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New CNS Agent Precursors. A Simple and Efficient Route for Synthesis of 6-Aminomethyl-4,5,6,7-tetrahydrobenzofuran-4-ones as Conformationally Constrained Butyrophenone Analogues

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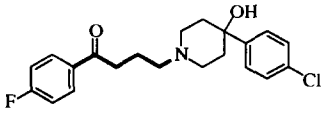
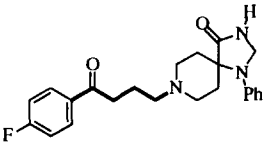
Abstract: Starting from 3,4,5-trimethoxybenzoic acid, we described a practical and efficient five-step synthesis of 6-aminomethyl-4,5,6,7-tetrahydrobenzofuran-4-ones as new CNS agent precursors in an overall yield of 20%. © 1997 Elsevier Science Ltd.

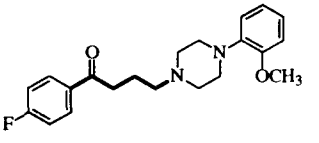
Schizophrenia is a devastating mental illness that affects ca to 1% of the world's population. The first-line of the antipsychotic therapy is represented by *classical neuroleptics* (or *classical antipsychotics*) such as haloperidol, the prototype of a group of butyrophenone derivatives with a very potent antipsychotic activity; among them, the most potent neuroleptics are spiperone and fluanisone which are 4-aminobutyrophenone derivatives.[1] At present, it is widely accepted that the dopaminergic system plays a key role in the manifestation of schizophrenic.[2] This belief is supported by the observation that all clinically effective antipsychotics agents act as antagonists at the dopaminergic D_2 receptor.[3] Unfortunately, dopamine receptor blockade is also intimately associated with their extrapiramidad side effects (EPS, a short-term parkinsonism like condition). Furthermore, the classical antipsychotics are not effective against the negative symptoms of schizophrenia. The shortcomings of all current antipsychotic drugs have led to an urgent need for better therapies.



Haloperidol

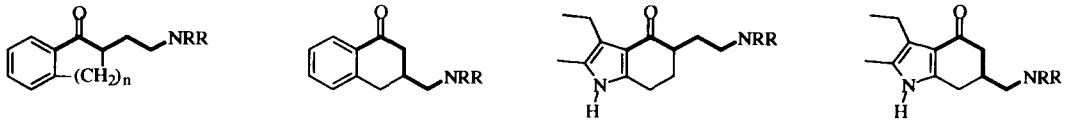


Spiperone

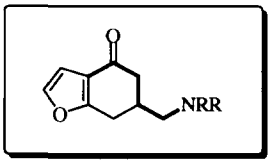


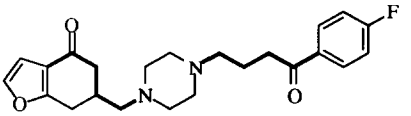
Fluanisone

In previous papers we have reported the synthesis and neuroleptic activity of 3-aminomethyltetralones[4,5] and 2-aminoethylbenzocycloalkanones[6,7] which are conformationally restricted butyrophenone analogues of haloperidol, with the aminobutyl side chain incorporated in a semirrigid framework. Later, we have prepared 5-aminoethyl and 6-aminomethyl-4,5,6,7-tetrahydroindol-4-ones[8-10] as butyrophenone derivatives in the indole series, as new CNS agent precursors.



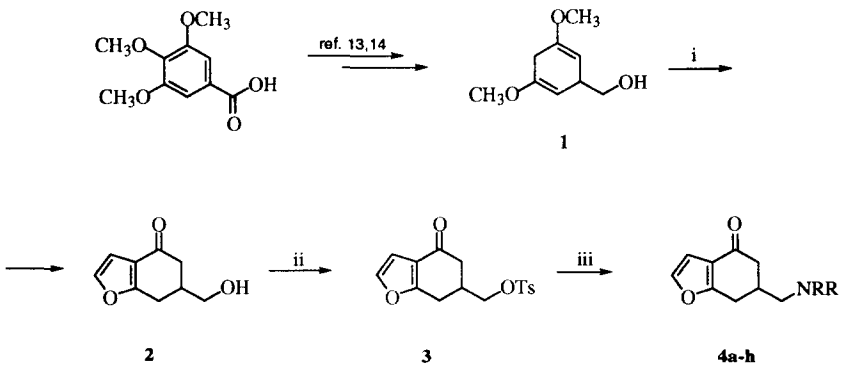
Now we wish to report a practical and efficient synthetic strategy for preparing 6-aminomethyl-4,5,6,7-tetrahydrobenzofuran-4-ones, cyclic butyrophenone derivatives in the furane series. The procedure is general for single and complex heterocyclic amines as arylpiperazines[11] or substituted piperidines (e.g. *p*-fluorobenzoylpiperidine[12]). As an exemplification of our methodology for synthesis of potential CNS agents, we also report the alkylation of the free piperazin nitrogen with a linear butyrophenone pharmacophore to give a *duplicate* **5i** with both pharmacophoric moieties linked across a piperazine bridge.





5i

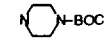
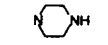
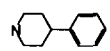
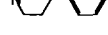
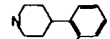
For the synthesis of the amines **4a-i** (scheme 1) we started from the 1,4-dihydro-3,5-dimethoxy benzyl alcohol **1**, which was readily prepared from the cheap 3,4,5-trimethoxybenzoic acid in 85% yield as previously described.[13,14] The furannulation of the compound **1** was achieved by mild acidic hydrolysis of the enol-ether groups with 1 N HCl in THF, concentration *in vacuo*, and condensation of the residue with chloroacetaldehyde in the presence of a base ($NaHCO_3$) followed by dehydratation by acid catalysis (1 N HCl) to give the 6-hydroxymethyl-4,5,6,7-tetrahydrobenzofuran-4-one **2** with 60% overall yield, after chromatographic purification.[15] To increase the yield of the condensation, the pH was within 6-9 through the process. Reaction of the alcohol **2** with *p*-toluenesulfonyl chloride in pyridine afforded the tosylate **3** as white crystalline solid (65%; m.p. 104-105°C, *iso*-PrOH). Nucleophilic displacement of the tosylate with amines in N-methyl-2-pyrrolidone (NMP) provided, after bulb to bulb distillation of NMP, the amines **4a-h**[16] as white crystalline solids with yields ranging 55-70% (Table I).[17]



Reagents: **i**: 1) 1N HCl, r.t., 2 h; 2) $ClCH_2CHO$, $NaHCO_3$, r.t., 12 h; 3) 1N HCl, r.t., 2 h; **ii**: Ts-Cl, Py, 0°C, 24 h; **iii**: HNRR, NMP, 85°C

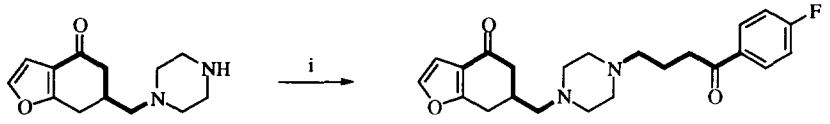
Scheme 1

Table 1. 6-Aminomethyl-4,5,6,7-tetrahydrobenzofuran-4-ones **4a-h**

Compound	NRR	m.p. (°C)[a]		Yield **3**→**4** (%)
		base	HCl salt	
4a (QF 1002B)		108-109	251-252	65
4b (QF 1001B)		133-134	138-139	70
4c		86-87	-	70
4d (QF 1009B)[b]		128-130	213-214	65
4e (QF 1007B)		121-122	198-199	75
4f (QF 1006B)		135-136	201-203	70
4e (QF 1008B)		108-109	128-130	80
4h (QF 1003B)		113-114	244-245	75

(a) All the compounds were recrystallized from *iso*-PrOH; (b) Obtained from **4c** by quantitatively BOC removal (TFA).

The 6-[4-[3-(*p*-fluorobenzoyl)propyl]piperazin-1-yl]methyl-4,5,6,7-tetrahydrobenzofuran-4-one **4i** (m.p. 198-200°C, *iso*-PrOH) was prepared with overall yield of 55% by alkylation of **4d** with 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)-butane in methyl isobutyl ketone and subsequent cleavage of the ketal as we have previously described in the benzene[6] and indole[10] series (Scheme 2).



4d **4i**

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

Scheme 2

In conclusion, we have developed a practical and efficient, five-step synthesis (overall isolated yields 20%) of new derivatives in the furane series from cheap and readily starting materials. Further applications of this methodology will provided new entries for later developing CNS acting agents. Works are in progress in our Laboratory which will be reported in due course.

Acknowledgement: This research was supported by the Spanish Interministerial Comission for Science and Tecnology (CICYT) and Xunta de Galicia under grants SAF 95-1081 and XUGA 20312 B95, respectively.

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11. Arylpiperazines are important tools in the field of Medicinal Chemistry. Every year, several new methods for the synthesis of such compounds are proposed. See Perez, M.; Potier, P.; Halazy, S. *Tetrahedron Lett.* **1996**, *47*, 8487-8488, and references cited therein.
12. The 4-(*p*-fluorobenzoyl)piperidine fragment may be considered as a butyrophenone moiety constrained in a six-membered ring. The importance of this fragment on CNS agents acting compounds is well known. See, among others, (a) Boswell, R. F., Jr.; Welstead, W. J., Jr.; Duncan, R. L., Jr.; Johnson, D. N.; Funderburk, W. H. *J. Med. Chem.* **1978**, 21, 136-138; (b) Herndon, J. L.; Ismaiel, A.; Ingher, S. P.; Teitler, M.; Glennon, R. A. *J. Med. Chem.* **1992**, *35*, 4903-4910; (c) Ismaiel, A. M.; Arruda, K.; Teitler, M.; Glennon, R. A. *J. Med. Chem.* **1995**, *38*, 1196-1202.
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15. *Experimental procedure:* To a solution of alcohol **1** (0.50 g, 3 mmol) in THF (15 ml) was added dropwise 1 N HCl (3 ml). The resulting solution was stirred at room temperature for 2 h and then the THF distilled under vacuum. The concentrated solution was added drop by drop (0.5 ml/min) with stirring into another solution of chloroacetaldehyde (50% aqueous sol., 1ml, 8 mmol) and $NaHCO_3$ (0.63 g, 7.5 mmol) in water (5 ml). After the addition was complete, the reaction mixture was further stirred overnight at room temperature. Through the reaction the acidity of the solution was within pH 6-9. To the mixture, ethyl acetate (5 ml) was added and the resulting solution was acidified (1 N HCl) until pH 1 and stirred 1-2 h at room temperature. The organic layer was separated, washed with 5% aqueous K_2CO_3, dried (Na_2SO_4) and concentrated under reduced presure. Silica gel chromatography of the residue (hexane/ethyl acetate 1:4 as eluent) gave the alcohol **2** (0.63 g, 60%) as yellow oil.
16. Data of **4a**: IR (KBr) 2949, 1665, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.30 (1H, d, J = 2 Hz, H-3), 6.40 (1H, d, J = 2 Hz, H-2), 3.11-2.98 (1H, m, H-6), 2.63-2.25 (6H, m, H-5, H-7, CH_2-NEt_2), 2.20 (2H, q, J = 7.3 Hz, N-CH_2-CH_3), 1.91 (2H, q, J = 6.8 Hz, N-CH_2-CH_3), 1.11 (3H, t, J = 7.1 Hz, -CH_3), 1.03 (3H, t, J = 7.1 Hz, -CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ 194.1, 166.9, 143.3, 121.4, 106.8, 63.6, 42.9, 42.3, 40.7, 33.3, 28.4, 14.6, 13.4 ppm. FABMS *m/z* 222 (M^+ + 1; 81%), 153 (46%), 148 (53%), 134 (22%), 105 (39%), 91 (82%), 86 (91%), 55 (100%). *Anal.* calcd. for $C_{13}H_{19}NO_2$: C, 70.55%; H, 8.65%; N, 6.32. Found: C, 70.81; H, 8.64; N, 6.13.
17. 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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