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Research paper

Branching tryptamines as a tool to tune their antiproliferative activity

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ABSTRACT

The influence of a series of tryptamine derivatives on the viability of normal (HEK293) and tumor (HepG2, Jurkat and SH-SY5Y) cells has been evaluated. All tryptamines tested were three different substitution types: *C*- and *N*-branching, and indole benzylation. All the derivations enhance the activity of compounds separately, although the effects of different substitutions were not additive. Thus, combinations of C- and N-branchings as well as C-branching and indole benzylation gave little or no increase in activity.

1. Introduction

Besides their traditional 5-HT agonist activity [1,2], tryptamine derivatives have been regarded as antitumor agents due to their high cytotoxicity [3–9]. However, unbranched primary amines are known to undergo rapid degradation in an organism by MAO enzymes [10,11]. In a previous report we have investigated the cytotoxicity of a range of 2-methyltryptamines with IC_{50} values down to 4.3 μM [12]. Therein we have found that derivatives monobenzylated at the amino group demonstrate increased cytotoxicity in comparison with both parent substances and dibenzylated tryptamines. The chain branching in amines is known to be a method to reduce the drug metabolism rate [13–15]. Recently, we have developed an approach to the synthesis of α-arylated tryptamines [16] via the domino Clock-Stevens/Grandberg rearrangement [17] of cyclopropylketone arylhydrazones. Thus, here we present an investigation of the influence of two branching substitutions onto the antiproliferative activity of tryptamine derivatives. The first one, *C–branching*, implies the use of α-arylated tryptamines, the second one, *N-branching*, assumes *N*-benzylation at the amino group nitrogen. Previously only few examples of β-C-branched tryptamine derivatives studied for cytotoxic properties have been described [9]. Additionally, in the previous article [12] we have shown that cytotoxicity increased upon benzylation at the indole nitrogen atom in comparison with that of the parent substance. Therefore we continued the investigation of the influence of this substitution on the activity of tryptamine derivatives.

2. Results and discussion

2.1. Chemistry

Within the investigation of cytotoxic properties of substituted tryptamines we primarily studied our previously reported α-arylTryptamines **1a–i** including enantiomerically pure (S)–**1f** [16], which were obtained by the reaction of arylhydrazine hydrochlorides **2** with 1-acetyl-2-arylcyclopropanes **3** via the rearrangement of *in situ* generated cyclopropylketone arylhydrazones **4** (Scheme 1). Herein the introduction of an aromatic substituent in position 2 of the cyclopropyl moiety leads to the ring-opening at the more

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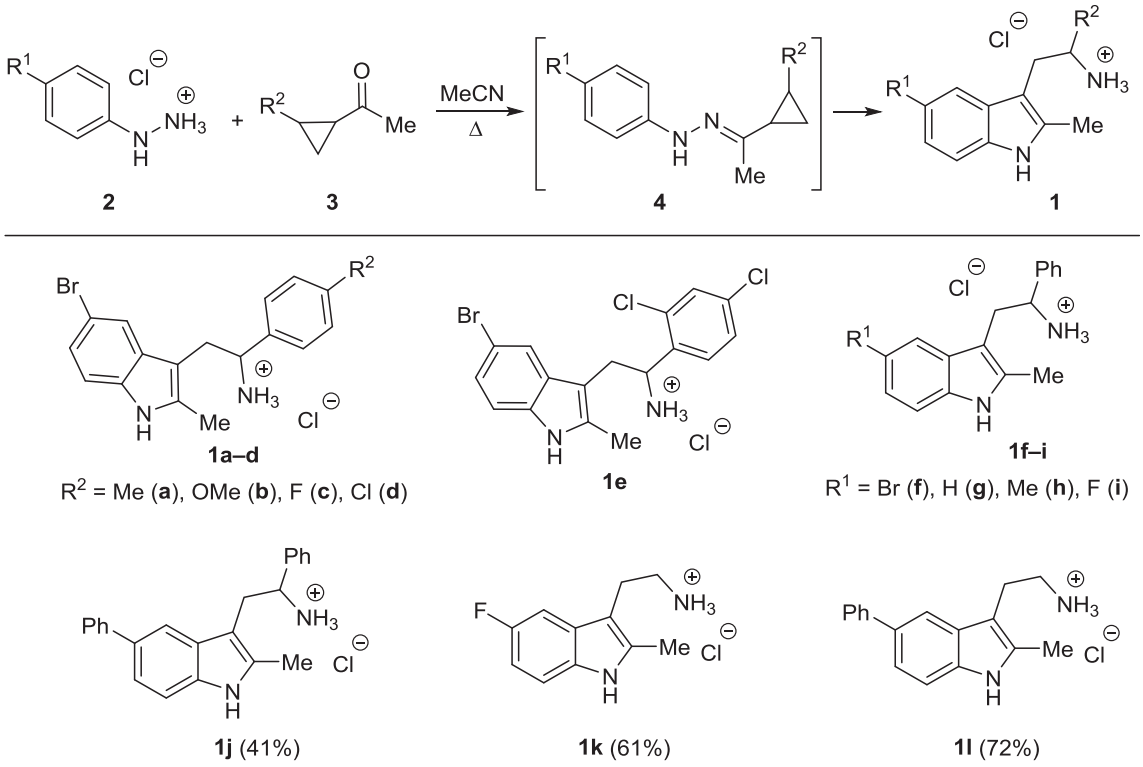
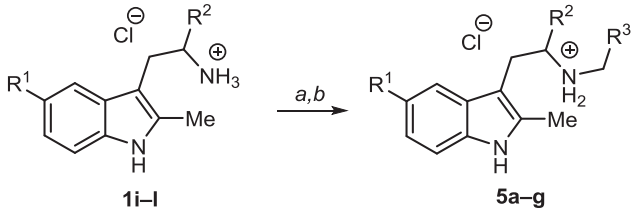


Scheme 1. Synthesis of 2-methyltryptamine derivatives **1a**–**l**.

substituted bond to give α-arylated derivatives. Furthermore this protocol was used for the synthesis of tryptamines **1j**–**l** from corresponding arylhydrazine hydrochlorides **2** (R^1 = F, Ph) and ketones **3** (R^2 = H, Ph). It is worth mentioning that previously we have reported the synthesis of **1l** via the Suzuki coupling reaction of the corresponding *N*-Boc-protected tryptamine **1** (R^1 = Br, R^2 = H) [12].

In our previous article [12] we investigated the influence of both aliphatic and aromatic nitrogen atom benzylations in 5-bromo-2-methyltryptamine on its antitumor properties. Here we performed these substitutions in a range of 5-fluoro and 5-phenyltryptamines, the latter has previously shown the lowest IC_{50} value amongst 5-substituted derivatives. The benzylation at the aliphatic nitrogen atom was accomplished using the reductive amination reaction with sodium cyanoborohydride. This procedure was applied to both α-phenylated **1i**–**j** and unbranched **1k**–**l** tryptamines using either benzaldehyde or 7-methoxybenzodioxole-5-carbaldehyde to give derivatives **5a**–**g** (Scheme 2, Table 1).

The benzylation at the indole nitrogen atom in **1i**–**l** required Boc-protection of the amino group to give **6a**–**d**, benzylation with benzylbromide and sodium hydride to form benzylated **7a**–**d** and subsequent deprotection into corresponding hydrochlorides **8a**–**d** (Scheme 3, Table 2).



Scheme 2. Substituents R^1, R^2 and R^3 are given in Table 1. Reagents and conditions: (*a*) $NaBH_3CN$, R^3CHO, AcOH, AcONa, MeOH (for benzaldehyde) or MeOH/THF for 7-methoxybenzodioxolyl-5-carbaldehyde; (b) HCl, MeOH.

2.2. Biological evaluation

All tryptamine hydrochlorides synthesized earlier [16] and in this work have been investigated on their ability to affect the viability of the HEK293 (human embryonic kidney cells), Jurkat (human T-cell lymphoblast-like cell line), HepG2 (hepatocellular carcinoma cells) and SH-SY5Y cells (human neuroblastoma cell line). In general, all the compounds tested demonstrated a stronger inhibitory effect on the viability of Jurkat and HepG2 cells in comparison to that of HEK293 cells (Table 3). With the exception of several derivatives tryptamines have shown little or no selectivity between HEK293 and tumor SH-SY5Y cells. Within the series of C-branched tryptamines minor influence of the nature of the α-aryl substituent on the activity was observed. Thus, compounds **1a**–**f** with the same core but various α-aryl groups have IC_{50} values in a range of 7.12–14.82 μM in HepG2 cell line. Conversely, within compounds **1f**–**j** bearing the same branched aliphatic moiety but varied substituents at position 5 of the indole ring a significant drop

Table 1
Synthesis of tryptamines **5a**–**g** via the reductive amination reaction with aldehydes.

Starting tryptamine	Product	R^1	R^2	R^3	Yield, %
1i	**5a**	F	Ph	Ph	53
1j	**5b**	Ph	Ph	Ph	69
1k	**5c**	F	H	Ph	63
1l	**5d**	Ph	H	Ph	60
1i	**5e**	F	Ph	7-methoxybenzodioxol-5-yl	88
1k	**5f**	F	H	7-methoxybenzodioxol-5-yl	87
1l	**5g**	Ph	H	7-methoxybenzodioxol-5-yl	66