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Synthesis and biological activity of 5-styryl and 5-phenethyl-substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles

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ABSTRACT

Syntheses, biological evaluation, and structure–activity relationships for a series of novel 5-styryl and 5-phenethyl analogs of dimebolin are disclosed. The novel derivatives and dimebolin share a broad spectrum of activities against therapeutically relevant targets. Among all synthesized derivatives, 2,8-dimethyl-5-[(*Z*)-2-phenylvinyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole and its 5-phenethyl analog are the most potent blockers of 5-HT_7, 5-HT_6, 5-HT_{2C}, Adrenergic α_2 and H_1 receptors. The general affinity rank order towards the studied receptors was *Z*-**3**(2) > **4**(2) ⩾ **4**(3) ≫ dimebolin, all of them having highest affinities to 5-HT_7 receptors.

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Dimebolin dihydrochloride, 2,8-dimethyl-5-[2-(2-methylpyridine-5-yl)ethyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**A**), is an excellent example of a drug that best illustrates a 'magic shotgun' concept.[1] This old antihistamine drug[2] was shown to exhibit neuroprotective activity[3] and is being successfully tested in clinical trials as a treatment for Alzheimer's[4] and Huntington's[5] diseases. It was established[6] that besides the histaminergic receptors (H_1 and H_2), dimebolin displays a rather broad spectrum of pharmacological activities targeting adrenergic receptors (α_{1A}, α_{1B}, α_{1D}, α_{2A}), dopaminergic receptors (D_1, D_{2L}, D_{2S}, D_3), serotonergic receptors (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, 5-HT_7) as well as some other receptors, ion channels and enzymes.

Due to the broad spectrum of Dimebon action on many therapeutically important targets, the precise mechanism of its anti-Alzheimer's activity is still elusive. Therefore, synthesis of dimebolin analogs and assessment of their effects on the therapeutic targets presents obvious value for improving efficacy of Alzheimer's disease treatment. Recently, we have shown syntheses and SAR analysis of dimebolin analogs, 2,8-disubstituted-5-(2-heterocyclylethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles.[6] These analogs exhibited broad spectra of biological activities with considerable sensitivity to substitutions in 2-, 5-, and 8-positions. In this work, we describe synthesis and preliminary testing results of previously unknown 5-(2-styryl)-, **3**, and 5-(2-phenethyl)-, **4**, derivatives of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles.

We found that at 80 °C, aryl acetylenes **2**(1–6) easily react with 2,3,4,5-tetrahydro-1*H*-γ-carbolines **1**(1–5) in a biphasic system DMSO–60% KOH in water solution in the presence of tetrabutylammonium sulfate as a phase-transfer catalyst. This reaction leads to formation of previously unknown mixtures of (*Z*)- and (*E*)-isomers of 2-methyl-5-styryl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **3**(1–15) (Scheme 1). The mixtures contain 90–95% of (*Z*)-isomer and 5–10% of (*E*)-isomer, some of which were chromatographically separated.

Unlike vinylpyridines,[6,7] styrene does not react with 2,8-dimethyl-2,3,4,5-tetrahydro-1*H*-γ-carboline **1**(1), which can be

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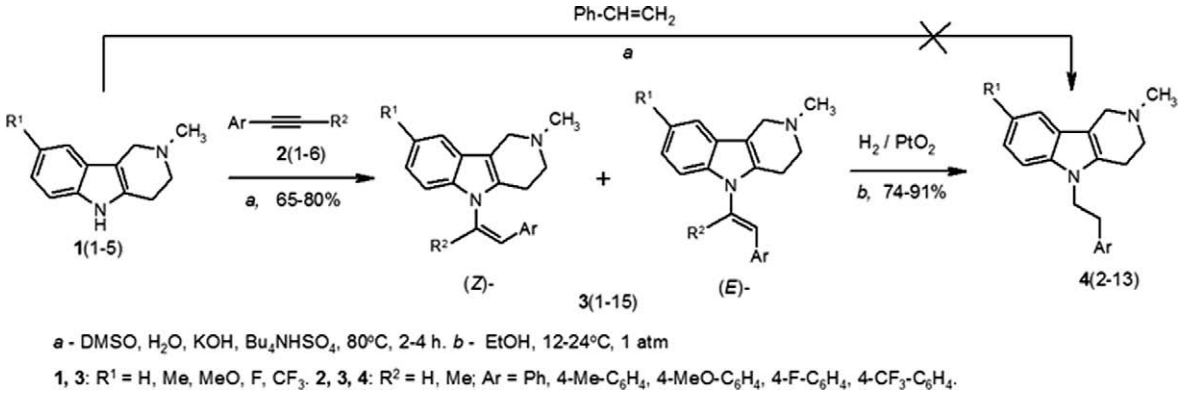

Scheme 1. Synthesis of compounds **3**(1–15) and **4**(2–13).

explained by weaker electrophilicity of the styrene double bond as compared to vinylpyridines. Therefore, desired 5-phenethyl-2,3,4,5-tetrahydro-1*H*-γ-carbolines **4**(2–13) were obtained by hydrogenation of 5-styrene-2,3,4,5-tetrahydro-1*H*-γ-carbolines **3**(2–13) in ethanol over PtO_2 with a 74–91% yield (Scheme 1).

The structures of compounds **3** and **4** were confirmed using LC–MS and ^{1}H NMR spectroscopy. Molecular mass of ions determined by LC–MS, as well as proton chemical shifts in ^{1}H NMR spectra, correspond to the expected molecules. In the ^{1}H NMR spectra of (*Z*)-isomers **3**(1–11), doublet proton signals of double bonds are present at 6.6–6.8 ppm with a coupling constant of 8.8 Hz. In the ^{1}H NMR spectra of (*E*)-isomers **3**(1,2,7), the doublet signals can be seen at 6.8–6.9 ppm with substantially higher coupling constant of 14.8 Hz. Such a difference in the constants is generally characteristic for *cis*- and *trans*-isomers. The structures of compounds **13**(14,15) were established based on Nuclear Overhouser Effect (NOE) NMR experiments. Two double-proton multiplets (AA'BB'-system) can be seen at 4.2–4.3 and 2.8–3.0 ppm in the **4**(2–11) salts spectra due to the presence of the aryl–ethyl group in position '5'.

5-HT_6 receptor antagonists have recently emerged as one of the highly promising approaches to treatment of CNS diseases.[8,9] In mammals, these receptors are exclusively localized in CNS and mainly in brain areas responsible for learning and memory.[10] It has also been shown that 5-HT_6 receptors are modulators of other neurotransmitter systems[11] including cholinergic, noradrenergic, glutaminergic, and dopaminergic systems, which play fundamental roles in cognitive processes and formation of normal and 'pathologic' memory. Taking into consideration that besides the histamine receptors, dimebolin exhibits a rather high affinity to 5-HT_6 receptors, we first studied 5-styryl- and 5-phenethyl-(compounds **3** and **4**, respectively) derivatives of the 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles for the ability to antagonize serotonin 5-HT_6 receptors (Table 1). The experiments were performed in a cell-based assay, where effects of the compounds were assessed by their ability to inhibit functional cellular responses to serotonin. Stimulation of the HEK-293 cells, expressing human recombinant 5-HT_6 receptor, with serotonin leads to increased intracellular levels of cAMP, as measured using cAMP-LANCE technology[12] (Perkin–Elmer).

As evident from the data in Table 1, the potency of the 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **3** and **4** profoundly depends on both the nature and stereochemistry of the substituents, with IC_{50} values varying from 0.087 μM ((*Z*)-**3**(2)) to 20.7 μM (**4**(10)). The most striking differences in 5-HT_6 receptor potency can be seen upon substitutions of compounds with the *Z* configuration. Transition from 8-unsubstituted styryl-derivatives (*Z*)-**3**(1), to corresponding 8-methyl (*Z*)-**3**(2), and 8-fluoro (*Z*)-**3**(7), derivatives led, respectively, to 66-fold and 6-fold increase in the antagonistic

Table 1
The ability of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **3**, **4** to block the activity of serotonin 5-HT_6 receptors in cell-based assays

Compounds	R^1	R^2	Ar (HetAr)	IC_{50} (μM)	
				Compd **3**	Compd **4**
Dimebolin	Me	H	2-Me–Py-5		1.16
(*Z*)-**3**(1)	H	H	Ph	5.73	
(*E*)-**3**(1)	H	H	Ph	2.58	
(*Z*)-**3**(2), **4**(2)	Me	H	Ph	0.087	0.158
(*E*)-**3**(2)	Me	H	Ph	1.68	
(*Z*)-**3**(3), **4**(3)	Me	H	4-Me–C_6H_4	0.91	0.276
(*Z*)-**3**(4), **4**(4)	Me	H	4-F–C_6H_4	0.18	0.977
(*Z*)-**3**(5), **4**(5)	Me	H	4-CF_3–C_6H_4	2.81	4.07
(*Z*)-**3**(6), **4**(6)	Me	H	4-MeO–C_6H_4	0.55	0.666
(*Z*)-**3**(7), **4**(7)	F	H	Ph	1.00	0.692
(*E*)-**3**(7)	F	H	Ph	1.75	
(*Z*)-**3**(8), **4**(8)	F	H	4-Me–C_6H_4	1.44	2.27
(*Z*)-**3**(9), **4**(9)	F	H	4-F–C_6H_4	2.95	1.13
(*Z*)-**3**(10), **4**(10)	F	H	4-CF_3–C_6H_4	5.58	20.7
(*Z*)-**3**(11), **4**(11)	F	H	4-MeO–C_6H_4	1.50	2.35
4(12)	CF_3	H	Ph		0.974
4(13)	MeO	H	Ph		1.05
(*Z*)-**3**(14)	Me	Me	Ph	1.98	
(*Z*)-**3**(15)	F	Me	Ph	3.72	

Each concentration curve was measured in duplicates (see Supplementary data for details).

potency. In corresponding *E*-isomers, substitution of hydrogen (*E*)-**3**(1) with either methyl-((*E*)-**3**(2)) or fluoro-((*E*)-**3**(7)) group did not produce substantial changes in their 5-HT_6 receptor antagonistic potencies.

Substitution of hydrogen in position R^2 of (*Z*)-**3**(2) and (*Z*)-**3**(7) with the methyl group leads to a 23-fold ((*Z*)-**3**(14)) and 4-fold ((*Z*)-**3**(15)) reduction in the compound potencies.

Substitution of the aryl fragment of the 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles profoundly affects their 5-HT_6 receptor antagonistic activity. Thus, in the series of 2,8-dimethyl-5-((*Z*)-styryl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles, (*Z*)-**3**(2–6), the IC_{50} values increase from 0.087 μM for (*Z*)-**3**(2) to 2.81 μM for (*Z*)-**3**(5) (32-fold maximal difference) with the potency rank order of the aryl substituents Ph (*Z*)-**3**(2) > 4-F–C_6H_4 (*Z*)-**3**(4) > 4-MeO–C_6H_4 (*Z*)-**3**(6) ⩾ 4-Me–C_6H_4 (*Z*)-**3**(3) > 4-CF_3–C_6H_4 (*Z*)-**3**(5). Interestingly, in the series of 2-methyl-8-fluoro-5-((*Z*)-styryl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles, (*Z*)-**3**(7–11), the aryl substitutions exhibit substantially lesser influence on the compound potencies (only sixfold difference between the IC_{50} values for the compounds with highest, (*Z*)-**3**(7), and lowest, (*Z*)-**3**(10), potency). The potency rank order is: Ph ⩾ 4-Me–C_6H_4 = 4-MeO–C_6H_4 > 4-F–C_6H_4 > 4-CF_3–C_6H_4. For this 8-fluoro series, (*Z*)-**3**(7–

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