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

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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 D_2 and serotonin 5-HT_{2A} and 5-HT_{2C} receptors were determined, showing in some cases an atypical antipsychotic profile.

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 D_2 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]

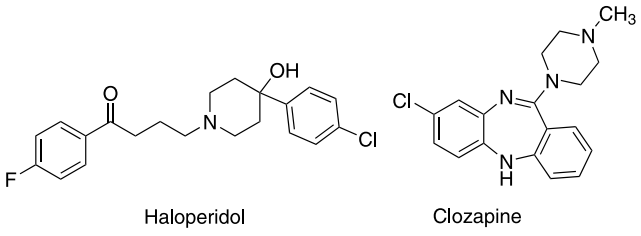

Figure 1. Prototypes of typical (haloperidol) and atypical (clozapine) antipsychotics.

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 serotoninergic 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 D_2 and 5-HT_{2A} receptors.[7] They proposed that the ratio 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;[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

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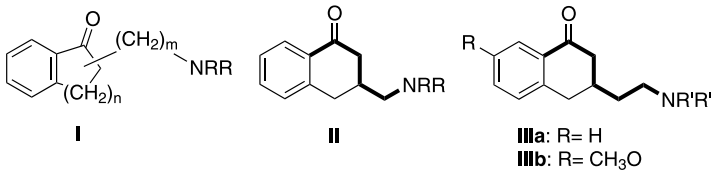


Figure 2.

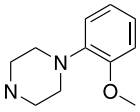
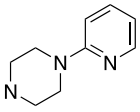
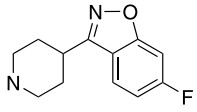
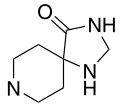
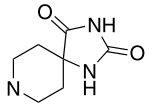
antipsychotic drugs and no currently available agents appear to have the spectrum of efficacy of this drug. However, treatment with clozapine is associated with an increased risk of agranulocytosis,[12] which strongly limits its therapeutic use. Hence, the discovery of a more effective side effects free 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 D_2, 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-tetralones **II** (conformationally restricted *aminobutyrophenones*). Although the butyrophenone moiety has been accepted as an optimized side chain for the D_2 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]

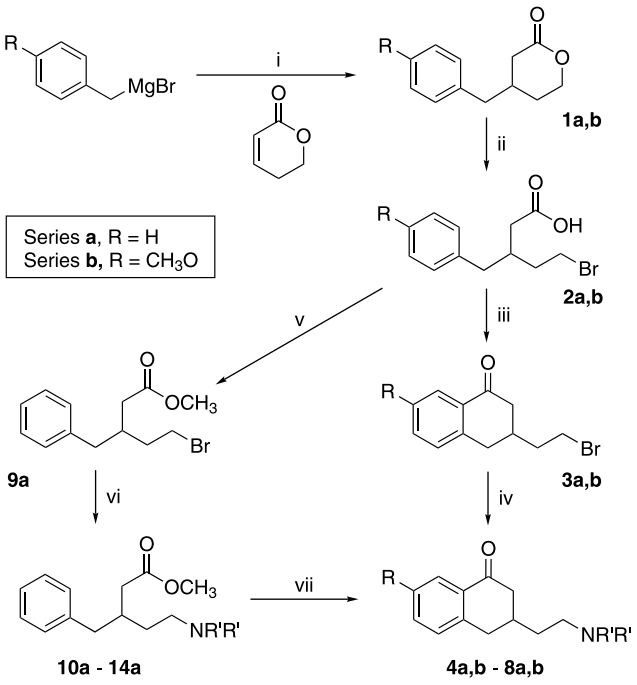
In the first stage of this research, we want to explore, as part of the general structure **III**, different amine moieties (Table 1) present in several CNS agents: arylpiperazines such as *N*-(2-methoxyphenyl)-piperazine and *N*-(2-pyridyl)piperazine (present in fluanisone and buspirone, respectively), 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 addition[18]

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%).



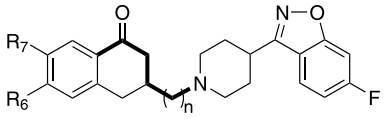
Scheme 1. Reagents: (i) CuI, TMEDA, TMSCl, THF (60–70%); (ii) HBr/AcOH 33% (88–95%); (iii) TFA, TFAA (75%); (iv) HNR′R′, Na_2CO_3, KI, MIK (50–90%); (v) CH_2N_2, Et_2O (98%); (vi) HNR′R′, Na_2CO_3, KI, MIK (30–75%); (vii) PPA (20–50%).

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 Na_2CO_3 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 D_2 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 D_2 receptors. Because of this low affinity at D_2 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	*n*	R_6	R_7	pK_i[a]			pK_i ratio
				5-HT_{2A}	5-HT_{2C}	D_2	5-HT_{2A}/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-triazaspirodecandione moiety (i.e., **8a** and **8b**) behave as 5-HT_2 selective ligands: display significant affinity for the 5-HT_2 receptors assayed, with about 10-fold higher affinity for 5-HT_{2C} receptors, and also lack affinity at D_2 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-triazaspirodecane derivatives.[20]

On the basis of the 5-HT_{2A}/D_2 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 D_2 receptor compound **6b** displays 10-fold higher affinity than **6a**, hinting at a favourable effect of the 7-methoxy substituent on the D_2 receptor binding.

In comparison with their butyrophenone analogues,[14] benzisoxazolylpiperidine compounds **6a** and **6b** (Table 2) exhibit similar affinities and selectivities for the 5-HT_{2A}, 5-HT_{2C} and D_2 receptors, with a pK_i ratio 5-HT_{2A}/D_2 higher than 1.15 in all five compounds. In conclusion, enlargement of the methylene bridge between piperidine and the tetralone ring by one CH_2 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 benzisoxazolylpiperidine compound **6b**, as potential antipsychotic compound, as a result of its good affinity and Meltzer's ratio.

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21. Data for selected compounds: **6a**: oil. IR: 1681. ^{1}H NMR ($CDCl_3$): 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. ($C_{24}H_{25}FN_2O_2 \cdot HCl \cdot 1.5H_2O$): C, H, N. **6b**: light orange solid, mp 121–123 °C. IR: 1678. ^{1}H NMR ($CDCl_3$): 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. $C_{25}H_{27}FN_2O_3 \cdot HCl \cdot 1/2H_2O$: C, H, N.