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NEW CYCLIC BUTYROPHENONE DERIVATIVES IN THE INDOLE SERIES AS POTENTIAL ATYPICAL ANTIPSYCHOTICS. A SIMPLE AND PRACTICAL SYNTHESIS OF 6-AMINOMETHYL-TETRAHYDROINDOL-4-ONES AND THEIR AFFINITIES FOR D_2 AND 5-HT_{2A} RECEPTORS[1]

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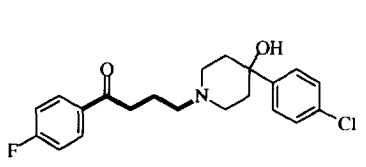
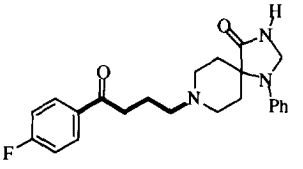
Abstract: A simple and efficient synthesis of novel 6-aminomethyl-tetrahydroindol-4-ones, which are butyrophenone analogues of molindone, is described. These compounds exhibit potent affinities for D_2 and 5-HT_{2A} receptors *in vitro*. The most active compounds, **6d** (**QF 0408B**) and **6e** (**QF 0409B**), with pK_i (5-HT_{2A}/D_2) ratios of 1.32 and 1.17 respectively, show an antipsychotic profile according to Meltzer's classification.

Introduction

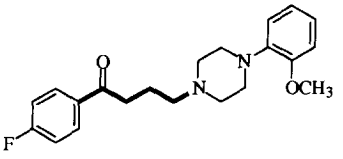
It is known that haloperidol is the prototype of a group of butyrophenone derivatives with a very potent antipsychotic activity; among them the most potent neuroleptics are spiperone and fluanisone, which are 4-amino-*p*-fluorobutyrophenone derivatives.[2] Several aminoketones also possess potent antipsychotic (neuroleptic) activity: molindone, first marketed in the USA in 1974, has been used in the treatment of schizophrenia and psychosis.[3] However, these "classical" or "typical" antipsychotics are ineffective against negative symptoms of schizophrenia and their incidence of extrapyramidal side effects (EPS) is significant.



Haloperidol



Spiperone



Fluanisone

The discovery of clozapine in the 1960's gave rise to a new group of "atypical" or "non-classical" antipsychotics, which have no EPS and are effective against negative symptoms.[4] The atypical antipsychotic profile of clozapine has been attributed to its ability to block not only dopamine receptors, but also serotonin 5-HT_{2A} receptors.[5] Clozapine does, however, have side effects of its own, such as agranulocytosis and seizures.[6]

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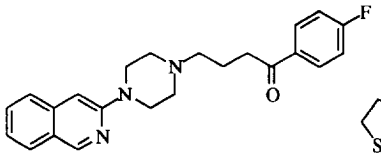
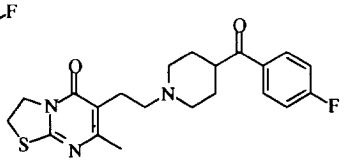
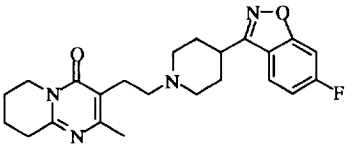
The shortcomings of all current antipsychotic drugs have led to an urgent need for better therapies. Meltzer *et al*[1] have suggested that the efficacy of atypical antipsychotic drugs against negative symptoms and their lack of EPS are determined by their relative affinities for D_2 and 5-HT_{2A} receptors: clozapine and clozapine-like antipsychotics have pKi (5-HT_{2A}/D_2) ratios ≥ 1.12, whereas for typical antipsychotics this ratio is < 1.09. A number of mixed 5-HT_{2A}/D_2 antagonists which may be considered as belonging to the butyrophenone group are now available, e.g. cinuperone, setoperone, ketanserine, risperidone and others.



Cinuperone

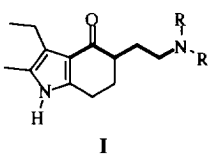


Setoperone

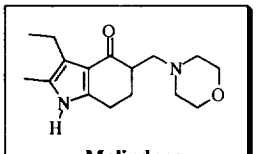


Risperidone

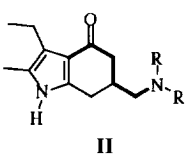
Recently, we have prepared and studied several 5-aminoethyl-1,2,3,4-tetrahydroindol-4-ones (**I**) as butyrophenone homologues of molindone.[8] Also, in previous papers,[9-12] we have reported the synthesis and atypical antipsychotic activity of 3-aminomethyl-tetralones and 2-aminoethyl-benzocycloalkanones which are conformationally restricted butyrophenone analogues of haloperidol, with the aminobutyl side chain partially incorporated in a semirigid framework.



I



Molindone



II

As a continuation, we wish to report here on a convenient methodology for the preparation of new 6-aminomethyl-4,5,6,7-tetrahydroindol-4-ones (**II**) as cyclic butyrophenone derivatives in the indole series, as well as the results of studies of the affinities of title compounds for D_2 and 5-HT_{2A} receptors. These compounds have two butyrophenone pharmacophores: the semirigid aminoalkyl indolone moiety and the 4-(*p*-fluorobenzoyl) or the 3-[4-[6-fluoro-1,2-benzisoxazole-3-yl)] piperidine fragments. The 4-(*p*-fluorobenzoyl)-piperidine fragment may be considered as a butyrophenone pharmacophore constrained in a six membered ring; this fragment is also an important feature for 5-HT_{2A} binding.[13,14] Moreover, the bioisosteric relationships between benzoyl and 1,2-benzisoxazol moieties[15] are noteworthy.

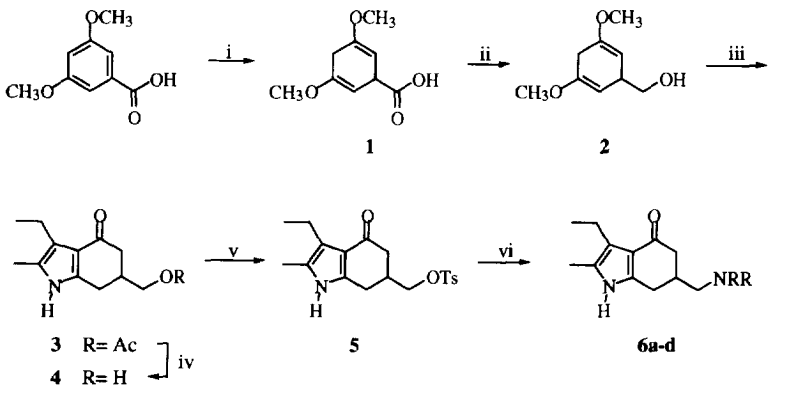
Chemistry

In a recent paper[16] we reported a practical procedure for preparing 6-aminomethyl-4-oxo-4,5,6,7-tetrahydroindoles containing aliphatic amines. We now describe a more convenient approach for these compounds with both aliphatic and aromatic amines.[17] As outlined in scheme 1, the reduction of the aromatic

ring is performed in the earlier steps of the synthesis, thus allowing the introduction of complex amine moieties later.

Birch reduction of 3,5-dimethoxybenzoic acid with lithium ammonia in methanol afforded 1,4-dihydro-3,5-dimethoxybenzoic acid **1**.[18] Treatment of this compound with lithium aluminum hydride in THF gave the hydroxymethyl alcohol **2**[19] in 85% yield over two steps.

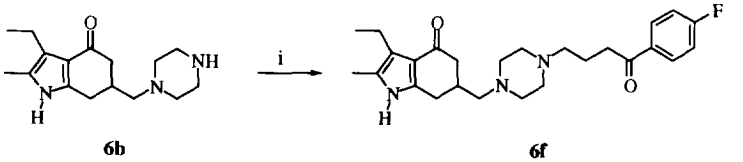
Scheme 1



i: Li/NH_3; ii: $LiAlH_4$; iii: $CH_3CNOHCOCH_2CH_3$, Zn, AcOH 70%; iv: KOH; v: Ts-Cl/Py; v: HNRR, NMP

Pyrrole ring formation was achieved by Knorr reaction with 2-isonitroso-3-pentanone in 70% acetic acid in the presence of zinc powder at reflux to yield a mixture of 2-methyl-3-ethyl-6-acetoxymethyl-4,5,6,7-tetrahydroindole-4-one **3** (30%) and of 2-methyl-3-ethyl-6-hydroxymethyl-4,5,6,7-tetrahydroindole-4-one **4** (30%). After chromatographic separation, the acetyl ester **3** on treatment with 10% ethanolic potassium hydroxide gave **4** (60%) as white crystalline compound. Reaction of the alcohol **4** with *p*-toluenesulfonyl chloride in pyridine afforded the tosylate **5**, which underwent subsequent nucleophilic displacement with heterocyclic amines, in N-methyl pyrrolidone (NMP) providing the amines **6a-d** as white crystalline solids with yields ranging 40-75%, (Table I).[20]

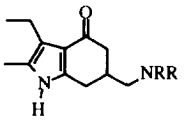
Scheme 2

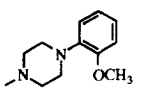
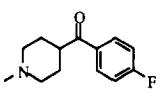
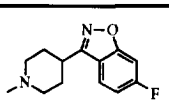
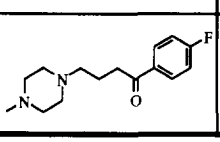


i: 1) 4-Chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane, KI, K_2CO_3, 2) HCl

2-Methyl-3-ethyl-6-[[4-[3-(*p*-fluorobenzoyl)propyl]piperazin-1-yl]methyl]-4,5,6,7-tetrahydroindol-4-one **6f** was prepared by alkylation of **6b** with 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl) butane in methyl isobuthyl ketone and subsequent acidic hydrolysis (73% over two steps) as we have previously described in benzene series[11] (Scheme II).

Table I: 6-Aminomethyl-4,5,6,7-tetrahydroindol-4-ones **6a-f**.



Compound	-NRR	M.p. (°C)	Recr. solvent	Yield from 5
6a		127-130	AcOEt/Hexane	75%
6b		176-178	*iso*-propanol	70%
6c		219-221	acetone	64%
6d		162-164	AcOEt/Hexane	40%
6e		203-205	*n*-buthanol	65%
6f		170-172	*iso*-propanol	51%

Results and discussion

Table II lists the results of experiments to evaluate the affinities of compounds **6c-6f** for dopamine D_2 and serotonine 5-HT_{2A} receptors. All the compounds inhibited the binding of ^{3}H-spiperone to D_2 receptors with pK_i values ranging between 6.02 and 7.04, and the binding of ^{3}H-ketanserine to 5-HT_{2A} receptors with pK_i values from 6.40 to 8.30. The five compounds synthesized displayed higher affinity for 5-HT_{2A} receptors than molindone. In keeping with the hypotheses suggested by Meltzer *et al*[7] regarding the combination of 5-HT_{2A} blocking and D_2-blocking activities, our compounds would have a more atypical profile than molindone.

Table II: Inhibition constants (pK_i) at D_2 and 5-HT_{2A} receptors.[a]

Compound	pK_i (D_2)	pK_i (5-HT_{2A})	pK_i (5-HT_{2A}) / pK_i (D_2)
6c (QF 0407B)	6.02	6.55	1.08
6d (QF 0408B)	6.20	8.21	1.32
6e (QF 0409B)	7.04	8.30	1.17
6f (QF 0410B)	6.55	6.40	0.97
Haloperidol	8.30	7.70	0.93
Clozapine	7.00	8.30	1.19
Molindone	7.48	5.85	0.78

[a]Inhibition constants (pK_i) for in vitro inhibition by the compounds under study of ^{3}H-ketanserine binding to rat frontal cortex membranes (5-HT_{2A}) and ^{3}H-spiperone binding to striatal membranes (D_2); methods for these assays have been published elsewhere.[10,11] pK_i values were calculated using the Cheng-Prusoff equation;[21] results shown are means of three inhibition curves constructed with each drug. The mean standard error of K_i values was 10-18%.

The *p*-fluorobenzoyl derivative **6d** exhibited a high affinity for 5-HT_{2A} receptors with a pK_i= 8.21, while the pK_i value for D_2 receptor was 6.20. The pK_i (5-HT_{2A}/D_2) ratio for compound **6d** was 1.32, higher than that for molindone (0.78), haloperidol (0.93) or even clozapine (1.19). According to Meltzer's classification, **6d** shows a profile of an atypical antipsychotic.

The replacement of the benzoyl piperidino fragment of **6d** by a 1,2-benzisoxazolylpiperidino moiety (compound **6e**) increased the affinity for both D_2 and 5-HT_{2A} receptors, with pK_i values of 7.04 and 8.30, respectively. These affinities are very close to those exhibited by clozapine. Meltzer's ratio for compound **6d** decreases to 1.17, but is still greater than 1.12.

The introduction of *o*-methoxyphenyl piperazino or linear, flexible butyrophenone pharmacophores does not seem to improve its affinity for 5-HT_{2A} and D_2 receptors.

In conclusion, we have developed a practical and efficient synthetic approach for obtaining butyrophenone derivatives in the indole series as atypical antipsychotics. The promising affinity for both D_2 and 5-HT_{2A} receptors shown by compound **6d (QF 0408B)** together with its high Meltzer's ratio has prompted us to choose this compound for further development.

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20. **6c**: ^{1}H-NMR ($CDCl_3$) δ: 7.86 (s, 1H), 7.03-6.85 (m, 4H), 3.86 (s, 3H), 3.07 (s, 4H), 2.95-2.87 (m, 1H), 2.71-2.36 (m, 11H), 2.26-2.17 (m, 1H), 2.15 (s, 3H), 1.12 (t, 3H, J=7.4 Hz). **6d**: ^{1}H-NMR ($CDCl_3$) δ: 7.99-7.94 (m, 3H), 7.13 (t, 2H, J=8.6 Hz), 3.25-3.15 (m, 1H), 3.00-2.83 (m, 3H), 2.68-2.60 (m, 2H), 2.58-2.30 (m, 5H), 2.23-2.12 (m, 5H), 2.08-1.89 (m, 1H), 1.85-1.80 (m, 4H), 1.11 (t, 3H, J=7.4 Hz). **6e:** ^{1}H-NMR ($CDCl_3$) δ: 7.90 (s, 1H), 7.67 (dd, 1H, J=8.7 Hz, J=5.1 Hz), 7.24 (dd, 1H, J=8.7 Hz, J=2.0 Hz), 7.05 (dt, 1H, J=8.8 Hz, J=2.1 Hz), 3.10-2.89 (m, 4H), 2.69-2.60 (m, 2H), 2.57-2.33 (m, 5H), 2.26-2.17 (m, 2H), 2.15 (s, 3H), 2.09-2.02 (m, 5H), 1.12 (t, 3H, J=7.4 Hz). **6f**: ^{1}H-NMR ($CDCl_3$) δ: 7.99 (dd, 2H, J=8.9 Hz, J=5.4 Hz), 7.88 (s, 1H), 7.12 (t, 2H, J=8.6 Hz), 2.97 (t, 2H, J=7.1 Hz), 2.90-2.82 (m, 1H), 2.68-2.59 (m, 2H), 2.57-2.23 (m, 15H), 2.21-2.11 (m, 4H), 1.93 (q, 2H, J=7.1 Hz), 1.11 (t, 3H, J=7.4 Hz).
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