Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 1583–1586

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

NOVEL DERIVATIVES OF 3-(DIPROPYLAMINO)CHROMAN. Interactions with 5-HT_{1A} and D_{2A} receptors.

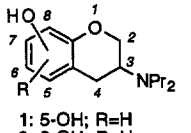
Patrizia Caldirola,[a,c] Ratan Chowdhury,[a,d] Lena Unelius,[b] Nina Mohell,[b] Uli Hacksell,[a,e] and Anette M. Johansson.[a*]

[a]Organic Pharmaceutical Chemistry, Uppsala Biomedical Centre, Uppsala University, Box 574, S-751 23 Uppsala, Sweden, [b]Dept. of Lead Generation, Preclinical R&D, Astra Arcus AB, SE-151 85 Södertälje, Sweden; [c]Current address: Dept. of Med. Chem., Pharmacia &Upjohn AB, SE-751 82 Uppsala, Sweden [d]Current address: Dept. of Chemical Engineering,Univ. of Melbourne, Parkville, Victoria 3152, Australia [e]Current address: ACADIA Pharmaceuticals, 3911 Sorrento Valley Blvd. San Diego, CA 92121, USA

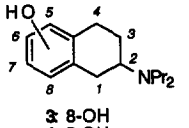
Received 22 February 1999; accepted 28 April 1999

Abstract: Novel 8-aryl and 8-aroyl substituted derivatives of 3-(dipropylamino)chroman are described. The compounds have been prepared by a palladium catalyzed reaction of iodoarenes and a stannylated derivative of [η^6-3-(dipropylamino)chroman]$Cr(CO)_3$. Several of the compounds have high affinity for 5-HT_{1A} receptors whereas the affinity for D_{2A} receptors is lower, the 8-arylated derivatives being slightly more potent than the 8-aroylated analogues.

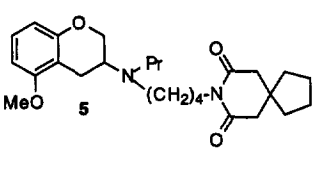
During the last ten years, various derivatives of 3-aminochroman have been prepared and evaluated as oxygen isosters of 2-aminotetralins. For example, **1** (5-OH-DPAC)[1] and **2** (8-OH-DPAC)[1a,c,d,2] have been synthesized as isosters of the well-characterized 5-HT_{1A} and D_2 receptor agonists 8- and 5-hydroxy-2-(dipropylamino)tetralins **3** (8-OH-DPAT)[3] and **4** (5-OH-DPAT).[4] Compound **1** has been characterized as a selective 5-HT_{1A} receptor agonist[1a,c,d] whereas **2** appears to be a D_2 receptor agonist with selectivity for presynaptic receptors.[1a,c,2,5] In addition, the interaction of **2** with D_2 receptors was shown to be stereoselective, the (-)-enantiomer being the most potent isomer.[1c] These results are in good agreement with those of the corresponding 2-aminotetralins.[6]



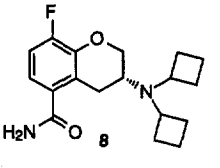
1: 5-OH; R=H
2: 8-OH; R=H
6: 5-OMe; R=8-Br
7: 5-OMe; R=8-SMe



3: 8-OH
4: 5-OH



5



8

In a few recent reports on derivatives of **1**, compound (+)-**5** was identified as a potent and selective 5-HT_{1A} receptor agonist.[7,8] Compound **6** appears to be a potent DA receptor agonist and **7** exhibits a mixed dopaminergic and serotonergic profile.[9] Furthermore, the recently published chroman derivative **8** appears to be a silent 5-HT_{1A} receptor antagonist.[10] However, few analogs of **2** have yet appeared in the literature.[1c,2,5b,11]

In the present communication we describe the preparation and pharmacological evaluation of a series of novel 8-aryl and 8-aroyl substituted derivatives of 3-(dipropylamino)chroman. The novel compounds were

*e-mail: anette@bmc.uu.se FAX: +46-18-471 4024

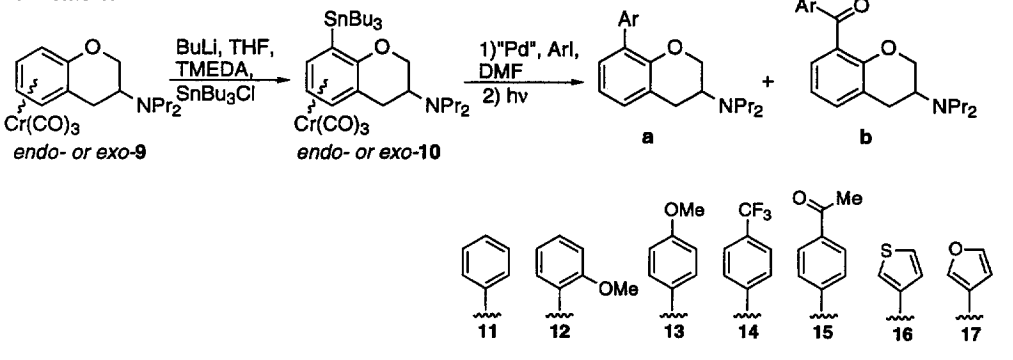
0960-894X/99/$ - see front matter
PII: S0960-894X(99)00232-2

synthesized by using palladium catalyzed coupling reactions of iodoarenes and stannylated (η^6-3-(dipropylamino)chroman)$Cr(CO)_3$ complexes. The affinities of the compounds for central 5-HT_{1A} and D_{2A} receptors were evaluated *in vitro*. Several of the new derivatives had high affinity to 5-HT_{1A} receptors whereas the affinity to D_{2A} receptors was lower.

Synthesis.

The synthesis of the racemic 8-arylated and 8-aroylated derivatives of 2-(dipropylamino)chroman was performed as shown in Scheme 1. *Endo-* or *exo-***9**[12] was regioselectively stannylated in the C8-position by treatment with BuLi followed by the addition of tributylchlorostannane to give the *endo-* or *exo-***10**, respectively. Palladium catalyzed coupling reactions between the *endo* or *exo-***10** isomers and an iodoarene followed by light induced decomplexation of the $Cr(CO)_3$ group produced either a separable (flash chromatoography) mixture of arylated and aroylated products or selectively one of the products (Table 1). In the reactions leading to the 8-aroylated analogs, the inserted CO is probably donated from the $Cr(CO)_3$ group, as no external CO is added.[13]

Scheme 1.

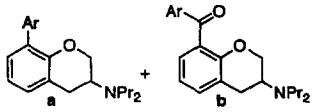


In vitro radioligand binding studies.

The ability of the novel compounds to inhibit [^{3}H]8-OH-DPAT binding to 5-HT_{1A} receptors in rat cortical and hippocampal membranes and [^{3}H]raclopride binding to cloned human D_{2A} receptors expressed in mouse fibroblast (Ltk$^-$) cells *in vitro* are given in Table 2.

Several of the novel derivatives displayed high affinity and selectivity for 5-HT_{1A} receptors over D_{2A} receptors. In general, the aryl substituted analogs had higher affinity for both 5-HT_{1A} and D_{2A} receptors than the aroylated derivatives. In the arylated series the electron withdrawing substituent CF_3 (**14a**) considerably decreased the affinity for 5-HT_{1A} receptors. The 3-furyl analogs **17a** and **17b** displayed slightly lower affinity to 5-HT_{1A} receptors than the corresponding 3-thienyl derivatives **16a** and **16b**. With the exception of **17a**, which has a moderate affinity to D_{2A} receptors (K_i=47.5 nM), the compounds tested displayed more than a 10 fold lower affinity to D_{2A} receptors than to 5-HT_{1A} receptors.

Table 1. Physical Data of Some Novel Chroman Derivatives.



substrate	"Pd"[a]	Product Compd	Ar	yield (%)	mp, (°C)	recrystn solvent[b]	Anal.[c]
exo-**10**	A + CuI	**11a**	Ph	60	195-198	I	$C_{21}H_{27}NO{\cdot}HCl$
		11b	Ph	26	153-154	II	$C_{22}H_{27}NO_2{\cdot}1.5C_2H_2O_4$
exo-**10**	A + CuI	**12a**	2-MeOPh	29	189-191	-	$C_{22}H_{29}NO_2{\cdot}HCl$
		12b	2-MeOPh	20	125-128	-	$C_{23}H_{29}NO_3{\cdot}HCl$
exo-**10**	A + CuI	**13a**	4-MeOPh	23[d]	186-188	I	$C_{22}H_{29}NO_2{\cdot}HCl$
endo-**10**	A	**13b**	4-MeOPh	39[e]	153-155	I	$C_{23}H_{29}NO_3{\cdot}HCl$
exo-**10**	A + CuI	**14a**	4-CF_3Ph	55[f]	203-205	I	$C_{22}H_{26}F_3NO{\cdot}HCl{\cdot}0.5H_2O$
endo-**10**	A	**14b**	4-CF_3Ph	50[g]	139-141	I	$C_{23}H_{26}F_3NO_2{\cdot}HCl$
exo-**10**	B	**15b**	4-MeCOPh	23[h]	150-152	I	$C_{24}H_{29}NO_3{\cdot}HCl$
exo-**10**	A + CuI	**16a**	3-thienyl	26	187-188	I	$C_{19}H_{25}NOS{\cdot}HCl$
		16b	3-thienyl	48	153-155	I	$C_{20}H_{25}NO_2S{\cdot}HCl$
endo-**10**	A + CuI	**17a**	3-furyl	20	119-121	I	$C_{19}H_{25}NO_2{\cdot}1.5C_2H_2O_4$
		17b	3-furyl	41	167-170	I	$C_{20}H_{25}NO_3{\cdot}HCl{\cdot}1.75H_2O$

[a]"Pd": A=$Pd_2(dba)_3$, Ph_3As; B=$(PPh_3)_4Pd$. [b]Recrystallization solvent: (I) Ether/MeOH; (II) MeCN. [c]The compounds were analyzed for C, H and N and the results were within 0.4% of theoretical values. Compound **15b** was analyzed by EI-HRMS; [d]**13b** (7%) was also isolated. [e]**13a** was not detected by GC analysis. [f]**14b** (15%) was also formed as determined by GC analysis. [g]**14a** was not detected by GC analysis. [h]**15a** (10%) was also formed as determined by GC analysis.

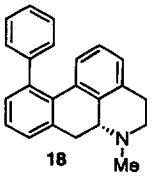
Table 2. Affinities of the Novel Derivatives to Rat Brain 5-HT_{1A} Receptors Labelled by [^{3}H]8-OH-DPAT and Cloned Human D_{2A} Receptors Expressed in Ltk$^-$ Cells Labelled by [^{3}H]Raclopride.

Compd	Ar	K_i (nM)[a] [^{3}H]8-OH-DPAT (5-HT_{1A})	[^{3}H]Raclopride (D_{2A})
11a	Ph	1.1 ± 0.1	590 ± 20
12a	2-MeOPh	1.1 ± 0.1	> 1000
13a	4-MeOPh	1.3 ± 0.1	1090 ± 120
14a	4-CF_3Ph	63.8 ± 17.7	763 ± 130
16a	3-thienyl	1.1 ± 0.2	398 ± 160
17a	3-furyl	5.7 ± 2.1	47.5 ± 2.8
11b	Ph	4.0 ± 0.5	>1000
12b	2-MeOPh	60.8 ± 0.9	>1000
13b	4-MeOPh	10.5 ± 1.0	>1000
14b	4-CF_3Ph	47.2 ± 4.6	>1000
15b	4-MeCOPh	11.0 ± 0.3	>1000
16b	3-thienyl	7.3 ± 0.7	>1000
17b	3-furyl	16.4 ± 7.7	1360 ± 45
1[b]		83	>3000
2[b]		>3000	128

[a]For experimental details see ref 16. The K_i values are means ± standard error of 2-3 experiments performed in duplicate. [b]From ref 1a, IC_{50}-values, 5-HT_{1A} receptors labelled by [^{3}H]5-HT and D_2 receptors labelled by [^{3}H]spiroperidol.

Conclusion.

The present study shows that replacement of the C8 hydroxyl group in the potent and selective D_2 receptor agonist **2** by an aryl or aroyl group results in a new class of chroman derivatives with high affinity and selectivity for 5-HT_{1A} receptors. In terms of structure-affinity relationship these results are in agreement with the recently published data on the high affinity 5-HT_{1A} receptor ligand **18** (K_i=1.8 nM) and derivatives thereof.[14] Therefore, it is possible that these novel aminochroman derivatives have a similar mode of interaction with 5-HT_{1A} receptors as **18**. The series of compounds presented herein may be valuable for the evaluation of a recently proposed homology based 5-HT_{1A} receptor model[14,15] and it may also provide leads for drug development. Current studies are aimed at exploring the pharmacology of the enantiomers of these novel 5-HT_{1A} receptor ligands.



18

Acknowledgment.

Financial support was obtained from Astra Arcus AB. Skillful technical assistance by Gun Torell Svantesson and Christina Fährstedt in the binding assays is gratefully acknowledged.

References and Notes.

1. a) Thorberg, S.-O., Hall, H., Åkesson, C., Svensson, K., Nilsson, J.L.G. *Acta Pharm. Suec.* **1987**, *24*, 169-182. b) Cossery, J.M., Perdicakis, C., Coudert, G., Guillamet, G., Pichat, L. *J. Labelled. Comp. Radiopharm.* **1987**, *25*, 833-853. c) Al Neirabeyeh, M., Reynaud, D., Podona, T., Ou, L., Perdicakis, C., Coudert, G., Guillaumet, G., Pichat, L., Gharib, A., Sarda, N. *Eur. J. Med. Chem.* **1991**, *26*, 497-504. d) Podona, T., Guardiola-Lemaître, B., Caignard, D.-H., Adam, G., Pfeiffer, B., Renard, P., Guillaumet, G. *J. Med. Chem.* **1994**, *37*, 1779-1793.
2. b) Wise, L.D., DeWald, H.A., Hawkins, E.S., Reynolds, D.M., Heffner, T.G., Meltzer, L.T., Pugsley, T.A. *J. Med. Chem.* **1988**, *31*, 688-691.
3. a) Arvidsson, L.-E., Hacksell, U., Nilsson, J.L.G., Hjorth, S., Carlsson, A., Lindberg, P., Sanchez, D., Wikström, H. *J. Med. Chem.* **1981**, *24*, 921-923. b) Middlemiss, D.N., Fozard, J.R. *Eur. J. Pharmacol.* **1983**, *90*, 151-153.
4. a) McDermed, J.D., McKenzie, G.M., Freeman, H.S. *J. Med. Chem.* **1979**, *19*, 547-549. b) Tedesco, J.T., Seeman, P., McDermed, J.D. *Mol. Pharmacol.* **1979**, *16*, 369-381.
5. a)Vermue, N.A., Kaptein, B., Tepper, P.G., de Vries, J.B., Horn, A.S. *Arch. Int. Pharmacodyn.* **1988**, *293*, 37-56. b) Horn, A.S., Kaptein, B., Vermue, N.A., de Vries, J.B., Mulder, T.B.A. *Eur. J. Med. Chem.* **1988**, *23*, 325-328.
6. a) Hacksell, U.; Liu, Y.; Yu, H.; Vallgårda, J.; Backlund Höök, B.; Johansson, A.M.; Lewander, T. *Drug Des. Discovery*, **1993**, *9*, 287-297. b) Hacksell, U.; Johansson, A.M.; Karlén, A.; Svensson, K.; Grol, C.J. In "Chirality and Biological Activity", Eds. H. Frank, B. Holmstedt, and B. Testa, Alan R. Liss, Inc., N.Y., **1989**, pp 247-266.
7. Cossery, J.M., Gozlan, H., Spampinato, U., Perdicakis, C., Guillaumet, G., Pichat, L., Hamon, M. *Eur. J. Pharmacol.* **1987**, *140*, 143-155.
8. Marot, M., Comoy, C., Viaud, M.C., Rettori, M.C., Pfeiffer, B., Morin-Allory, L., Guillaumet, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1077-1082.
9. Andersson, B., Wikström, H., Hallberg, A. *Acta Chem. Scand.* **1990**, *44*, 1024-1028.
10. Johansson, L.; Sohn, D.; Thorberg, S.-O.; Jackson, D.M.; Kelder, D.; Larsson, L.-G.; Rényi, L.; Ross, S.B.; Wallsten, C.; Eriksson, H.; Hu, P.-S.; Jerning, E.; Mohell, N.; Westlind-Danielsson, A. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 216-225.
11. Chumpradit, S.; Kung, M.-P.; Vessotskie, J.; Foulon, C.; Mu, M.; Kung, H.F. *J. Med. Chem.* **1994**, *37*, 4245-4250.
12. Brisander, M., Caldirola, P., Johansson, A.M., Hacksell, U. *J. Org. Chem.* **1998**, *63*, 5362-5367.
13. Caldirola, P., Chowdhury, R., Johansson, A.M., Hacksell, U. *Organometallics*, **1995**, *14*, 3897-3900.
14. Hedberg, M.H., Linnanen, T., Jansen, J.M., Nordvall, G., Hjorth, S., Unelius, L., Johansson, A.M. *J. Med. Chem.* **1996**, *39*, 3503-3513.
15. Hedberg, M.H.; Jansen, J.M.; Nordvall, G.; Hjorth, S.; Unelius, L.; Johansson, A.M. *J. Med. Chem.* **1996**, *39*, 3491-3502.
16. *In vitro* radioligand binding to 5-HT_{1A} and D_{2A} receptors, see: Jackson, D.M.; Mohell, N.; Georgiev, J.; Bengtsson, A.; Larsson, L.-G.; Magnusson, O.; Ross, S.B. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1995**, *351*, 146-155 and Malmberg, Å.; Jackson, D.M.; Eriksson, A.; Mohell, N. *Mol. Pharmacol.* **1993**, *43*, 749-754.