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Synthesis of substituted tetralones as intermediates of CNS agents via palladium-catalyzed cross-coupling reactions☆

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Abstract—A series of substituted tetralones as intermediates of CNS agents has been synthesized via Pd-catalyzed coupling reactions of 3-(methoxycarbonyl)-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl trifluoromethanesulfonate (**5**) with a variety of organometallic reagents.

The discovery and development of novel therapeutics for schizophrenia, one of the most devastating brain disorders (affecting about 1% of the world's population), is now one of the most challenging areas of CNS research. The introduction of the butyrophenone haloperidol (Haldol®, Fig. 1) into the clinic in 1959 was a significant advancement in the treatment of schizophrenia, due to its efficacy in countering the hallucinatory and delusional (positive) symptoms of the disease.[1] However, haloperidol is ineffective in the treatment of negative symptoms and neurocognitive deficits,[2] a therapeutic profile that could be rationalized by the relatively low affinity for 5-HT_{2A} receptors compared to D_2 receptors.[3] On the other hand, the safety advantages of second-generation (atypical) antipsychotic drugs, characterized by their high affinity for serotonin 5-HT_{2A} receptors, have been questioned because of their propensity to induce weight gain and alter glucose and lipid metabolism.[4]

In the last few years we have been working on modulation of the butyrophenone system with the aim of combining antagonism at 5-HT_2 family and D_2 receptors in a single molecule.[5] We have reported the synthesis, pharmacological activity and molecular modelling of the aminoalkylbenzocycloalkanones **I** (Fig. 1), which

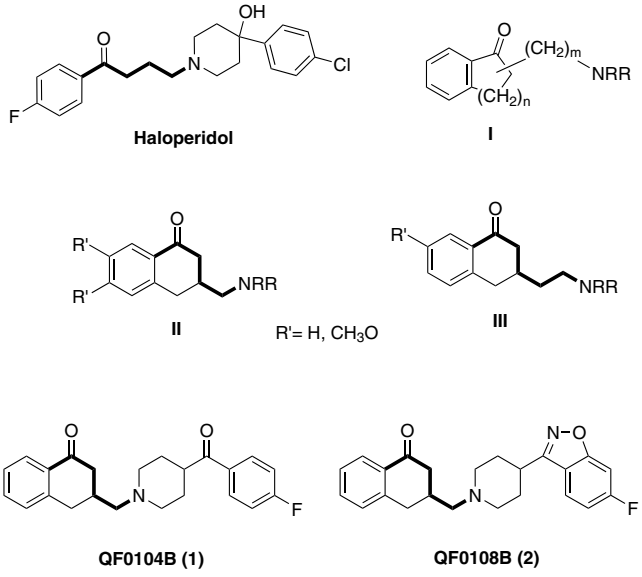

Figure 1.

are conformationally restricted butyrophenone analogues of haloperidol.[6] Among these compounds, the favourable pharmacological profile of the tetralone derivatives **II**[7] and **II**[8] has prompted us to explore the structure–activity relationships of this system as a scaffold for the design of new analogues of haloperidol. Aminobutyrophenones QF0104B (**1**) and QF0108B (**2**) (Fig. 1) showed high affinity for the 5-HT_{2A} receptor subtype with K_i values of 1.6 and 2.7 nM, respectively, with compound **1** being the most selective for the

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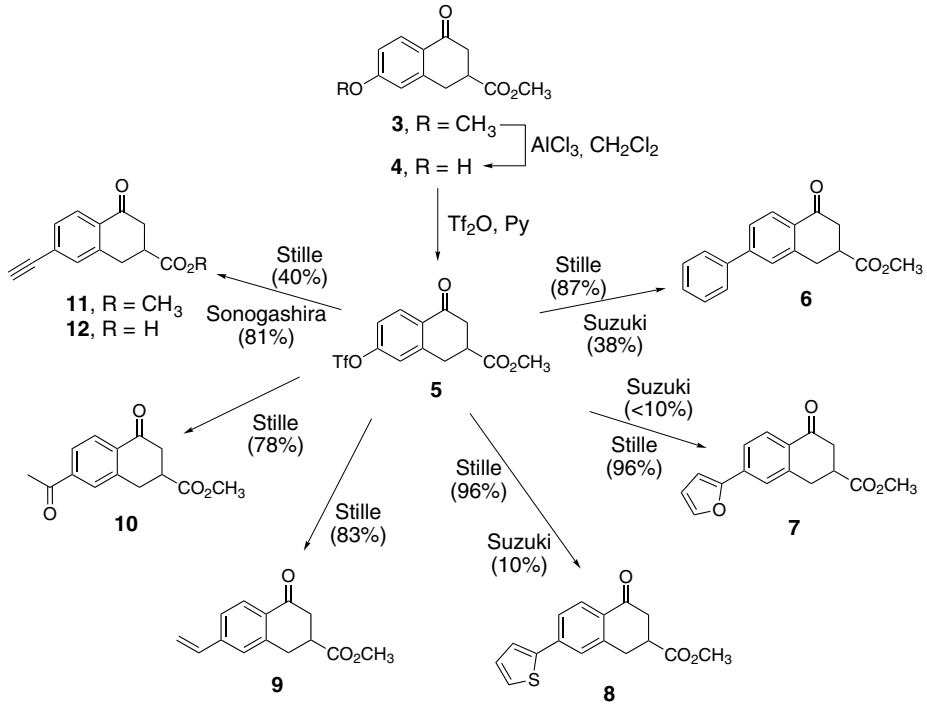
serotonin 5-HT_{2A} receptor subtype, with a 5-HT_{2A}/5-HT_{2C} K_i ratio as high as 150.[7] These compounds are also potent D_2 receptor antagonists, although they display K_i values higher than those at 5-HT_{2A} receptors.

In these series, our preliminary results showed that methoxy groups at the tetralone ring do not significantly affect the binding affinity towards any of the receptors studied, which suggests that their interaction with such receptors is not significant. However, a more in-depth study of the effect of substituents at the aromatic ring on affinity for serotonin and dopamine receptors is necessary. The addition of substituents to a lead structure is often used to find additional binding interactions with the target. This strategy involves the addition of hydrophobic regions by adding alkyl or aryl groups, and also other functional groups can be added to probe for extra hydrogen or ionic bonding interactions. In this letter, we report the synthesis of a series of substituted aminomethyltetralones through palladium-catalyzed coupling reactions, as intermediates in the synthesis of new CNS agents.

For this study, 3-(methoxycarbonyl)-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl trifluoromethanesulfonate (**5**) was used as the starting material, which was prepared by cleavage of the methylether group of the known compound **3**[7] (Scheme 1) with $AlCl_3$ in CH_2Cl_2, and subsequent reaction of the phenol derivative obtained (**4**) with trifluoromethanesulfonic anhydride in pyridine (66% yield, two steps).[9] The first reaction studied was the Suzuki arylation[10] of triflate **5** with boronic acids. Reactions were carried out by refluxing a mixture of **5** and the appropriate boronic acid (phenyl, 2-furyl or 2-thienyl) in the presence of a base, using tetrakis(triphenylphosphine)palladium(0) as a catalyst. After some optimization of the experimental conditions, for phenylboronic acid it was found that phenyl coupling of **5** involved heating in DMF in the presence of 1% $Pd(PPh_3)_4$ with 3 equiv of K_2CO_3. Under these conditions, the phenyltetralone (**6**) was obtained in 38% yield.

Disappointingly, all attempts to couple triflate **5** with 2-furylboronic or 2-thienylboronic acids under a variety of conditions were unsuccessful. Repeated assays where catalyst, base and solvent were varied afforded poor yields (<10%) of 7-furyltetralone **7**, or 7-thienyltetralone **8**,[11] leading in some cases to the formation of the detriflated compound (methyl 4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate) or the phenol derivative **4**.

Since Suzuki couplings of triflate **5** with phenyl- and heterocyclic boronic acids were unsatisfactory, we decided to apply the Stille methodology[12] for the cross-coupling arylation of **5**. In our hands, the reaction of the triflate derivative (**5**) with 1 equiv of tributyl- (or trimethyl-) phenylstannane and 10% $Pd(PPh_3)_4$ in the presence of LiCl (3 equiv) in dioxane at 110 °C under argon were the best conditions. Under these conditions, the 7-phenyltetralone derivative (**6**) was obtained in 86% yield (Table 1, entries 1 and 2).[13] Similarly, Stille coupling of **5** with 2-(tributylstannyl)furan (entry 3) or 2-(tributylstannyl)thiophene (entry 4) using the above-mentioned conditions led to the expected 7-substituted tetralones **7** and **8**, respectively, in excellent yields. Remarkably, Stille couplings with these heterocyclic stannanes occurred cleanly and rapidly, and little starting triflate remained after a few minutes. With these results in our hands, we decided to extend the Stille methodology to the coupling of triflate **5** with other



Scheme 1.