

Synthesis and binding affinity of novel 3-aminoethyl-1-tetralones, potential atypical antipsychotics[☆]

Mario Alvarado,^a Alberto Coelho,^a Christian F. Masaguer,^a Enrique Raviña,^{a,*} José Brea,^b
J. Fernando Padín^b and María I. Loza^b

^a*Departamento de Química Orgánica, Laboratorio de Química Farmacéutica, Facultad de Farmacia,
Universidad de Santiago de Compostela. E-15782, Santiago de Compostela, Spain*

^b*Departamento de Farmacología, Facultad de Farmacia, Universidad de Santiago de Compostela. E-15782,
Santiago de Compostela, Spain*

Received 4 February 2005; revised 1 April 2005; accepted 14 April 2005

Available online 5 May 2005

Abstract—A series of 3-aminoethyl-1-tetralones, conformationally constrained higher homologues of haloperidol (standard for typical antipsychotic profile), have been obtained by a four-step route from valerolactone. Their binding affinities at dopamine D₂ and serotonin 5-HT_{2A} and 5-HT_{2C} receptors were determined, showing in some cases an atypical antipsychotic profile.
© 2005 Elsevier Ltd. All rights reserved.

Schizophrenia is a disease of unknown aetiology affecting approximately 1% of the population. Classical (typical) neuroleptics such as haloperidol (**Fig. 1**) are currently used for the treatment of this disease, but their use is associated with severe mechanism-related side effects, including induction of acute extrapyramidal symptoms (EPS).¹ The clinical efficacy of classical antipsychotics in the treatment of schizophrenia and

other psychotic disorders is directly related to their ability to block dopamine D₂ receptors in the brain;² however, it has been reported that dopamine receptor blockade in the striatum is closely associated with their extrapyramidal side effects.³

The introduction of clozapine for treatment-resistant schizophrenia gave rise to a new group of atypical or non-classical antipsychotics, which have no EPS and are effective against negative symptoms.⁴ These drugs exhibit potent antagonism at multiple receptor subtypes including dopamine and specially serotonin receptors, hinting at the implication of the serotonergic system in this pathology.⁵ Meltzer et al.⁶ suggested that in the efficacy of clozapine and other atypical antipsychotics the most important factor is their relative affinities for D₂ and 5-HT_{2A} receptors.⁷ They proposed that the ratio between pK_i for 5-HT_{2A} and pK_i for D₂ may be used to discriminate atypical antipsychotics (ratio >1.12) from classical antipsychotics (ratio <1.09). Experimental and clinical studies seem to confirm the major role of the 5-HT_{2A} receptor for the atypical profile of the antipsychotics;⁸ on the other hand, many of these drugs block not only 5-HT_{2A} but other serotonin receptors, particularly 5-HT_{2C} receptors,⁹ and this blockade has been suggested to be responsible for reducing EPS.¹⁰ These findings have given cause for 5-HT_{2C} receptor to be also considered as a potential target in the treatment of psychotic illnesses.¹¹ Clozapine remains the prototype of atypical

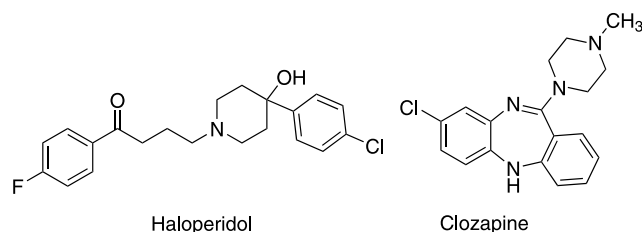


Figure 1. Prototypes of typical (haloperidol) and atypical (clozapine) antipsychotics.

Keywords: Aminoethyltetralones; Valerophenones; Dopamine receptors; Serotonin receptors; Antipsychotics.

[☆]This is the 32nd paper in the series 'Synthesis and CNS Activity of Conformationally Restricted Butyrophenones'; for preceding paper, see Ref. 14.

* Corresponding author. Tel.: +34 981 594 628; fax: +34 981 594 912; e-mail: qofara@usc.es

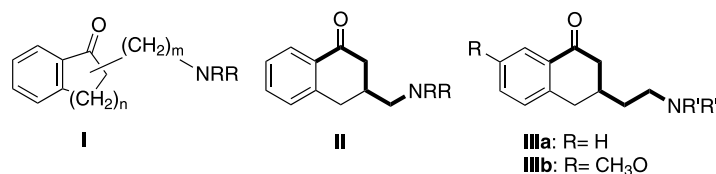


Figure 2.

antipsychotic drugs and no currently available agents appear to have the spectrum of efficacy of this drug. However, treatment with clozapine is associated with an increased risk of agranulocytosis,¹² which strongly limits its therapeutic use. Hence, the discovery of a more effective side effects free therapy for the treatment of schizophrenia remains a challenging research goal.

We have reported the synthesis, pharmacological activity and molecular modelling of the aminoalkylbenzocycloalkanones **I** (Fig. 2), which are conformationally restricted butyrophenone analogues of haloperidol,¹³ as part of a program aimed at developing potential atypical antipsychotic compounds. Between these compounds, the favourable pharmacological profile of the tetralone derivatives **II**¹⁴ has prompted us to explore the structure–activity relationships of this system as a scaffold for the design of new analogues of haloperidol. Herein, we wish to report the synthesis of 3-aminoethyl-1-tetralones (**IIIa**) and 3-aminoethyl-7-methoxy-1-tetralones (**IIIb**), and their binding affinities on D₂, 5-HT_{2A} and 5-HT_{2C} receptors. These compounds correspond to a series of CNS agents (*aminovalerophenones*), which are higher homologues of the 3-aminomethyl-1-tetra-

lones **II** (conformationally restricted *aminobutyrophe-nones*). Although the butyrophenone moiety has been accepted as an optimized side chain for the D₂ receptor,¹ remarkable increases in affinity at this receptor have been described with the elongation of the chain length of the butyrophenone to the valerophenone moiety.¹⁵ Also, extension of butyrophenones to valerophenones has been reported to enhance σ -receptor affinity,¹⁶ and these receptors have been pointed out as potential sites of action of atypical antipsychotics.¹⁷

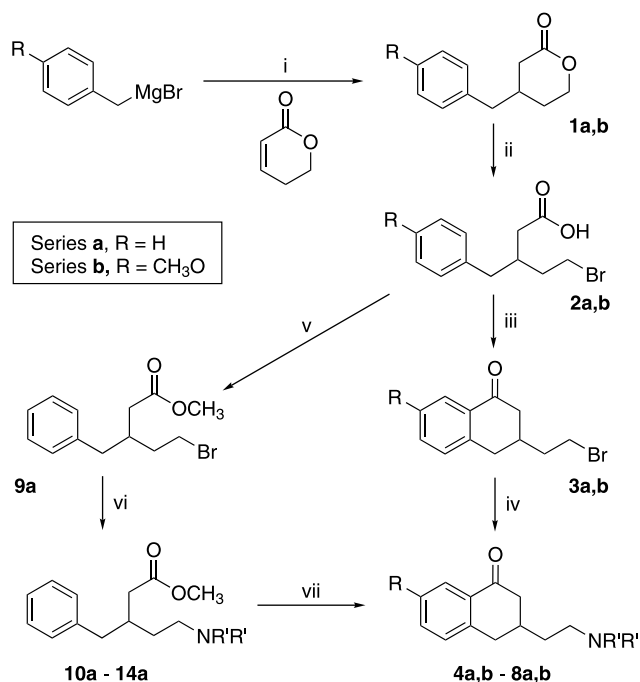
In the first stage of this research, we want to explore, as part of the general structure **III**, different amine moieties (Table 1) present in several CNS agents: arylpiperazines such as *N*-(2-methoxyphenyl)-piperazine and *N*-(2-pyridyl)piperazine (present in fluanisone and buspirone, respectively), a substituted piperidine (*N*-(6-fluorobenzisoxazol-3-yl)piperidine, the amine of the antipsychotic risperidone), and two 1,3,8-triazaspirodecanones related to spiperone.

The target 3-aminoethyltetralones **IIIa–b** were prepared as shown in Scheme 1. Benzyl-lactones **1a,b** were synthesized by TMSCl-TMEDA activated cuprate addition¹⁸

Table 1. Binding affinities for aminoethyltetralones **4a,b–8a,b** (see Scheme 1) and reference antipsychotics^a

Compound	R	NR'R'	pK _i ^b			pK _i ratio 5-HT _{2A} /D ₂
			5-HT _{2A}	5-HT _{2C}	D ₂	
4a	H		6.59 ± 0.29	6.35 ± 0.10	6.97 ± 0.19	0.95
4b	OCH ₃		6.65 ± 0.07	5.72 ± 0.21	6.55 ± 0.34	1.01
5a	H		6.54 ± 0.11	<5	<5	—
5b	OCH ₃		6.33 ± 0.11	5.81 ± 0.20	<5	—
6a	H		8.29 ± 0.25	7.06 ± 0.11	5.98 ± 0.42	1.38
6b	OCH ₃		8.23 ± 0.14	6.89 ± 0.19	7.04 ± 0.31	1.17
7a	H		<5	<5	<5	—
7b	OCH ₃		<5	<5	<5	—
8a	H		6.15 ± 0.13	7.05 ± 0.18	<5	—
8b	OCH ₃		5.98 ± 0.15	6.90 ± 0.21	<5	—
Haloperidol			6.78 ± 0.25	5.14 ± 0.18	9.22 ± 0.12	0.73
Clozapine			8.04 ± 0.31	7.98 ± 0.11	6.65 ± 0.17	1.21

^a For binding assay methods, see Ref. 13.^b Values are means of three separate experiments (s.e.m. less than 6%).



Scheme 1. Reagents: (i) CuI, TMEDA, TMSCl, THF (60–70%); (ii) HBr/AcOH 33% (88–95%); (iii) TFA, TFAA (75%); (iv) HNR'R', Na₂CO₃, KI, MIK (50–90%); (v) CH₂N₂, Et₂O (98%); (vi) HNR'R', Na₂CO₃, KI, MIK (30–75%); (vii) PPA (20–50%).

of benzyl (or 4-methoxybenzyl) to 5,6-dihydro-2*H*-pyran-2-one in 60–70% yield. Reaction of lactones **1a,b** with hydrogen bromide in acetic acid afforded the stable 5-bromo-3-benzylvaleric acids **2a,b**, which were cyclized with trifluoroacetic acid-trifluoroacetic anhydride to give the corresponding 3-bromoethyltetralones **3a,b** in 75–78% yield. Subsequent nucleophilic substitution of bromine with secondary amines (see Table 1) in basic methyl isobutyl ketone led to the 3-aminoethyltetralones **4a,b–8a,b** in good to excellent yields.

Alternatively, bromoacid **2a** was esterified with diazomethane to quantitatively afford the bromoester **9a**, which, by nucleophilic substitution with amines in the presence of Na₂CO₃ and catalytic IK, led to the β-benzyl-ω-aminoesters **10a–14a** in 30–75% yield. Finally, acid-catalyzed ring closure with polyphosphoric acid gave the final aminoethyltetralones in 20–50% yield.

The binding affinities of the aminoethyltetralones **4a,b–8a,b** at the 5-HT_{2A}, 5-HT_{2C} and dopamine D₂ receptors are summarized in Table 1. Aminoethyltetralones containing a 4-(*o*-methoxyphenyl)piperazine fragment (compounds **4a** and **4b**) show modest and similar affinity at the three receptors tested, while those compounds bearing a 4-(2-pyridyl)piperazine, that is **5a** and **5b**, lack appreciable affinity for dopamine D₂ receptors. Because of this low affinity at D₂ receptors, compounds **5a** and **5b** do not possess interest as potential antipsychotics, but **5a** could have an interesting profile as selective 5-HT_{2A} compound. However, some of these piperazine compounds could bind at σ receptors because they possess structural characteristics that are favourable for such binding.¹⁹

Table 2. Binding affinities for aminovalerophenones **6a,b** and aminobutyrophenones **15–17**

Compd	<i>n</i>	R ₆	R ₇	p <i>K</i> _i ^a			p <i>K</i> _i ratio 5-HT _{2A} /D ₂
				5-HT _{2A}	5-HT _{2C}	D ₂	
6a	2	H	H	8.29	7.06	5.98	1.38
6b	2	H	OCH ₃	8.23	6.89	7.04	1.17
15^b	1	H	H	8.57	6.89	7.24	1.18
16^b	1	OCH ₃	H	7.34	5.79	6.34	1.16
17^b	1	OCH ₃	OCH ₃	8.02	6.83	6.82	1.18

^a Values are means of three separate experiments (s.e.m. less than 6%).

^b Data from Ref. 14.

The 1,3,8-triazaspirodecanone derivatives **7a** and **7b** lack affinity at the three targeted receptors. On the contrary, compounds bearing a 1,3,8-triazaspirodecanone moiety (i.e., **8a** and **8b**) behave as 5-HT₂ selective ligands: display significant affinity for the 5-HT₂ receptors assayed, with about 10-fold higher affinity for 5-HT_{2C} receptors, and also lack affinity at D₂ receptors. The extra carbonyl group in **8a,b** versus **7a,b** seems to enhance affinity at 5-HT_{2C} receptors and, to a small extent, at 5-HT_{2A} receptors, which is in accordance with the binding profile of some reported 1,3,8-triazaspirodecanone derivatives.²⁰

On the basis of the 5-HT_{2A}/D₂ antagonism hypothesis, it is worth mentioning compounds **6a** and **6b** as potential atypical antipsychotics,²¹ with a Meltzer's ratio of 1.38 and 1.17, respectively, both higher than 1.12, the value from which Meltzer predicts an atypical profile for antipsychotics.⁶ Both compounds exhibit similar affinities at 5-HT_{2A} and 5-HT_{2C} receptors, while at the D₂ receptor compound **6b** displays 10-fold higher affinity than **6a**, hinting at a favourable effect of the 7-methoxy substituent on the D₂ receptor binding.

In comparison with their butyrophenone analogues,¹⁴ benzisoxazolyloxy-piperidine compounds **6a** and **6b** (Table 2) exhibit similar affinities and selectivities for the 5-HT_{2A}, 5-HT_{2C} and D₂ receptors, with a p*K*_i ratio 5-HT_{2A}/D₂ higher than 1.15 in all five compounds. In conclusion, enlargement of the methylene bridge between piperidine and the tetralone ring by one CH₂ did not cause decrease of affinity at the three receptors tested.

In summary, we have described the synthesis and binding affinity of new 3-aminoethyltetralones as conformationally constrained higher homologues of haloperidol. From this work has emerged the benzisoxazolyloxy-piperidine compound **6b**, as potential antipsychotic compound, as a result of its good affinity and Meltzer's ratio.

Acknowledgements

This work was supported by Spanish *Comisión Interministerial de Ciencia y Tecnología* (CICYT) under Grants

SAF2002-04195-C03-02, by Xunta de Galicia under Grant PGIDT01-PXI20306PR, and by the Fundació La Marató de TV3.

References and notes

- Altar, C. A.; Martin, A. R.; Thurkauf, A. In *Burger's Medicinal Chemistry and Drug Discovery*, 6th ed; Abraham, D. J., Ed.; John Wiley & Sons: New Jersey, 2003; Vol. 6, p 599.
- (a) Seeman, P.; Chou-Wong, M.; Tadesco, J.; Wong, K. *Nature* **1976**, *261*, 717; (b) Peroutka, S. J.; Snyder, S. H. *Am. J. Psychiatry* **1980**, *137*, 1518; (c) Hartman, D. S.; Civelli, O. *Prog. Drug Res.* **1997**, *48*, 173.
- (a) Sanberg, P. R. *Nature (London)* **1980**, *284*, 472; (b) Nowak, K.; Welsch-Kunze, S.; Kuschinsky, K. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1988**, *337*, 385.
- (a) Fitton, A.; Heel, R. C. *Drugs* **1990**, *40*, 722; (b) Schwarz, J. T.; Brotman, A. W. *Drugs* **1992**, *44*, 981; (c) Rosenheck, R.; Cramer, J.; Xu, W.; Thomas, J.; Henderson, W.; Frisman, L.; Fye, C.; Charney, D. N. *Engl. J. Med.* **1997**, *337*, 809.
- Sanders-Buch, E.; Mayer, S. E. In *The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon, R. W., Goodman, A., Eds.; McGraw-Hill: New York, 1996, p 249.
- (a) Meltzer, H. Y.; Matsubara, S.; Lee, J. C. *Psychopharmacol. Bull.* **1989**, *25*, 390; (b) Roth, B. L.; Tandra, S.; Burgess, L. H.; Sibley, D. R.; Meltzer, H. Y. *Psychopharmacology* **1995**, *120*, 365; (c) Roth, B. L.; Meltzer, H. Y.; Khan, N. *Adv. Pharmacol.* **1998**, *42*, 482.
- Lowe, J. A., III. *Curr. Med. Chem.* **1994**, *1*, 50.
- (a) Van Oekelen, D.; Luyten, W. H. M. L.; Leysen, J. E. *Life Sci.* **2003**, *72*, 2429; (b) Sipes, T. E.; Geyer, M. A. *Brain Res.* **1997**, *761*, 97; (c) Okuyama, S.; Chaki, S.; Kawashima, N.; Suzuki, Y.; Ogawa, S.; Kumagai, T.; Nakazato, A.; Nagamine, M.; Yamaguchi, K.; Tomisawa, K. *Brit. J. Pharmacol.* **1997**, *121*, 515.
- Di Matteo, V.; Cacchio, M.; Di Giulio, C.; Di Giovanni, G.; Esposito, E. *Pharmacol. Biochem. Behav.* **2002**, *71*, 607.
- Reavill, C.; Kettle, A.; Holland, V.; Riley, G.; Blackburn, T. P. *Br. J. Pharmacol.* **1999**, *126*, 572.
- Wood, M. D.; Heidbreder, C.; Reavill, C.; Ashby, C. R., Jr.; Middlemiss, D. N. *Drug Dev. Res.* **2001**, *54*, 88.
- Pirmohamed, M.; Park, K. *CNS Drugs* **1997**, *7*, 139.
- Brea, J.; Rodrigo, J.; Carrieri, A.; Sanz, F.; Cadavid, M. I.; Enguix, M. J.; Villazón, M.; Mengod, G.; Caro, Y.; Masaguer, C. F.; Raviña, E.; Centeno, N. B.; Carotti, A.; Loza, M. I. *J. Med. Chem.* **2002**, *45*, 54, and references cited therein.
- Caro, Y.; Torrado, M.; Masaguer, C. F.; Raviña, E.; Padín, F.; Brea, J.; Loza, M. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 585.
- Mewshaw, R. E.; Silverman, L. S.; Mathew, R. M.; Kaiser, C.; Sherrill, R. G.; Cheng, M.; Tiffany, C. W.; Karbon, E. W.; Bailey, M. A.; Borosky, S. A.; Ferkany, J. W.; Abreu, M. E. *J. Med. Chem.* **1993**, *36*, 1488.
- Ablordepey, S. Y.; Issa, H.; Fischer, J. B.; Howie, K. J. B.; Glennon, R. A. *Med. Chem. Res.* **1993**, *3*, 131.
- (a) Leonard, B. E. *Pharmacopsychiatry* **2004**, *37*, S166; (b) Hayashi, T.; Su, T.-P. *CNS Drugs* **2004**, *18*, 269.
- van Heerden, P. S.; Bezuidenhout, B. C. B.; Ferreira, D. *Tetrahedron* **1996**, *52*, 12313.
- (a) Ablordepey, S. Y.; Fischer, J. B.; Law, H.; Glennon, R. A. *Bioorg. Med. Chem.* **2002**, *10*, 2759; (b) Ablordepey, S. Y.; Fischer, J. B.; Glennon, R. A. *Bioorg. Med. Chem.* **2000**, *8*, 2105.
- Weinhardt, K. K.; Bonhaus, D. W.; De Souza, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2687.
- Data for selected compounds: **6a**: oil. IR: 1681. ¹H NMR (CDCl₃): δ 1.52–1.64 (m, 2H); 1.72–2.10 (m, 6H); 2.13–2.44 (m, 4H); 2.61–2.74 (m, 2H); 2.92–2.98 (m, 4H); 6.95 (dt, 1H, *J* = 8.8, 2.0); 7.10–7.23 (m, 3H); 7.38 (t, 1H, *J* = 7.4); 7.58–7.71 (m, 1H); 7.91 (d, 1H, *J* = 7.8). MS (EI, *m/z*): 392 (M⁺). *Hydrochloride*: mp 243–244 °C. Anal. (C₂₄H₂₅FN₂O₂·HCl·1.5H₂O): C, H, N. **6b**: light orange solid, mp 121–123 °C. IR: 1678. ¹H NMR (CDCl₃): δ 1.64–1.70 (m, 2H); 2.04–2.14 (m, 6H); 2.22–2.53 (m, 4H); 2.60–2.77 (m, 2H); 2.96–3.08 (m, 4H); 3.84 (s, 3H); 7.04–7.09 (m, 2H); 7.16–7.22 (m, 2H); 7.50 (d, 1H, *J* = 2.7); 7.67–7.69 (m, 1H). MS (EI, *m/z*): 422 (M⁺). *Hydrochloride*: mp 239–240 °C. Anal. C₂₅H₂₇FN₂O₃·HCl·1/2H₂O: C, H, N.