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Chemoenzymatic synthesis and binding affinity of novel (*R*)- and (*S*)-3-aminomethyl-1-tetralones, potential atypical antipsychotics

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Abstract—A series of (*R*)- and (*S*)-3-aminomethyl-1-tetralones, conformationally constrained analogues of haloperidol, have been obtained by enzymatic resolution of the corresponding racemic 3-hydroxymethyl-1-tetralones using *Pseudomonas fluorescens* lipase. Their binding affinities at dopamine D_2 and serotonin 5-HT_{2A} and 5-HT_{2C} receptors were determined showing in some cases an atypical antipsychotic profile with Meltzer's ratio higher than 1.30.

Schizophrenia is a complex disorder affecting approximately 1% of the population.[1] 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),[2] and they are ineffective against negative symptoms of schizophrenia. The clinical efficacy of classical antipsychotics in the treatment of schizophrenia and other psychotic disorders is directly related to their ability to block dopamine D_2 receptors in the brain;[3] however, it has been reported that dopamine receptor blockade in the striatum is closely associated with their extrapyramidal side effects.[4]

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.[5] These drugs exhibit potent antagonism at multiple receptor subtypes including serotonin and dopamine receptors, suggesting the implication of the serotoninergic system in this pathology.[6] Meltzer et al.[7] suggested that in the efficacy of clozapine and other atypical antipsychotics such as risperidone or olanzapine, the most important factor is their relative affinities for D_2 and 5-HT_{2A} receptors.[8] They proposed that the ratio pK_i's 5-HT_{2A}/D_2 between pK_i for 5-HT_{2A} and pK_i for D_2 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.[9]

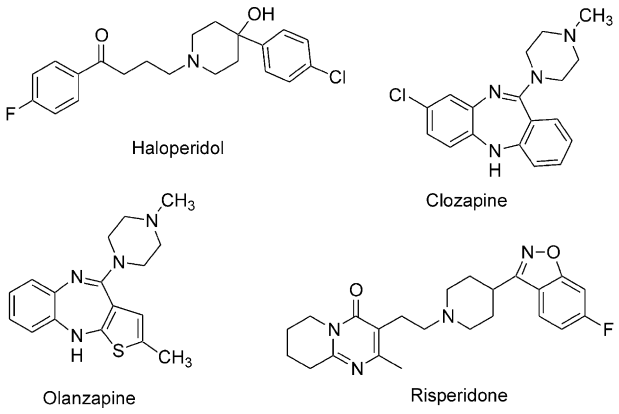

Figure 1. Some typical and atypical antipsychotics.

Keywords: Aminomethyltetralones; Enzymatic resolution; Dopamine receptors; Serotonin receptors; Antipsychotics.
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Additionally, many of the atypical antipsychotic agents block not only 5-HT_{2A} but other serotonin receptors, particularly 5-HT_{2C} receptors.[10] It has been also suggested that 5-HT_{2C} receptor blockade is responsible for reducing EPS.[11] These findings have given cause for 5-HT_{2C} receptor to be considered as a potential target in the treatment of psychotic illnesses.[12]

Four decades after its introduction into the clinic, clozapine remains the prototype of atypical 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,[13] 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.

As part of a program aimed at developing potential atypical antipsychotic compounds we have reported the synthesis, pharmacological activity and molecular modelling of aminoalkylbenzocycloalkanones (Fig. 2) which are conformationally restricted butyrophenone analogues of haloperidol.[14] These compounds represent some of our efforts on modulation of the butyrophenone system with the aim of combining antagonism at 5-HT_2 family and D_2 receptors in a single molecule.[15] The known chiral discriminatory properties of drug–receptor interactions have prompted us to further investigate whether the receptor affinities of these compounds are associated with absolute stereochemistry by means of the preparation of these compounds as single enantiomers. Herein we describe the chemoenzymatic synthesis of (*R*)- and (*S*)-6,7-dimethoxy-, 6-methoxy- or unsubstituted 3-aminomethyl-1-tetralones **7**–**9** (Scheme 1), and their binding affinities on D_2, 5-HT_{2A} and 5-HT_{2C} receptors.

The target 3-aminomethyltetralones **7**–**9** were prepared as shown in the Scheme 1. 3-Hydroxymethyltetralones

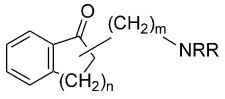
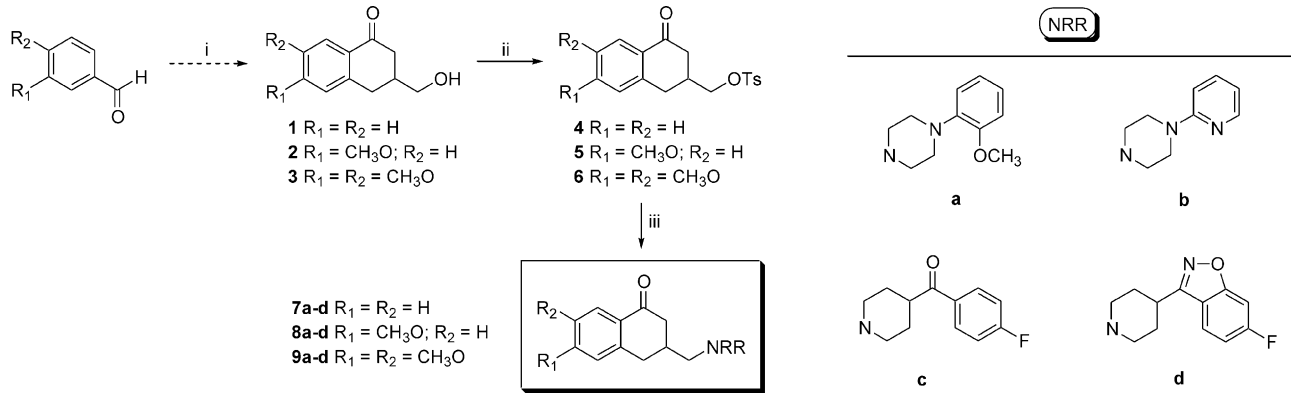


Figure 2. General formula of aminoalkylbenzocycloalkanones.

(±)-**1**–**3** were synthesized from the corresponding benzaldehydes in a five step procedure (30–40% overall yield) as described previously.[16] Tosylation of the hydroxyketones (±)-**1**–**3** with *p*-toluenesulfonyl chloride in pyridine afforded the corresponding tosylates (±)-**4**–**6**. Alkylation of the secondary amine **a**–**d** with the tosylates (±)-**4**–**6** gave the conformationally constrained aminobutyrophenones (±)-**7a**–**d**, (±)-**8a**–**d** and (±)-**9a**–**d**.

The synthesis of the optically pure aminobutyrophenones (+)- and (−)-**7**–**9** was accomplished by resolution of the intermediates (±)-**1**–**3**. Between the different method of resolution we chose the lipase catalyzed kinetic resolution methodology, which has proven to have substantial advantages over conventional chemistry-based methods.[17] Preliminary studies carried out with the hydroxytetralone (±)-**1** were reported previously by us.[18] The best results (Table 1) were achieved using lipase from *Pseudomonas fluorescens* (PF) adsorbed on Celite®[19] in benzene, which yielded the hydroxyketone (*R*)-(−)-**1** (93% ee), and the acetate (*S*)-(+)-**10** (91% ee). Accordingly, racemic hydroxymethyltetralones (±)-**2**–**3** were submitted to enzymatic kinetic resolution using PF lipase adsorbed on Celite® (Scheme 2) in different solvents.[20] Optimized results are shown in Table 1. Resolution of alcohol (±)-**2** afforded enantiomerically pure acetate (*S*)-(+)-**11** in THF ($E > 200$), while enantiopure residual hydroxyketone (*R*)-(−)-**2** could be obtained when the reaction was carried out in vinyl acetate ($E = 45$). Complete resolution ($E > 200$) of hydroxymethyltetralone (±)-**3** was accomplished with vinyl acetate as solvent. In these compounds, lipase PF reacts preferently with the (*S*) enantiomers to produce the (*S*)-acetates. Finally, ester hydrolysis of (*S*)-(+)-**10**–**12** with LiOH afforded the corresponding hydroxymethyltetralones (*S*)-(+)-**1**–**3** in 90% yield (Scheme 2). The absolute configurations of (+)- and (−)-**1**–**3** were determined on the basis of the reported X-ray crystallography of their tosylates.[16,18]

Tosylation of the enantiomerically pure alcohols followed by nucleophilic displacement of the tosyl group with amines **c** and **d** (Scheme 1) gave (*R*)-(−)-/(*S*)-(+)-**7**–**9c**, and (*R*)-(−)-/(*S*)-(+)-**7**–**9d**, which hydrochloride salts prove to be aceptable forms for binding assays. The two-step transformations of (*R*)- and (*S*)-**1**–**3** to

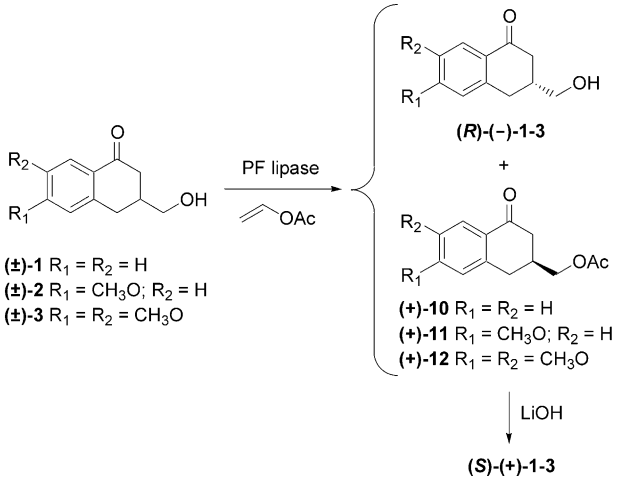


Scheme 1. (i) See ref 19; (ii) TsCl, Py (70–85%); (iii) HNRR (2 equiv), NMP (50–80%).

Table 1. Enzymatic resolution of 3-hydroxymethyl-1-tetralones using PF lipase adsorbed on Celite®

Compd	Solvent[a]	T (h)	Conversion (%)	Hydroxyketone (−)-**1**–**3**		Acetate (+)-**10**–**12**		E^b
				Yield (%)	ee (%)[c]	Yield (%)	ee (%)[c]	
1	Bencene	7.5	50	35	93	40	91	94
2	THF	1.5	48	52	91	43	99.9	>200
2	VA	0.25	58	20	99.9	75	72.5	45
3	VA	0.6	50	47	99.9	45	99.9	>200

[a] VA: vinyl acetate.
[b] Enantioselectivity was calculated from the formula $E = \ln[1-c(1-ee_s)]/\ln[1-c(1+ee_s)]$.[21]
[c] Determined by chiral HPLC (Chiracel® OD-H column, Daicel), except for acetate (+)-**10**, which was determined after alkaline hydrolysis to the corresponding alcohol.[22]



Scheme 2. Enzymatic resolution of 3-hydroxymethyl-1-tetralones.

(*R*)- and (*S*)-**7**–**9**, respectively, were achieved in 40–65% overall yield.

The binding affinities of the racemic aminomethyltetralones (±)-**7a**–**d**, (±)-**8a**–**d** and (±)-**9a**–**d** at the 5-HT_{2A}, 5-HT_{2C}, and dopamine D_2 receptors are summarized in Table 2.[23] Aminomethyltetralones containing a piperazine (**a** or **b**, Scheme 1) fragment (compounds (±)-**7a**,**b**, (±)-**8a**,**b**, and (±)-**9a**,**b**) show modest or low affinity at the three receptors tested. In general, these derivatives display receptor selectivity (potent D_2 relative to 5-HT_{2A} affinity) similar to classical neuroleptics: the pK_i ratios 5-HT_{2A}/D_2 (Meltzer's ratio) were lower than 1.09. Because of their low affinity at D_2 receptors, compounds (±)-**8b** and (±)-**9b** do not possess interest as potential antipsychotics, though (±)-**9b** could have interest as selective 5-HT_{2A} compound.

In general, aminomethyltetralones bearing a substituted piperidine moiety, i.e., (±)-**7c**,**d**, (±)-**8c**,**d**, and (±)-**9c**,**d**, exhibited higher affinity (pK_i > 7.3 or K_i < 50 nM) and selectivity (K_i ratios > 10) for the 5-HT_{2A} receptor than the mentioned piperazine group. With the exception of the dimethoxy derivative (±)-**9c**, these compounds showed higher affinity at D_2 than at 5-HT_{2C} receptors: the trend of the binding potency displayed was 5-HT_{2A} > D_2 > 5-HT_{2C}. Since all the compounds in this group have a Meltzer's ratio higher than 1.15, an atypical antipsychotic profile could be predicted for these compounds. In general, the methoxy groups at the tetralone ring in these series do not affect significantly to the binding affinity at any of the receptors studied, which suggests that their interaction with such receptors is not significant.

Table 2. Binding affinities and selectivities for aminomethyltetralones (±)-**7a**–**d**, (±)-**8a**–**d** and (±)-**9a**–**d**

Compd	pK_i[a]			5-HT K_i ratio	pK_i ratio
	5-HT_{2A}	5-HT_{2C}	D_2	2C/2A	5-HT_{2A}/D_2
(±)-**7a**	6.29	5.55	6.69	5.5	0.94
(±)-**8a**	6.05	7.33	6.65	0.05	0.91
(±)-**9a**	5.63	<5	6.08	—	0.93
(±)-**7b**	6.01	5.48	6.40	3.4	0.94
(±)-**8b**	6.16	5.34	<5	6.7	—
(±)-**9b**	6.18	<5	<5	—	—
(±)-**7c**	7.88	6.30	6.65	38.1	1.18
(±)-**8c**	7.75	5.93	6.71	66.1	1.15
(±)-**9c**	8.22	7.08	6.56	13.8	1.25
(±)-**7d**	8.57	6.89	7.24	47.6	1.18
(±)-**8d**	7.34	5.79	6.34	35.5	1.16
(±)-**9d**	8.02	6.83	6.82	15.5	1.18
Haloperidol	6.78	5.14	9.22	43.6	0.73
Clozapine	8.04	7.98	6.65	1.1	1.21
Risperidone	9.30	8.13	nd[b]	14.8	nd

[a] Values are means of three separate experiments (s.e.m. less than 6%).
[b] nd = not determined.

Those compounds with higher 5-HT_{2A} affinity and Meltzer's ratios (**7c**–**d**, **8c**–**d**, and **9c**–**d**) were synthesized as pure enantiomers, and their binding affinities were measured (Table 3). In general, all examples in this series show excellent potency for the 5-HT_{2A} receptor, reaching pK_i values as high as 8.83 (K_i = 1.5 nM) for compound (+)-**8d**. Also it is remarkable the increased selectivity showed for some enantiomers at the 5-HT_{2A} receptor over the 5-HT_{2C} and D_2 receptors with respect to the racemic compound. Thus, compounds (−)-**7c**, (−)-**7d**, and (+)-**8d** have particularly higher 5-HT_{2C}/5-HT_{2A} ratios than their corresponding racemates. The same happens with the D_2/5-HT_{2A} ratios of (+)-**8d** and (−)-**9c** versus (±)-**8d** and (±)-**9c**, respectively. Unfortunately, the effective differences in affinity at the 5-HT_{2A}, 5-HT_{2C}, and D_2 receptors for these corresponding (*R*)/(*S*) pairs is insignificant, and it is not possible to establish a general rule that connect the stereochemistry of the chiral centre with potency in any of the receptors studied.

Table 3. Binding affinities and selectivities for aminomethyltetralones (+)- and (−)-**7c–d**, **8c–d** and **9c–d**

Compd	pK_i[a]			5-HT K_i ratio	pK_i ratio
	5-HT_{2A}	5-HT_{2C}	D_2	2C/2A	5-HT_{2A}/D_2
(+)-**7c**	7.63	6.31	6.47	20.9	1.18
(−)-**7c**	8.23	6.11	6.98	131.8	1.18
(+)-**8c**	7.95	5.96	6.27	97.7	1.27
(−)-**8c**	7.79	6.01	6.42	60.3	1.21
(+)-**9c**	7.36	6.24	6.50	13.2	1.13
(−)-**9c**	8.25	6.78	6.00	29.5	1.37
(+)-**7d**	7.53	6.18	6.67	22.4	1.13
(−)-**7d**	8.20	6.08	7.19	131.8	1.14
(+)-**8d**	8.83	6.29	6.30	346.7	1.40
(−)-**8d**	7.58	6.08	6.36	31.6	1.19
(+)-**9d**	7.79	6.85	6.97	8.7	1.11
(−)-**9d**	8.14	6.85	6.79	19.5	1.20
Haloperidol	6.78	5.14	9.22	43.5	0.73
Clozapine	8.04	7.98	6.65	1.1	1.21
Risperidone	9.30	8.13	nd[b]	14.8	nd

[a] Values are means of three separate experiments (s.e.m. less than 6%).
[b] nd = not determined.

However, it is worth mentioning compounds (+)-**8d** and (−)-**9c** as potential atypical antipsychotics, with a Meltzer's ratio of 1.40 and 1.37, respectively, both higher than that of clozapine (1.21).[24] Benzisoxazolylpiperidine compound (+)-**8d** exhibits, at 5-HT_{2A} receptor, the highest affinity (pK_i = 8.83, K_i = 1.5 nM) and selectivity (>300-fold over 5-HT_{2C} and D_2 receptors), while benzoylpiperidine derivative (−)-**9c** displays high affinity at 5-HT_{2A} receptor (pK_i = 8.25, K_i = 5.6 nM), and 177-fold selectivity over D_2 receptor (pK_i = 6.00, K_i = 1000 nM), and both compounds have affinity and selectivity profiles at 5-HT_{2A} receptor significantly different than those of their counterparts. Although methoxy groups have not afforded significantly pharmacological advances, these groups open a chemical access to a large range of substituents in the aromatic portion of the tetralones, research in progress now in our group.

In summary, we have described the synthesis and binding affinity of new 3-aminomethyltetralones as conformationally constrained analogues of haloperidol. Those compounds with a more interesting binding profile were prepared as single enantiomers by a chemoenzymatic route using *Pseudomonas fluorescens* lipase, and their binding affinities and selectivities at D_2, 5-HT_{2A}, and 5-HT_{2C} receptors were examined. From this effort have emerged the benzisoxazolylpiperidine compound (+)-**8d** and the benzoylpiperidine derivative (−)-**9c** as potential antipsichotic compounds, as a result of their good affinities, selectivities and Meltzer's ratios.

Acknowledgements

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20. General procedure: To a solution of the hydroxymethyltetralone (±)-**1**–**3** (1.0 mmol) in a solvent (Table

1), vinyl acetate (55 μL, 0.6 mmol), and *Pseudomonas fluorescens* lipase on Celite® (100 mg) was added. The mixture was stirred at room temperature, filtered through Celite® and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc: hexane, 1:3) to give the (*R*)-3-hydroxymethyltetralones (−)-**1**–**3** and the (*S*)-acetates (+)-**10**–**12**.

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22. (***R***)-(−)-**1**: $[\alpha]_D^{20} = -26.5$ (*c* 1.0, AcOEt), 93% ee. Chiralcel® OD-H, hexane–2-propanol 94:6, flow 0.5 mL/min, λ 254 nm, $t_R = 49$ min. (***R***)-(−)-**2**: $[\alpha]_D^{20} = -36.3$ (*c* 0.5, AcOEt), 99.9% ee. Chiralcel® OD-H, hexane:2-propanol 90:10, flow 0.3 mL/min, λ 254 nm, $t_R = 64$ min. (***R***)-(−)-**3**: $[\alpha]_D^{20} = -53.0$ (*c* 0.5, AcOEt), 99.9% ee. Chiralcel® OD-H, hexane–2-propanol 90:10, flow 0.3 mL/min, λ 254 nm, $t_R = 104$ min. (***S***)-(+)-**11**: $[\alpha]_D^{20} = +31$ (*c* 1.0, AcOEt), 99.9% ee. Chiralcel® OD-H, hexane–2-propanol 90:10, flow 0.3 mL/min, λ 254 nm, $t_R = 70$ min. (***S***)-(+)-**12**: $[\alpha]_D^{20} = +40$ (*c* 1.0, AcOEt), 99.9% ee. Chiralcel® OD-H, hexane–2-propanol 90:10, flow 0.3 mL/min, λ 254 nm, $t_R = 112$ min.
23. Methods for binding assays have been published in ref 14(c).
24. Data for selected compounds: (***S***)-(+)-**8d**: white solid, mp 162–163 °C. $[\alpha]_D^{20} = +23.3$ (*c* 1.5, AcOEt). IR: 1667. ^{1}H NMR ($CDCl_3$): δ 2.04–2.45 (m, 10H); 2.65–2.84 (m, 2H); 2.95–3.11 (m, 4H); 3.85 (s, 3H); 6.72 (d, 1H, $J = 2.2$); 6.81 (dd, 1H, $J = 8.7$, 2.4); 7.04 (dt, 1H, $J = 8.8$, 2.1); 7.19–7.24 (m, 1H); 7.69 (dd, 1H, $J = 8.7$, 5.1); 7.97 (d, 1H, $J = 8.7$). MS (CI, *m*/*z*): 409 (MH^+). *Hydrochloride*: mp 230 °C (decomp.). Anal. ($C_{24}H_{25}FN_2O_3 \cdot HCl$): C, H, N. (***R***)-(−)-**9c**: white solid, mp 153–155 °C. $[\alpha]_D^{20} = -39.6$ (*c* 0.8, AcOEt). IR: 1668. ^{1}H NMR ($CDCl_3$): δ 1.87 (br.s, 4H); 2.05–2.47 (m, 6H); 2.58–2.75 (m, 2H); 2.88–3.06 (m, 3H); 3.12–3.24 (m, 1H); 3.88, 3.92 (s, 3H); 6.68 (s, 1H); 7.05–7.17 (t, 2H, $J = 8.5$); 7.47 (s, 1H); 7.95 (dd, 2H, $J = 8.7$, 5.5). MS (CI, *m*/*z*): 426 (MH^+). *Hydrochloride:* mp 244–245 °C. Anal. $C_{25}H_{28}FNO_4 \cdot HCl \cdot {}^1/_2H_2O$: C, H, N.