Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 1570–1574

Synthesis and in vitro binding studies of substituted piperidine naphthamides. Part II: Influence of the substitution on the benzyl moiety on the affinity for D_{2L}, $D_{4.2}$, and 5-HT_{2A} receptors

Pascal Carato,[a] Amaury Graulich,[b] Niels Jensen,[c] Bryan L. Roth[c] and Jean-François Liégeois[b,*]

[a]*Laboratoire de Chimie Thérapeutique, Université du Droit et de la Santé Lille II, rue du Professeur Laguesse 3, BP83, F-59006 Lille, France*
[b]*Drug Research Center, Laboratory of Medicinal Chemistry, University of Liège, avenue de l'Hôpital, 1 (B36), B-4000 Liège 1, Belgium*
[c]*Department of Pharmacology School of Medicine and Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina Chapel Hill Medical School, 8032 Burnett-Womack Building, CB# 7365, Chapel Hill, NC 27599, USA*

Received 24 November 2006; revised 20 December 2006; accepted 26 December 2006
Available online 8 January 2007

Abstract—In continuation of our work on *N*-(piperidin-4-yl)-naphthamides, the effect of substituted benzyl groups on D_{2L}, $D_{4.2}$, and 5-HT_{2A} receptor affinity was evaluated. In the 1-naphthamide series most compounds were highly selective for $D_{4.2}$ over D_{2L} and 5-HT_{2A} receptors. Halogen and methyl substitution in position 3 or 4 of the benzyl group increased $D_{4.2}$ affinity. In the 2-naphthamide series a similar high $D_{4.2}$ over D_{2L} selectivity was retained while 5-HT_{2A} affinity was increased. 3-Methoxy, 3-methyl, and 4-methyl substituents were favorable for $D_{4.2}$ affinity while halogens reduced affinity. 2-Naphthamides with a 3-bromo- or a 3-methyl group were mixed $D_{4.2}$/5-HT_{2A} ligands similar to their unsubstituted parent compound. All compounds from both series with significant affinity for $D_{4.2}$ and 5-HT_{2A} receptors were antagonists.

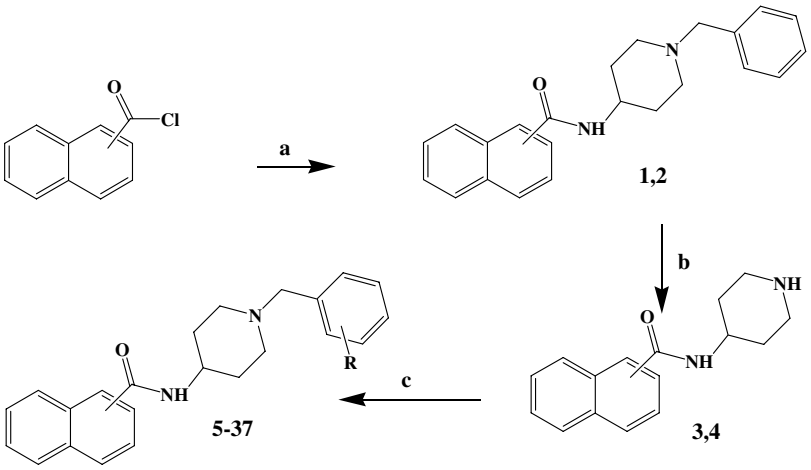
Clozapine profoundly modified the concept of antipsychotic drugs a few decades ago and, due to several side effects, has also stimulated the search for safer and more effective antipsychotics. The discovery of new and safer antipsychotic drug is still an enormous challenge in the treatment of psychotic disorders.[1–4] Although some compounds have been marketed during the last decade, progress is slow, also caused by the fact that the molecular and cellular mechanisms underlying the development of schizophrenia remain unclear.[5] Taking into account some structural features of clozapine, we have developed a first series of compounds based on *N*-(piperidin-4-yl)- and *N*-(piperidin-1-yl)-naphthamide template.[6] Clozapine can be characterized by two structural parameters: as a basic nitrogen and an electronically rich aromatic ring separated by a distance of 7.72 Å.[7] In the first part of this work, we have found that the position of the amide linkage has a significant influence on the binding to the tested receptors. *N*-(1-benzyl-piperidin-4-yl) derivatives were found to be superior compared to their 4-substituted amino-piperidin-1-yl analogues when tested for binding to $D_{4.2}$ and 5-HT_{2A}receptors. Therefore, we have focused our further chemical effort on the *N*-(1-benzyl-piperidin-4-yl) series.

In this publication, we report the preparation and the in vitro $D_{4.2}$, D_{2L}, and 5-HT_{2A} binding of a series of substituted benzyl analogues of *N*-(1-benzylpiperidin-4-yl)-1-naphthamide (**1**) or *N*-(1-benzylpiperidin-4-yl)-2-naphthamide (**2**). Intrinsic activity was tested for compounds presenting a significant affinity for these receptor sites.

The synthesis of these compounds was accomplished by the sequence of reactions outlined in Scheme 1. 1-Naphthoyl chloride or 2-naphthoyl chloride in ethyl acetate was reacted with 4-amino-1-benzyl-piperidine to afford *N*-(1-benzylpiperidin-4-yl)-1-naphthamide (**1**)

Keywords: $D_{4.2}$ receptors; 5-HT_{2A} receptors; Antagonist; Schizophrenia.
* Corresponding author. Tel.: +32 43 66 43 77; fax: +32 43 66 43 62; e-mail: JF.Liegeois@ulg.ac.be

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.12.106



Scheme 1. Reagents and conditions: (a) 4-amino-1-benzylpiperidine, EtOAc, Et_3N; (b) 10% Pd/C, ammonium formate, MeOH; (c) R–C_6H_4–CH_2–Cl or C_5H_4N–CH_2–Cl, KI, Et_3N, anhydrous acetone. 1- and 2-Naphthamide derivatives: **R** = H (**1**, **2**), 2-Cl (**5**, **20**), 3-Cl (**6**, **21**), 4-Cl (**7**, **22**), 2-Br (**8**, **23**), 3-Br (**9**, **24**), 4-Br (**10**, **25**), 3-CF_3 (**11**, **26**), 4-CF_3 (**12**, **27**), 2,3,4,5,6-F (**13**, **28**), 4-NO_2 (**14**, **29**), 3-MeO (**15**, **30**), 4-MeO (**16**, **31**), 2-Me (**17**, **32**), 3-Me (**18**, **33**), 4-Me (**19**, **34**).

or *N*-(1-benzylpiperidin-4-yl)-2-naphthamide (**2**). These compounds were used for preparing other compounds in the series. *N*-(1-Benzylpiperidin-4-yl)-1-naphthamide (**1**) was first debenzylated with ammonium formate and Pd/C in refluxing methanol to give the corresponding *N*-(piperidin-4-yl)-1-naphthamide (**3**). *N*-(1-Benzylpiperidin-4-yl)-2-naphthamide (**2**) was debenzylated under 10 bar hydrogen in the presence of Pd/C to give *N*-(piperidin-4-yl)-2-naphthamide (**4**). Amines (**3-4**) were alkylated by using the appropriate benzyl halide under basic conditions to give the corresponding *N*-substituted benzyl analogues (**5**–**37**).

The affinity of compounds for cloned human $D_{4.2}$ and D_{2L}, and native rat 5-HT_{2A} receptors was evaluated in in vitro binding assays using the radioligands [^{3}H]nemonapride, [^{3}H]spiperone, and [^{3}H]ketanserin, respectively, according to previously described procedures.[8] An initial screen at 1 μM was performed and drugs which had significant activity (>50% inhibition) had detailed inhibition isotherms performed and K_i values calculated according to the Cheng–Prusoff equation.[9] The in vitro receptor binding data are reported in Tables 1 and 2. Compounds with significant affinity were tested for agonistic effects at $D_{4.2}$ and 5-HT_{2A} receptors as described previously.[6] Antagonism was further verified at a concentration of 5 μM in the presence of 500 nM dopamine for $D_{4.2}$receptors and 100 nM serotonin for 5-HT_{2A} receptors.

None of the compounds had appreciable affinity for D_{2L} receptors. Unsubstituted *N*-benzyl derivatives (**1**, **2**) possessed moderate to high affinity for D_4 receptors with negligible affinity for D_{2L} receptors, while compound **2** had additional affinity for 5-HT_{2A} receptors.

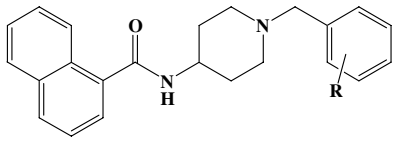
In this series of compounds a clear difference in binding to $D_{4.2}$ and 5-HT_{2A} receptors was observed between the 1- and 2-naphthamide series. Several 1-naphthamide derivatives had a significant selectivity for $D_{4.2}$ sites versus D_{2L} and 5-HT_{2A} sites. In comparison with the corresponding unsubstituted derivative (**1**), the presence of a substituent such as a chloro (**6, 7**), bromo (**9, 10**), trifluoromethyl (**11**, **12**) or methyl group (**17**–**19**) in position 3 or 4 of the benzyl moiety increased the affinity for $D_{4.2}$ receptors. A nitro group in position 4 (**14**) was not tolerated. A methoxy group either in position 3 or 4 (**15, 16**) did not seem to be favorable. An electron withdrawing substituent in position 2 of the benzyl moiety (**5**, **8**) reduced $D_{4.2}$ affinity. The pentafluoro substituent (**13**) was unfavorable.

In 2-naphthamide series, a mixed $D_{4.2}$ and 5-HT_{2A} profile was observed. The unsubstituted (**2**), the 3-bromo (**24**) or the 3-methyl (**33**) derivatives were the most potent. For further in vivo biological evaluation the substituted derivatives (**24**, **33**) have a lower solubility which can be a drawback. In this series, the affinity for 5-HT_{2A} sites was more affected by the substitution on the benzyl moiety than the $D_{4.2}$ affinity. The presence of a nitro group in position 4 (**29**) was better tolerated than in the 1-naphthamide series. The pentafluoro substitution (**28**) was not favorable. The replacement of the aromatic ring by a pyridine was deleterious whatever the position of the pyridine nitrogen was.

In functional assays for determining intrinsic activity on $D_{4.2}$ and 5-HT_{2A} receptors, all tested compounds (see Tables 1 and 2) had no agonistic activity. The antagonism of these compounds was further verified by co-application with the respective agonists. All tested compounds blocked the effects of dopamine and serotonin at the respective receptors. This is in agreement with their binding affinities together with their absence of agonism.

The present chemical modifications did not increase D_{2L} affinity. The absence of an *ortho*-methoxy group in the vicinity of the carboxamide group in the previous series leads to a reduction in the affinity for D_{2L} sites in

Table 1. In vitro binding affinities of substituted *N*-(1-benzylpiperidin-4-yl)-1-naphthamides for D_{2L}, $D_{4.2}$, and 5-HT_{2A} receptors



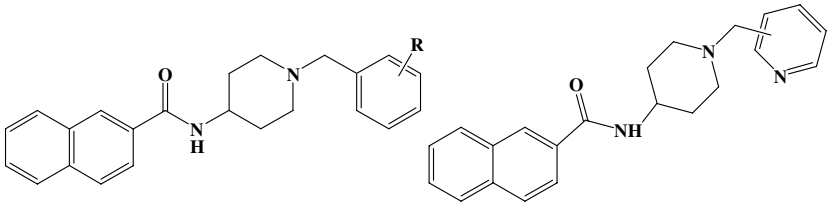
Compound	R	$D_{4.2}$[a]	5-HT_{2A}[a]	D_{2L}[a]
1	H	162 ± 48[b]	>1000[b]	>1000
5	2-Cl	329 ± 214[b]	—	—
6	3-Cl	116 ± 18[b]	49%	0%
7	4-Cl	43 ± 19[b]	23%	0%
8	2-Br	35%	—	8%
9	3-Br	66 ± 35[b]	462 ± 93[b]	—
10	4-Br	44 ± 2[b]	—	4%
11	3-CF_3	119 ± 18[b]	—	0%
12	4-CF_3	96 ± 13[b]	32%	0%
13	2,3,4,5,6- F	0%	228 ± 62	0%
14	4-NO_2	42%	20%	0%
15	3-MeO	168 ± 40[b]	23%	0%
16	4-MeO	223 ± 74[b]	—	3%
17	2-Me	155 ± 30[b]	26%	9%
18	3-Me	77 ± 16[b]	38%	11%
19	4-Me	69 ± 15[b]	33%	13%

[a] K_i (in nM; means ± SD; $n \geqslant 2$ if unspecified) or percentage of inhibition at 1 μM.

[b] The compound had no agonistic activity in functional assays and blocked the effect of 100 nM serotonin (5-HT_{2A} receptors) or 500 nM dopamine ($D_{4.2}$ receptors).

accordance with previous data.[10,11] This reduction was not necessarily due to the basic side chain as we have previously found in a pyridobenzodiazepine series that an 4-amino-1-benzyl-piperidine side chain leads to molecules with significant D_{2L}, $D_{4.2}$, and 5-HT_{2A} receptor affinity.[8] Therefore, if an increase of D_2 affinity is needed, it is suggested to prepare the respective *ortho*-methoxy derivatives. The degree of D_2 receptor blockade needed for antipsychotic activity still remains unknown. Clozapine, for instance, is a weak D_2 blocker but possesses a clear anti-schizophrenic potential. Neuroimaging studies have shown that an optimal D_2 receptor occupancy of 60–70% is sufficient to produce an atypical antipsychotic effect.[12–14] If D_2 receptor occupancy is too high, the atypical profile can be lost even in the presence of high 5-HT_2 occupancy.[14] Dopamine and serotonin systems have been implicated in the pathophysiology of schizophrenia and other psychotic disorders. The high affinity of clozapine for the D_4 and 5-HT_{2A} receptor versus the D_2 receptor contributes to a low risk of extrapyramidal side effects. The development of D_4 ligands for treating schizophrenia failed particularly when evaluating the efficacy of L-745,870[15]or, more recently, sonepiprazole.[16] In some cases, agonist activity was detected and could be the explanation for low efficiency.[17,18] However, D_4 receptors may act in synchrony with other neurotransmitter receptors to mediate, at least in part, the beneficial therapeutic effects of several

Table 2. In vitro binding affinities of substituted *N*-(1-benzylpiperidin-4-yl)- and *N*-(1-(pyridylmethyl)-piperidin-4-yl)- 2-naphthamides for D_{2L}, $D_{4.2}$, and 5-HT_{2A} receptors



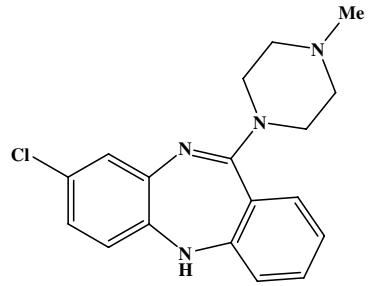
2-34 **35-37**

Compound	R	$D_{4.2}$[a]	5-HT_{2A}[a]	D_{2L}[a]
2	H	11 ± 1[b]	44 ± 5[b]	>1000
20	2-Cl	48%	133 ± 18[b]	0%
21	3-Cl	54 ± 4[b]	133 ± 2[b]	29%
22	4-Cl	37 ± 4[b]	242 ± 50[b]	15%
23	2-Br	31%	47%	0%
24	3-Br	36 ± 19[b]	53 ± 10[b]	—
25	4-Br	34 ± 11[b]	223 ± 60[b]	—
26	3-CF_3	103 ± 48[b]	15%	9%
27	4-CF_3	84 ± 7	36%	0%
28	2,3,4,5,6- F	0%	4%	0%
29	4-NO_2	181 ± 55[b]	278 ± 112[b]	0%
30	3-MeO	16 ± 2[b]	158 ± 8[b]	0%
31	4-MeO	31 ± 4[b]	151 ± 37[b]	18%
32	2-Me	26 ± 4[b]	175 ± 28[b]	6%
33	3-Me	11 ± 6[b]	87 ± 13[b]	20%
34	4-Me	21 ± 4[b]	222 ± 68[b]	42%
35	2-Pyridyl	299 ± 8	545 ± 175	5%
36	3-Pyridyl	326 ± 78	524 ± 105	4%
37	4-Pyridyl	32%	695 ± 172	5%

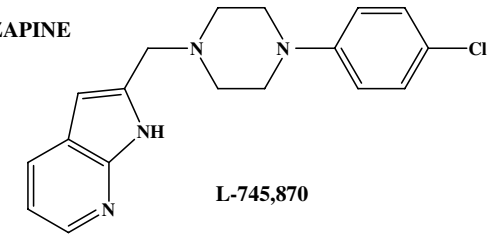
[a] K_i (in nM; mean ± SD; $n \geqslant 2$ if unspecified) or percentage of inhibition at 1 μM.

[b] The compound had no agonistic activity in functional assays and blocked the effect of 100 nM serotonin (5-HT_{2A} receptors) or 500 nM dopamine ($D_{4.2}$ receptors).

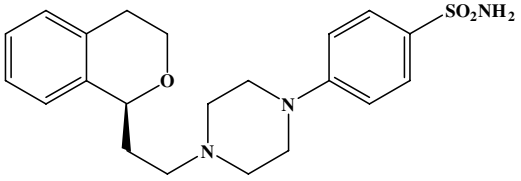
antipsychotics in patients with schizophrenia and other psychotic disorders. Indeed, an involvement of D_4 receptors in hippocampal neurons' activity by depressing *N*-methyl-D-aspartate (NMDA) receptor activity through the activation of platelet-derived growth factor receptors was reported.[19] An inhibition of glutamatergic signaling in the frontal cortex was also shown.[20] Both effects tend to link this receptor and the glutamate signaling system which has been clearly associated with cognition. The evaluation of the mixed D_4/5-HT_{2A} ligand fananserin in schizophrenic patients was unsuccessful.[21] Nevertheless, the role of these receptors' needs to be clarified since it has been shown that chronic clozapine or related antipsychotics increase D_4 receptors density and decrease 5-HT_{2A} receptor density in brain areas involved in psychotic disorders.[22–24]



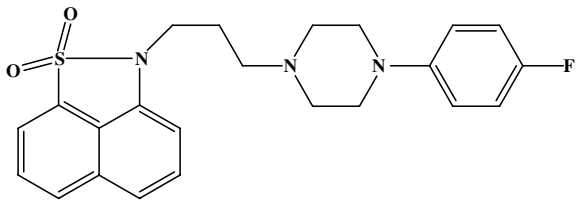
CLOZAPINE



L-745,870



SONEPIPRAZOLE



FANANSERIN

.

In summary, the naphthamides presented in this and the previous article act as antagonists at $D_{4.2}$ and 5-HT_{2A} receptors with highly varying selectivities. These data will be useful in future molecular modeling studies for the development of new CNS drugs and, finally, to increase our understanding of CNS disorders.

Acknowledgments

The technical assistance of Y. Abrassart, S. Counerotte is gratefully acknowledged. A.G. is a Research Fellow of the 'Fonds pour la formation à la Recherche Industrielle et Agricole (F.R.I.A.)'. J.F.L. is a Senior Research Associate of the 'Fonds National de la Recherche Scientifique de Belgique (F.N.R.S.)'. P.C. was supported by a post-doctoral fellowship of the University of Liège. Functional data were generously provided in the context of the National Institute of Mental Health's Psychoactive Drug Screening Program (NIMH PDSP) Contract NO1MH32004.

References and notes

1. Wong, A. H. C.; Van Tol, H. H. M. *Neurosci. Biobehav. Rev.* **2003**, *27*, 269.
2. *Neurotransmitter Receptors in Actions of Antipsychotic Medications; Pharmacology and Toxicology Series*; Lidow, M. S., Ed.; CRC Press, 2000.
3. Raviña, E.; Masaguer, C. F. *Curr. Med. Chem. CNS Agents* **2001**, *1*, 43.
4. Raggi, M. A. (guest editor) Pharmacological treatment of schizophrenia: Recent antipsychotic drugs and new therapeutic strategies. *Curr. Med. Chem.* **2004**, *11*, 267.
5. Roth, B. L.; Sheffler, D. L.; Kroeze, W. K. *Nat. Rev. Drug Discov.* **2004**, *3*, 353.
6. Carato, P.; Graulich, A.; Jensen, N.; Roth, B. L.; Liégeois, J.-F. *Bioorg. Med. Chem. Lett.*, (**2007**), in press, doi:10.1016/j.bmcl.2006.12.096.
7. Petcher, T. J.; Weber, H.-P. *J. Chem. Soc. Perkin Trans. II* **1976**, 1415.
8. Liégeois, J.-F.; Eyrolles, L.; Ellenbroek, B. A.; Lejeune, C.; Carato, P.; Bruhwyler, J.; Géczy, J.; Damas, J.; Delarge, J. *J. Med. Chem.* **2002**, *45*, 5136.
9. Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
10. Högberg, T. *Drugs future* **1991**, *16*, 333.
11. Arora, J.; Bordeleau, M.; Dube, L.; Jarvie, K.; Mazzocco, L.; Peragine, J.; Tehim, A.; Egle, I. *Biorg. Med. Chem. Lett.* **2005**, *15*, 5253.
12. Kapur, S.; Seeman, P. *J. Psychiatry Neurosci.* **2000**, *25*, 161.
13. Kapur, S.; Seeman, P. *Am. J. Psychiatry* **2001**, *158*, 360.
14. Nyberg, S.; Eriksson, B.; Oxenstierna, G.; Halldin, C.; Farde, L. *Am. J. Psychiatry* **1999**, *156*, 869.
15. Kramer, M. S.; Last, B.; Getson, A.; Reines, S. A. *Arch. Gen. Psychiatry* **1997**, *54*, 567.
16. Corrigan, M. H.; Gallen, C. C.; Bonura, M. L.; Merchant, K. M., et al. *Biol. Psychiatry* **2004**, *55*, 445.
17. Gazi, L.; Bobirnac, I.; Danzeisen, M.; Schupbach, E.; Bruinvels, A. T.; Geisse, S.; Sommer, B.; Hoyer, D.; Tricklebank, M.; Schoeffter, P. *Br. J. Pharmacol.* **1998**, *124*, 889.
18. Gazi, L.; Bobirnac, I.; Danzeisen, M.; Schupbach, E.; Langenegger, D.; Sommer, B.; Hoyer, D.; Tricklebank, M.; Schoeffter, P. *Br. J. Pharmacol.* **1999**, *128*, 613.
19. Kotecha, S. A.; Oak, J. N.; Jackson, M. F.; Perez, Y.; Orser, B. A.; Van Tol, H. H. M.; MacDonald, J. F. *Neuron* **2002**, *35*, 1111.
20. Rubinstein, M.; Cepeda, C.; Hurst, R. S.; Flores-Hernandez, J.; Ariano, M. A.; Falzone, T. L.; Kozell, L. B.; Meshul, C. K.; Bunzow, J. R.; Low, M. J.; Levine, M. S.; Grandy, D. K. *J. Neurosci.* **2001**, *21*, 3756.

21. Truffinet, P.; Tamminga, C. A.; Fabre, L. F.; Meltzer, H. Y.; Riviere, M. E.; Papillon-Downey, C. *Am. J. Psychiatry* **1999**, *156*, 419.
22. Tarazi, F. I.; Zhang, K.; Baldessarini, R. J. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 711.
23. Tarazi, F. I.; Zhang, K.; Baldessarini, R. J. *Psychopharmacology* **2002**, *161*, 263.
24. Moran-Gates, T.; Massari, C.; Graulich, A.; Liégeois, J.-F.; Tarazi, F. I. *J. Neurosci. Res.* **2006**, *84*, 675.