4 - 6 concentrations, run in triplicate, by a non-linear regression analysis.

Changes in naphthalene substitution were poorly tolerated (Table 2). As in the case of previously studied benzamide compounds,⁵ the adjacent methoxy group appears to be important because hydrogen bonding with the amide hydrogen locks the structure into a rigid conformation. Halogen substitution para to the methoxy group also seems to be required. Unlike the pyrrolidine analog where X = CN (1),⁶ the corresponding phenyl piperazine analog with cyano substitution on the naphthalene ring 19 has significantly weaker D₃ binding affinity.

Table 3: Stimulation of mitogenesis in D₃-transfected CHO p-5 cells. Percent maximal effect compared to that of the full DA agonist quinpirole.



Compound	R	hD ₃ binding ^a (K _i nM)	DA D ₃ receptor mitogenesis ^b	
			% maximal effect ^c	EC ₅₀ ^d (nM)
3	H	24	55	68
4	2 Me	66	17	>1000
7	2,3 diMe	50	31	68
8	2 Cl	39	57	83
9	3 Cl	40	83	28
11	2,3 diCl	8	100	13

^aSee footnote for Table 1. ^bMeasurement of [³H]thymidine incorporation in CHO p-5 cells expressing human D₃ receptors. ^cPercent maximal effect compared to that of the full DA agonist quinpirole (100%). ^dEC₅₀ values were obtained from 10 concentrations, n = 4.

Acknowledgment: We would like to thank L. M. Georgic, Y.-H. Shih and K. T. Zoski for biological testing.

References and Notes

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2. Rognan, D.; Mann, A.; Wermuth, C.-G.; Martres, M.-P.; Giros, B.; Sokoloff, P.; Schwartz, J.-C.; Lecomte, J.-M.; Garrido, F. Eur. Pat. Appl. EP 539, 281, 1993, *Chem. Abstr.*, 119, 139085a.
3. All new compounds had satisfactory ¹H NMR, IR, MS and microanalysis.
4. Binding assays were carried out in triplicate at cloned human D_{2L}, D₃ and D₄ receptors transfected into CHO-K1 cells versus [³H]spiperone as previously described: Pugsley, T. A.; Davis, M. D.; Akunne, H. C.; MacKenzie, R. G.; Shih, Y. H.; Damsma, G.; Wikström, H.; Whetzel, S. Z.; Georgic, L. M.; Cooke, L. W.; DeMattos, S. B.; Corbin, A. E.; Glase, S. A.; Wise, L. D.; Dijkstra, D.; Heffner, T.G. *J. Pharmacol. Exp. Ther.* 1995, 275, 1355.
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