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BUTYROPHENONE ANALOGUES: SYNTHESIS OF 2-METHYL-3-ETHYL-5-AMINOETHYL-4,5,6,7-TETRAHYDROINDOL-4-ONES, AND THEIR AFFINITIES FOR D_1, D_2 AND 5-HT_{2A} RECEPTORS

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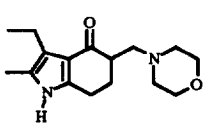
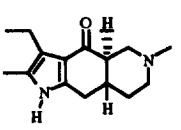
Abstract. Starting from 2-methyl-3-ethyl-1H-4,5,6,7-tetrahydroindol-4-one **3** we have prepared 2-methyl-3-ethyl-5-morpholinoethyl-1H-4,5,6,7-tetrahydroindol-4-one, (**1**) and 2-methyl-3-ethyl-5-(4-*o*-methoxyphenyl-1-piperazinoethyl)-1H-4,5,6,7-tetrahydroindol-4-one (**2**) as butyrophenone analogues of the neuroleptic molindone. The affinities of these compounds for D_1 and D_2 dopamine and 5-HT_{2A} serotonin receptors were evaluated *in vitro*. The affinity of **1** for D_2 receptors is less than that of molindone (pKi's 6.23 and 7.48 respectively) and that of **2** similar (pK_i 7.55). Both compounds bind to 5-HT_{2A} receptors, the affinity of **2** being significantly greater than that of molindone (pK_i's of 7.04 and 5.85, and pA_2's of 7.50 and 6.18, respectively).

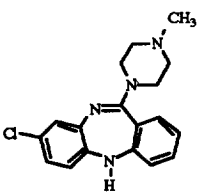
Several aminoketones possess potent antipsychotic (neuroleptic) activity: molindone[1], first marketed in the USA in 1974, has been used in the treatment of schizophrenia and psychosis, but its associated incidence of extrapyramidal side effects (EPS) is significant; the pyrrolo[2,3-g]isoquinoline piquindone (Ro 22-1319)[2] is an antipsychotic with a low propensity to induce EPS; and haloperidol is the prototype of a group of butyrophenone derivatives with very potent antipsychotic activity, among them the most potent neuroleptics, spiperone and fluanisone, which are 4-amino-*p*-fluorobutyrophenone derivatives. 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[3-5]; however, it has been reported that dopamine receptor blockade in the striatum is closely associated with their extrapyramidal side effects[6-8]. Furthermore, the classical antipsychotics are ineffective against negative symptoms of schizophrenia such as apathy, motor retardation, flat affectivity and poverty of speech.



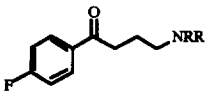
Molindone



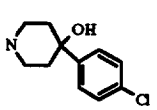
Piquindone



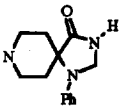
Clozapine



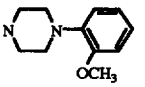
NRR



Haloperidol



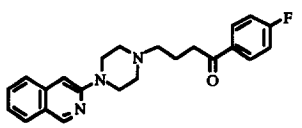
Spiperone



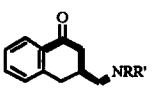
Fluanisone

The discovery of clozapine in the 1960's gave rise to a new group of "atypical" or "non-classical" antipsychotics which have reduced propensity to produce EPS and are effective against negative symptoms. The atypical antipsychotic profile of clozapine has been attributed to its ability to block not only dopamine receptors but also 5-HT receptors. Meltzer *et al* [9,10] 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 and risperidone; clinical studies with risperidone have supported the theory that blockade of 5-HT_{2A} receptors may ameliorate the EPS associated with D_2 dopamine receptor blockade[11].

In previous papers[12-14] we have reported the neuroleptic activity of 3-aminomethyl α-tetralones (**I**) and 2-aminoethyl benzocycloalkanones (**II**), both of which are conformationally restricted butyrophenone analogues of haloperidol. Here we describe the preparation of **1** (a butyrophenone homologue of molindone) and the piperazine derivative **2**, and the results of studies of the affinities of both compounds for D_1, D_2 and 5-HT_{2A} receptors[15].

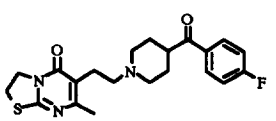


Cinuperone

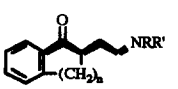


I

NRR
Heterocyclic monoamines
N^4-substituted piperazines



Setoperone



II

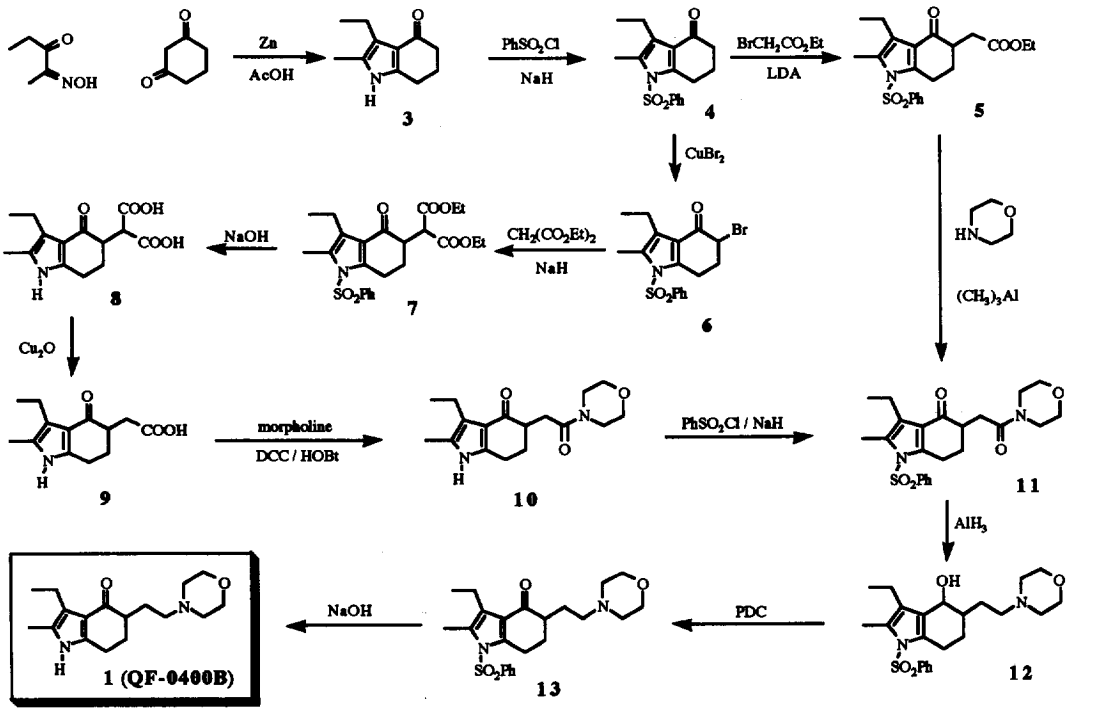
p-Fluorobenzoyl piperidine

The syntheses of the compounds studied are outlined in Schemes I and II[16]. In Scheme I, Knorr condensation of 2-hydroxyimino-3-pentanone with 1,3-cyclohexadione in 70% acetic acid afforded the dihydroindolone 2-methyl-3-ethyl-1H-4,5,6,7-tetrahydroindol-4-one (**3**)[17] (60% yield); protection of the nitrogen of **3** with benzenesulfonyl chloride in the presence of sodium hydride (NaH) gave the ketone **4** (60%); and alkylation of **4** with ethyl bromoacetate in the presence of lithium diisopropylamide (LDA) gave the ketoester

5 (45%)[18]. Alternatively, bromination of **4** with cupric bromide afforded the 5-bromoderivative **6** (80%), which was reacted with diethyl malonate in the presence of NaH in DMF to give the ketodiester **7** (70%); hydrolysed with ethanolic sodium hydroxide to give diacid **8** (85%); then decarboxylated in the presence of Cu_2O to give the unprotected monoacid **9** (95%).

The protected morpholino amides **11** (Scheme I) and **16** (Scheme II) were prepared in 65-85% yield by reaction of protected ketoester **5** with the appropriate dimethylaluminium amide (*prepared in situ*). Alternatively, DCC-mediated coupling of the amine (1 equivalent) and the unprotected ketoacid (**9**)[19] in the presence of 1-hydroxybenzo-triazole (HOBt) in methylene chloride afforded amides **10** (Scheme I) and **15** (Scheme II) in 55-80% yield[20]. The nitrogen atom of the pyrrole ring was protected by reaction with benzenesulfonyl chloride as previously described[18]. Reduction of the carbonyl group with aluminium hydride (AlH_3) in THF yielded amino alcohols **12** (Scheme I) and **17** (Scheme II) in quantitative yields. These amino alcohols were oxidized with pyridinium dichromate (PDC) to give aminoketones **13** (Scheme I) and **18** (Scheme II) in 50-60% yields. The target compounds, **1** and **2**, were obtained by removing the benzenesulfonyl protecting groups with ethanolic sodium hydroxide.

SCHEME I



SCHEME II

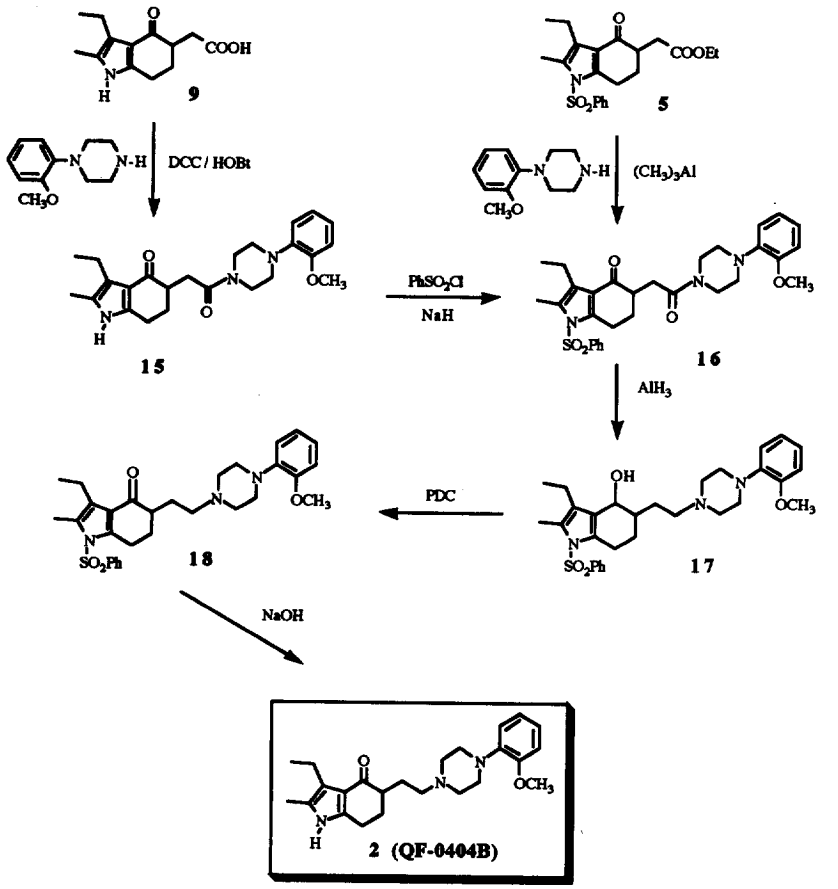


Table I lists the results of experiments to evaluate the affinities of compounds **1** and **2** for dopamine and serotonin receptors. Both compounds inhibited the binding of ^{3}H-spiperone to D_2 receptors (pK_i = 6.23 for **1** and 7.55 for **2**), but were less active inhibitors than haloperidol (pK_i = 8.30); the pK_i of compound **2** was similar to that of molindone, pK_i = 7.48. The affinities of both compounds for D_1 receptors were likewise lower than that of haloperidol.

Both compounds also inhibited the binding of ^{3}H-ketanserine to 5-HT_{2A} receptors. The affinity of compound **2** (pK_i = 7.04) for 5-HT_{2A} receptors is only slightly lower than that of haloperidol (pK_i = 7.70) and significantly higher than that of molindone (pK_i = 5.85); while the affinity of **1** (pK_i = 6.04) for 5-HT_{2A} receptors is just slightly higher than that of molindone. The new compounds also exhibited pA_2 values of 6.98 (**1**)-7.50 (**2**), both higher than that of molindone (6.18), in suppressing serotonin-induced contractions in rat aorta ring stripped of endothelium[13] (Table I).

In conclusion, introducing a butyrophenone structure into the molindone molecule does not seem to improve its affinity for D_2 and 5-HT_{2A} receptors. However, when the morpholine moiety of that butyrophenone

is replaced by an *o*-methoxyphenylpiperazine, the affinity for 5-HT_{2A} of the resulting compound (**2**) is significantly higher than that of molindone, while its affinity for D_2 receptors is similar. These preliminary results, together with our previously reported conclusions[12-14] justify further study of indolones containing piperazine fragments or other pharmacophores that are active at dopamine and serotonin receptors.

Table I

Compound	pK_i's[a]			pK_i ratios		pA_2(5-HT_{2A})[b]
	D_1	D_2	5-HT_{2A}	D_1/D_2	5-HT_{2A}/D_2	
Haloperidol	7.01	8.30	7.70	0.85	0.93	
Molindone	5.80	7.48	5.85	0.77	0.78	6.18±0.16
1 (QF-0400B)	5.67	6.23	6.04	0.91	0.97	6.98±0.23
2 (QF-0402B)	5.93	7.55	7.04	0.79	0.97	7.50±0.2

[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-SCH 23390 or ^{3}H-spiperone binding to striatal membranes (D_1 or D_2, respectively); detailed methods for these assays have been published elsewhere.[12-14] pK_i values were calculated using the Cheng-Prusoff equation[21]; and results shown are means of three inhibition curves constructed with each drug. The mean standard error of K_i values was 10-18%.

[b] Aorta ring experiments: competitive antagonism was quantified as pA_2, which was calculated from a Schild plot of log (dose ratio-1) for three antagonist concentrations; six replicate experiments were performed.

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20. Replacing dicyclohexylcarbodiimide (DCC) by 1-[(3-dimethylamino)propyl-3-ethyl]carbodiimide led to poorer yields of the amides.
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