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Original article

Synthesis and biological evaluation of a series of aminoalkyl-tetralones and tetralols as dual dopamine/serotonin ligands

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ABSTRACT

A series of novel α-tetralone and α-tetralol derivatives was synthesized, and their binding affinities for 5-HT_{2A} and D_2 receptors, the most important targets implicated in the anti-schizophrenia drug action, were evaluated to elucidate how substitutions in the aromatic ring of the pharmacophore affect to the affinity or selectivity for these receptors. The replacement of the H-7 in the tetrahydronaphthalene system by an amino group resulted in privileged 5-HT_{2A} affinity of the 6-fluorobenzo[*d*]isoxazol derivative **36** and the alcohol **25** both showing a pK_i value for 5-HT_{2A} higher than 8.3 and good binding affinities for D_2 receptor leading to a Meltzer's ratio characteristic of an atypical antipsychotic profile. Additionally, a small collection of 3-aminomethyltetralone derivatives was prepared and examined here for their affinities and selectivities as 5-HT_{2A}/D_2 dual ligands. Compound **11** shows the best profile with good pK_i values for 5-HT_{2A} and D_2 receptors leading to a Meltzer's ratio characteristic of a typical antipsychotic behaviour. These three compounds behaved as competitive antagonists of both 5-HT_{2A} and D_2 receptors, and might be promising pharmacological tools for the investigation of the dual function of the 5HT_{2A}-D_2 ligands.

1. Introduction

Schizophrenia is a severe mental disorder affecting around 24 million people worldwide, and it typically begins in late adolescence or early adulthood. It is characterized by a complex symptomatology, which, in general, involves alterations in cognitive and emotional functioning. Its symptoms can be grouped as positive, negative and cognitive: positive symptoms including altered behaviour, such as delusions, hallucinations, extreme emotions, excited motor activity, and incoherent speech. Negative symptoms are described as a lack of behaviour, such as poverty of speech, social withdrawal, avolition, anhedonia and affective blunting. At last, cognitive symptoms consist of reduction in working memory, attention, and verbal fluency [1]. However, there are no specific focal characteristics for the diagnosis of schizophrenia, and no single symptom is consistently present in all patients. Consequently, its diagnosis as a single disorder, or as a variety of different disorders, is still debated.

Furthermore, the co-occurrence of depressive symptoms is common in patients with schizophrenia, with estimates of the prevalence in clinical populations ranging from 25 to 60%. Depressive symptoms are of great prognostic significance since they are associated with compromised quality of life and increased risk of psychotic relapse and suicide [2].

For decades, dopamine receptor blockers such as haloperidol have been the treatment of choice for schizophrenia, but despite the effectiveness of this approach, dopamine antagonism has a number of drawbacks, causing serious side effects such as motor disorders, tardive dyskinesia, and hyperprolactinemia [3,4]. Newer antipsychotic drugs, the so-called atypical antipsychotics, show a wider efficacy against the negative and positive symptoms due to a multireceptorial affinity profile that could be the reason why, four decades after its introduction into the clinic, clozapine still remains the prototype for use in cases of treatment-resistant schizophrenia [5].

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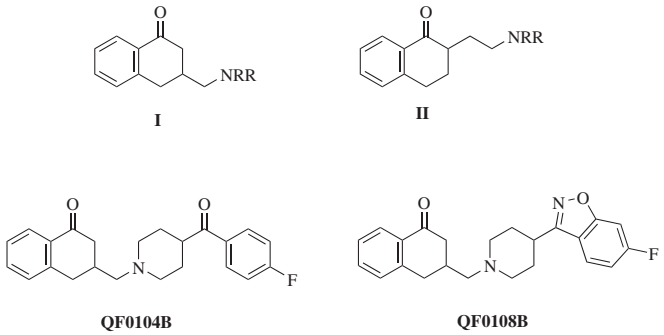

Fig. 1. Chemical structure of some representative reported tetralone derivatives.

As a result, the discovery of a more effective, side-effect free therapy for the treatment of schizophrenia is still needed and remains a challenging research goal.

In the last decades we have been working on the modulation of the butyrophenone system with the aim of combining the antagonism at the 5-HT_2 family and the D_2 receptors in a single molecule. So far, in an attempt to synthesize more efficient compounds for prospective use as antipsychotics, we have reported the synthesis, pharmacological activity and molecular modelling of the aminoalkylbenzocycloalkanones, which are conformationally restricted butyrophenone analogues of haloperidol [6]. Among these compounds, the favourable pharmacological profile of some tetralone derivatives owing to the general structures **I** [7] and **II** [6] (Fig. 1), has prompted us to explore the structure–activity relationships of this system as a scaffold for the design of new improved analogues of haloperidol. For example, aminobutyrophenones **QF0104B** and **QF0108B** (Fig. 1) showed high affinity for the 5-HT_{2A} receptor subtype with pK_i values of 8.79 and 8.56 nM, respectively, being **QF0104B** the most selective compound for the serotonin 5-HT_{2A} receptor subtype, with a 5-HT_{2A}/5-HT_{2C} K_i ratio as high as 150 [6]. Moreover, these compounds display pK_i values at D_2 receptor slightly lower than those at 5-HT_{2A} receptors which is in accordance to the proposed binding profile for an atypical antipsychotic.

In an extension of our work on the development of new conformationally constrained aminobutyrophenones as potential dual antagonists on dopamine D_2 and serotonin 5-HT_{2A} human receptors, we report herein the synthesis and binding affinities of a novel collection of compounds based on the 1-tetralone and 1-tetralol scaffolds (Fig. 2): 6-acetyl- and 6-phenyl-3-(aminomethyl)-1-tetralones (**III**), 7-amino- and 7-nitro-2-(aminoethyl)-1-tetralones (**IV**), and 7-amino- and 7-nitro-(2-aminoethyl)-1-tetraloles (**V**). The addition of substituents to a lead structure to achieve an in-depth study of the effect of different groups at the aromatic ring on affinity for serotonin and dopamine receptors is necessary and often used to find additional binding interactions with the target. This strategy involves, for instance, the addition of substituents such as nitro or amino groups to probe for extra hydrogen or ionic bonding interactions.

2. Results and discussion

2.1. Chemistry

2.1.1. 6-Acetyl- and 6-phenyl-3-(aminomethyl)-1-tetralones

In a continuation of our study to indentify new structures as dopamine and serotonin ligands, we have reported the synthesis of some intermediates belonging to the 1-tetralone scaffold using Stille, Suzuki and Sonogashira palladium-catalysed cross-coupling reactions from triflate **1** (Scheme 1) [8]. Among these intermediates we selected the 6-acetyl- and 6-phenyl-1,2,3,4-tetrahydro-4-oxonaphthalen-2-carboxylates **2** and **3** as starting materials of a new series of compounds bearing the tetralone core substituted by a polar or a bulky group (**10**–**13**).

As it is depicted in Scheme 1, the synthesis started with the simultaneous reduction of both carbonyl groups in **2** and **3** using $LiAlH_4$ in THF at room temperature giving the corresponding trihydroxy derivative **4** and diol **5**, respectively, in good yield. The selective oxidation of the secondary hydroxyl group with MnO_2 afforded the hydroxyketones **6** and **7** in 70% yield. Next, activation of the hydroxyl group as a tosyl led to the sulfonates **8** and **9** in satisfactory yields. Finally, nucleophilic replacement with two different piperidines, 4-(6-fluorobenzisoxazol-3-yl)piperidine (A) and 4-(4-fluorobenzoyl)piperidine (B), afforded the targeted 6-acetyl- and 6-phenyl-3-aminoketones **10**–**13** in fair to good yields.

2.1.2. 7-Amino- and 7-nitro-2-(aminoethyl)-1-tetralone, and 7-amino- and 7-nitro-2-(aminoethyl)-1-tetralol series

The synthetic route for the preparation of the target tetralones and tetralols started from commercially available α-tetralone. As depicted in Scheme 2, α-tetralone underwent thermal condensation with glyoxylic acid and *p*-TsOH to give the unsaturated acid **14**, which was reduced with zinc in acetic acid to afford 1,2,3,4-tetrahydro-l-oxo-naphthalene-2-acetic acid (**15**) both steps according to previously reported procedures [9,10]. Despite an effective direct nitration of acid **15** has not been previously reported, a similar approach to the Hay's method [11] using a 33% mixture of nitric acid in concentrated sulphuric acid was applied to give the 7-nitroacid **16** in satisfactory yield.

An alternative route *via* 7-nitrotetralone was considered for the preparation of the acid **16**: nitration of α-tetralone was accomplished with the mentioned method giving the 7-nitrotetralone **17** in 65% yield. Compound **17** was submitted to thermal condensation with glyoxylic acid in good yield followed by reduction with zinc and acetic acid of the resulting alkanylidene acetic acid **18** to give the 7-nitroketoacid **16** in 49% overall yield. Coupling of acid **16** with secondary amines was carried out within dichloromethane in the presence of 1-HOBt and DCC to gain the ketoamides **19** and **20** in yields around 80%.

As outlined in Scheme 3, the 7-nitrotetralols **21** and **22** and their 7-amino counterparts **23** and **24** were readily obtained from key compounds **19** and **20**: aluminium hydride reduction of these ketoamides gave their corresponding 7-nitroalcohols **21** and **22** in moderate yield. We attribute the low yield achieved to the chemical instability of starting materials in the presence of reducing agents

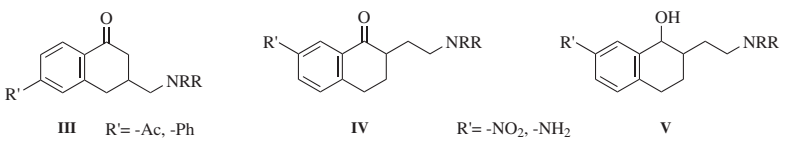

Fig. 2. General structures of new compounds based on the 1-tetralone and 1-tetralol scaffolds.