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BUTYROPHENONE ANALOGUES IN THE CARBAZOLE SERIES: SYNTHESIS AND DETERMINATION OF AFFINITIES AT D_2 AND 5-HT_{2A} RECEPTORS

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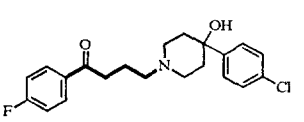
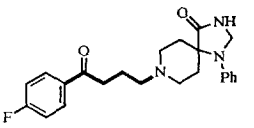
Abstract: We describe a practical and efficient route for synthesis of 2-aminomethyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-ones using an effective Fisher indole methodology. The most active compounds, **4b (QF 2003B)** and **4c (QF 2004B)**, with pKi (5-HT_{2A}/D_2) ratio of 1.28 show an antipsychotic profile according to Meltzer's classification.

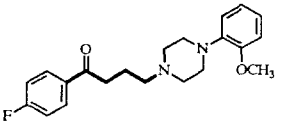
Schizophrenia is a serious and debilitating mental illness for which there is still a great need for novel drug therapy. Afflicted individuals may demonstrate a wide range of behavioural patterns characterized at one end by hallucinations, paranoia, disorganised behaviour (positive symptoms) and the other end by social withdrawal, catatonia, affective flattening of the personality (negative symptoms).[1]



Haloperidol



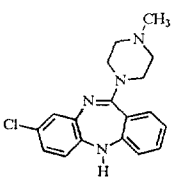
Spiperone



Fluanisone

It is accepted that the dopaminergic system plays a key role in the manifestation of schizophrenic illness, a belief supported by the observation that all clinically effective antipsychotic agents act as antagonists of the dopamine D_2 receptor.[2] Classical or typical antipsychotics (or neuroleptics) such as haloperidol constitute the first-line antipsychotic therapy. Haloperidol is the prototype of a group of butyrophenone derivatives with a very potent antipsychotic activity including the potent neuroleptics spiperone and fluanisone which are 4-aminobutyrophenone derivatives. Unfortunately, their use is associated with severe, mechanism-related side effects including induction of extrapyramidal symptoms (EPS), tardive dyskinesia and problems such as galactorrhea due to increase prolactin release. Furthermore, the classical antipsychotics are no effective against the negative symptoms of schizophrenia.

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.[3] Clozapine does, however, have side effects of its own, such as agranulocytosis and seizures.[4] The shortcomings of all current antipsychotic drugs have led to an urgent need for new and improved therapies.



Clozapine

Several strategies have emerged in search of a more versatile side effect therapy. One hypothesis is based on the correlation between clinical improvement of the negative symptoms of schizophrenia with 5-

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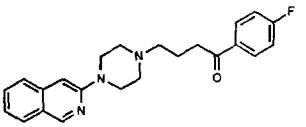
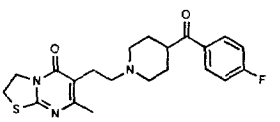
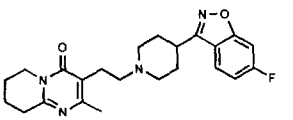
hydroxytriptamine (5-HT_2) receptor blockade. The linear amino butyrophenone cinuperone and the constrained butyrophenone setoperone (atypical antipsychotics) have been reported to attenuate some of the negative symptoms of the schizophrenia.[5] The clinical available risperidone, which possesses potent 5-HT_2 and D_2 antagonist properties, has been reported to ameliorate negative symptoms of this disease.[6] Therefore the right balance of 5-HT_2 and D_2 antagonism is an important guide for successful therapeutic treatment of this debilitating illness. Meltzer *et al.*[7] 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: clozapine and other atypical antipsychotics have a pK_i (5-HT_{2A}/D_2) ratio > 1.12, whereas for typical antipsychotics this ratio is < 1.09.



Cinuperone

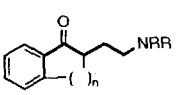


Setoperone

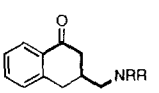


Risperidone

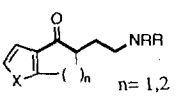
In previous papers[8-11] we have reported the synthesis and antipsychotic activity of aminoalkylbenzocycloalkanones (**I, II**) which are conformationally restricted butyrophenone analogous of haloperidol, with the aminobutyl side chain incorporated in a semi-rigid structure. Later, we have prepared 5-aminoethyl and 6-aminomethyl-4,5,6,7-tetrahydroindole-4-ones (**III, VI**), 4,5,6,7-tetrahydrobenzo[b]thiophen-4-ones (**IV, VII**) and 4,5,6,7-tetrahydrobenzo[b]furan-4-ones (**V, VIII**) as conformationally constrained butyrophenone derivatives in the indole, benzothiophene and benzofuran series, respectively, as putative atypical antipsychotics.[12-18]



I

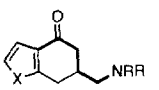


II



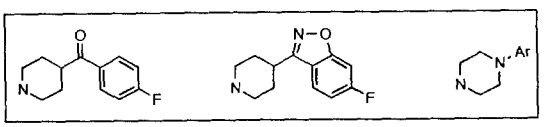
n= 1,2

III X: NH
IV X: S
V X: O

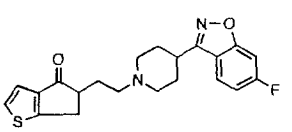


VI X: NH
VII X: S
VIII X: O

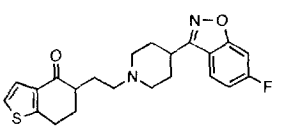
NRR:



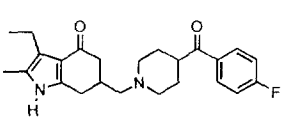
Most of such heterocyclic restricted butyrophenones (e.g. QF 0510B,[17] QF 0610B[17] and QF 0408B,[15] listed below) show a very favourable 5-HT_{2A}/D_2 balance and its cataleptogenic activity is low.[19]



QF 0510B pKi 5-HT_{2A} / D_2 = 1.14



QF 0610B pKi 5-HT_{2A} / D_2 = 1.47



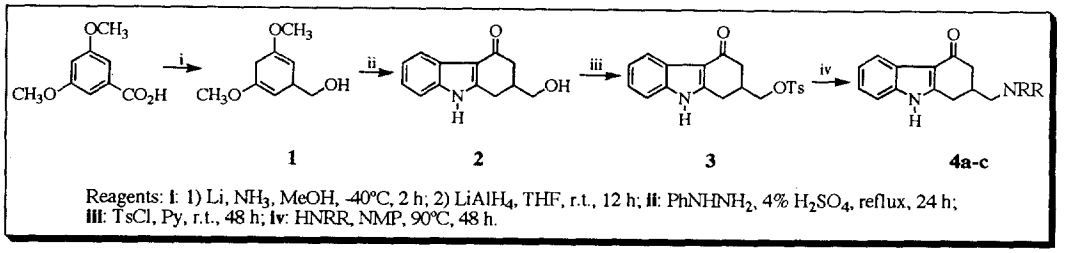
QF 0408B pKi 5-HT_{2A} / D_2 = 1.32

As a continuation, within of a program of research of new CNS acting agents, we wish now to report a practical and efficient synthetic strategy for preparing new 2-aminomethyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-ones (**4a-f**), cyclic butyrophenone derivatives in the carbazole 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.[20] Moreover, the bioisosteric relationships between benzoyl and 1,2-benzisoxazol moieties are noteworthy.[21]

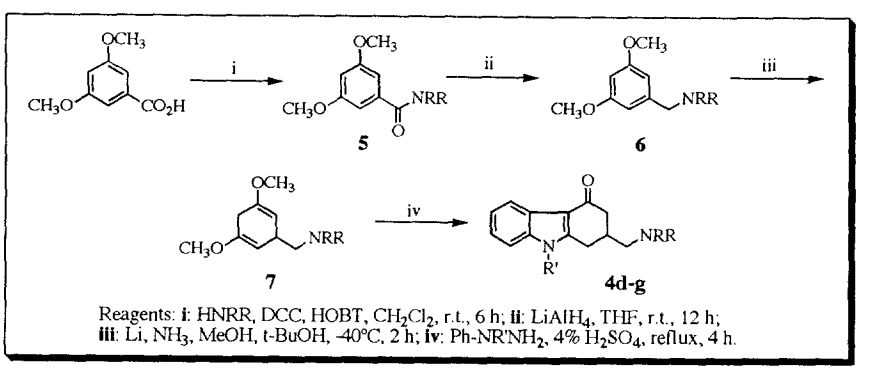
Chemistry

For the synthesis of the carbazolones **4a-c** (method A) we started from the 1,4-dihydro-3,5-dimethoxybenzyl alcohol **1** (scheme 1), which was readily prepared from the cheap 3,5-dimethoxy- (or 3,4,5-trimethoxy-) benzoic acid in 85% yield as previously described.[22] Application of the Fischer indole methodology[23] with phenylhydrazine in 4% H_2SO_4 solution allowed the construction of the desired carbazole intermediate **2** (m.p. 210-211°C, AcOEt) in 40-50% yield after chromathographic purification.



Scheme 1

Reaction of the resulting 2-hydroxymethyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one **2** with *p*-toluenesulfonyl chloride in pyridine afforded the tosylate **3** as white crystalline solid (70%; m.p. 215-216°C, CH_3CN). Nucleophilic displacement of the tosylate with amines (single or complex, heterocyclic amines such as piperazines or substituted piperidines, *e.g.* *p*-fluorobenzoylpiperidine, 4-(6-fluoro-1,2-benzisoxazol-3-yl)-piperidine[24-26]) in N-methyl-2-pyrrolidone (NMP) provided, after bulb to bulb distillation of NMP, the amines **4a-c**[27] as white crystalline solids with yields ranging 55-70% (Table 1).[28]

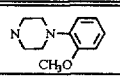
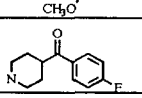
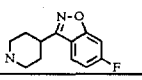


Scheme 2

Alternatively (Method B), aminomethyl carbazolones with non-aromatic amine fragments have been prepared from the corresponding 1,4-dihydro-3,5-dimethoxybenzylamines **7**, obtained following our previously reported methodology for the indole series (Scheme 2).[14] The direct conversion of these amines by

the Fischer indole reaction into a new class of potential atypical antipsychotics, the 2-aminomethyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-ones **4d-f**, was achieved by reaction with phenylhydrazine or N-methyl-N-phenylhydrazine in 4% H_2SO_4 solution at reflux temperature, with yields between 60 and 70% (Table 1).

Table 1. 2-Aminomethyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-ones **4a-f**

Compound	NRR	R'	Method	m.p. (°C)	Yield (%)
4a		H	A	229-230 (AcOEt)	62
4b		H	A	217-219 (AcOEt)	55
4c		H	A	222-223 (*i*-PrOH)	70
4d	NEt_2	H	B	184-185 (CH_3CN)	66
4e	NEt_2	CH_3	B	192-193 (Acetone)	70
4f		H	B	207-208 (AcOEt)	60

Results and discussion

Table 2 lists the results of experiments to evaluate the affinities of compounds **4a-4f**, for dopamine D_2 and serotonin 5-HT_{2A} receptors. Compounds **4a-c** inhibited the binding of ^{3}H-spiperone to D_2 receptors with pK_i values ranging between 5.81 and 6.85, and the binding of ^{3}H-ketanserine to 5-HT_{2A} receptors with pK_i values from 6.20 to 8.80. Compounds **4d-f**, bearing simple amines, did not show affinity for both D_2 and 5-HT_{2A} receptors. The most active compounds, **4b (QF 2003B)** and **4c (QF 2004B)**, show a pK_i (5-HT_{2A}/D_2) ratio of 1.28. In keeping with the hypotheses suggested by Meltzer *et al*[7] regarding the combination of 5-HT_{2A} blocking and D_2-blocking activities, the compounds **4b,c** are thought to have an atypical antipsychotic profile.

The *p*-fluorobenzoyl derivative **4b** exhibited a high affinity for 5-HT_{2A} receptors with a pK_i= 8.04, while the pK_i value for D_2 receptor was 6.25. The pK_i (5-HT_{2A}/D_2) ratio for compound **4b** was 1.28, higher than that for haloperidol (0.91), risperidone (1.20) or clozapine (1.23). This compound also exhibited a pA_2 value of 9.2 in suppressing serotonin-induced contractions in rat aorta ring stripped of endothelium.[9] According to Meltzer's classification, **4b** shows a profile of an atypical antipsychotic.

The replacement of the benzoyl piperidino fragment of **4b** by a 1,2-benzisoxazolylpiperidino moiety (compound **4c**) increased the affinity for both D_2 and 5-HT_{2A} receptors, with pK_i values of 6.85 and 8.80, respectively. The affinity for 5-HT_{2A} receptors (pK_i and pA_2) is higher than that exhibited by clozapine. Consequently Meltzer's ratio for this compound increases to 1.28.

The introduction of *o*-methoxyphenyl piperazino or amines with non-aromatic fragments does not improve its affinity for 5-HT_{2A} and D_2 receptors.

In conclusion, we have developed a practical and efficient 4 (for amines with non-aromatic fragments) or 5 (for amines with aromatic cycles) steps synthesis of new derivatives in the carbazol series from cheap and readily starting materials, as atypical antipsychotics. The promising affinity for both D_2 and 5-HT_{2A} receptors shown by compound **4c (QF 2004B)** together with its high Meltzer's ratio has prompted us to choose this compound for further development.

Table 2: Inhibition constants (pK_i) at D_2 and 5-HT_{2A} receptors[a] and pA_2 values.[b]

Compound	pK_i (D_2) ± s.e.m.	pK_i (5-HT_{2A}) ± s.e.m.	pK_i's ratios (5-HT_{2A}/D_2) ± error	pA_2 (5-HT_{2A}) ± s.e.m.
4a (QF 2006B)	5.81 ± 0.33	6.20 ± 0.05	1.07 ± 0.05	6.5 ± 0.20
4b (QF 2003B)	6.25 ± 0.24	8.04 ± 0.34	1.29 ± 0.10	9.2 ± 0.27
4c (QF 2004B)	6.85 ± 0.21	8.80 ± 0.41	1.28 ± 0.10	9.5 ± 0.32
4d (QF 2002B)	<5	<5	-	N.T.[c]
4e (QF 2014B)	<5	<5	-	N.T.[c]
4f (QF 2001B)	<5	<5	-	N.T.[c]
Haloperidol	8.48 ± 0.12	7.70 ± 0.22	0.91	-
Clozapine	6.58 ± 0.05	8.12 ± 0.07	1.23	8.62 ± 0.05

[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.[11,12] pK_i values were calculated using the Cheng-Prusoff equation;[29] results shown are means of three inhibition curves constructed with each drug. [b] pA_2 values were calculated for the antagonism of compounds at denuded rat aorta. [c] No tested.

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25. Recently has been suggested that multiple orientations or modes of binding are possible for 5-HT_{2A} receptor interactions. A key structural feature that may play a prominent role in these interactions would be the benzylic carbonyl group. Ismaiel, A. M.; Arruda, K.; Teitler, M.; Glennon, R. A. *J. Med. Chem.* **1995**, *38*, 1196-1202.
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27. Data of **4a**: IR (KBr) 3177, 2956, 1618, 1472 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.71 (1H, br. s), 8.24-8.21 (1H, m), 7.35-7.28 (1H, m), 7.26-7.20 (2H, m), 7.04-6.98 (1H, m), 6.95-6.93 (2H, m), 6.87 (1H, d, J = 7.6 Hz), 3.86 (3H, s), 3.17 (1H, dd, J = 16.4, 3.6 Hz), 3.09 (4H, app. s), 2.82-2.55 (7H, m), 2.48 (2H, t, J = 6.3 Hz), 2.38 (1H, dd, J = 15.7, 9.6 Hz) ppm. EIMS *m/z* 389 (M^+), 205 (100%). *Anal.* calcd. for $C_{24}H_{27}N_3O_2$: C, 74.01%; H, 6.99%; N, 10.79%. Found: C, 73.88%; H, 7.25%; N, 10.87%. **4e**: IR (KBr) 2967, 1636, 1475 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.26-8.23 (1H, m), 7.33-7.24 (3H, m), 3.72 (3H, s), 3.15 (1H, dd, J = 16.0, 3.1 Hz), 2.69-2.41 (9H, m), 2.31 (1H, dd, J = 16.0, 9.5 Hz), 1.00 (6H, t, J = 7.1 Hz) ppm. EIMS *m/z* 284 (M^+), 198, 86 (100%). *Anal.* calcd. for $C_{18}H_{24}N_2O$: C, 76.02%; H, 8.51%; N, 9.85%. Found: C, 76.30%; H, 8.63%; N, 9.57%.
28. Complete details of the synthesis and spectral data will be published elsewhere in a full paper. All compounds gave satisfactory mycroanalytical data (C, H, N ±0.4%) and spectral data (^{1}H and ^{13}C-NMR, FTIR, MS). Yields given correspond to isolated pure compounds.
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