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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.

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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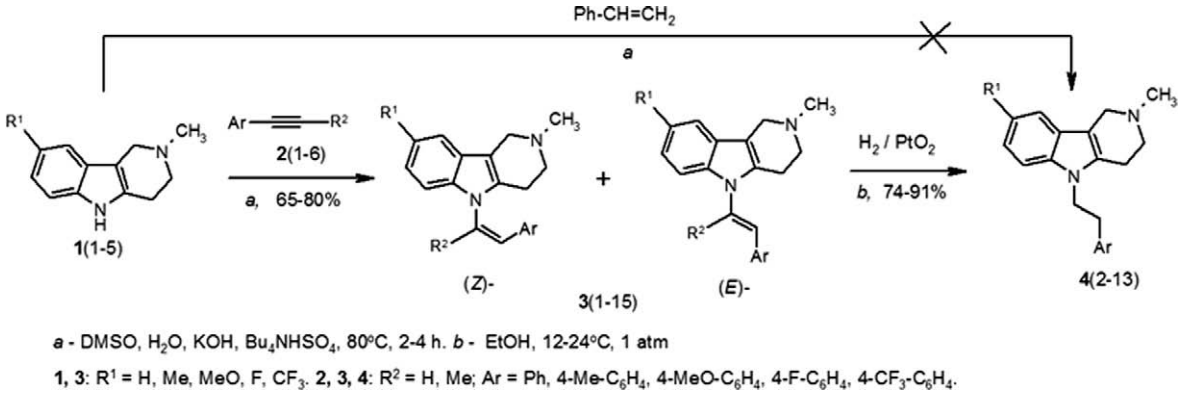

Scheme 1. Synthesis of compounds **3**(1–15) and **4**(2–13).

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–

11) in general is similar to that of the 8-methyl series (*Z*)-**3**(2–6), with the Ph-substituted compounds having highest and 4-CF_3–C_6H_4-substituted ones having lowest potencies.

Similar rank order trends in the aryl substituents' effect on the compound potencies as antagonists of 5-HT_6 receptors were found in the series of 8-methyl-substituted **4**(2–6) and 8-fluoro-substituted **4**(7–11) 5-phenethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles. Substitution of Me-Pyr in dimebolin with Me–C_6H_4 in **4**(3) or with F–C_6H_4 in (Z)-**3**(4) leads to 4–6-fold increase in the potency. Generally, the compounds with a phenyl moiety showed lowest IC_{50} and compounds with a 4-CF_3–C_6H_4 moiety—highest IC_{50} values. In all cases, the compounds with 4-Me–C_6H_4 and 4-MeO–C_6H_4 moieties were practically equipotent.

Considering the role of an 8-substituent in 5-phenethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles, we showed that the potency of the 8-methyl substituted compound **4**(2) (IC_{50} = 0.158 μM) is 4–7-fold reduced upon its substitution with either 8-F (**4**(7)), or 8-CF_3 (**4**(12)), or 8-MeO (**4**(13)).

The stereo orientation in the 5-styrene position plays a significant role in determining 5-HT_6 receptor antagonistic potency. For example, comparison of the most potent 5-HT_6 receptor antagonist 2,8-dimethyl-5-((*Z*)-styryl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole, (*Z*)-**3**(2), with its isomer, (*E*)-**3**(2), shows almost 20-fold decrease in the potency, and reduction of the styrene double bond in **4**(2) leads to further twofold reduction in the potency. However, change in the orientation of substituents around the styrene bond upon transition from the low potency compound (*Z*)-**3**(1) to its isomer (*E*)-**3**(1) is not accompanied by substantial changes in the potency.

Originally, dimebolin, (2,8-dimethyl-5-[2-(6-methylpyridin-3-yl)ethyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole dihydrochloride), was developed as an antihistamine drug,[2,3] therefore, it was prudent to test several of the synthesized analogs of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **3** and **4** for their ability to interact with histamine H_1 receptors. Kinetics of the calcium intracellular concentrations, $[Ca^{2+}]_i$, induced by histamine addition to the SK-N-SH cells endogenously expressing H_1 receptors, were measured using calcium-sensitive ratiometric fluorescent dye Fura-2[13] on a spectrofluorometer RF-5301PC. Effectiveness of the compounds was assessed by their ability to affect the calcium fluxes induced by histamine. Upon activation of the H_1 receptors with histamine, the $[Ca^{2+}]_i$ changes exhibit biphasic kinetics, fast $[Ca^{2+}]_i$ increase in Phase 1 and much slower reduction of $[Ca^{2+}]_i$ in Phase 2 (Fig. 1).

Phase 1 is caused by release of calcium ions from intracellular stores.[14] Phase 2 is a superposition of at least two counter-fluxes;[15] Ca^{2+} removal by Ca^{2+} pumps, and their entry from extracellular media. The Ca^{2+} fluxes in Phase 2 could also be controlled by the same receptor activation.[16,17] The synthesized compounds were tested in two experimental settings as exemplified in Figure 1 for (*Z*)-**3**(2). To assess their effect on the histamine-induced peak $[Ca^{2+}]_i$ values in Phase 1, the compounds were added to the cells 15–20 s before histamine (Fig. 1A). To assess the compound effect on a rate of $[Ca^{2+}]_i$ dissipation from the cytoplasm in Phase 2, the compounds were added 20–30 s after histamine (Fig. 1B).

The data are summarized in Table 2. It can be seen that the 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **3** and **4** are highly potent blockers of histamine-induced stimulation of the Phase 1 in Ca^{2+} mobilization from intracellular stores with IC_{50} values varying from 0.03 μM (**4**(4)) to 0.345 μM ((*E*)-**3**(1)). Potencies of the compounds to increase Ca^{2+} removal rate in Phase 2 were 2–5.5 times lower than potency in blocking Phase 1, and varied from 0.13 μM (**4**(7)) to 2.13 μM ((*E*)-**3**(1)) depending on the substituents.

Substitution of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole in the 8-position with methyl, (*Z*)-**3**(2), did not produce substantial increase in potency against H_1 receptor compared with non-substituted (*Z*)-**3**(1), in contrast to the effect of this substitution on 5-HT_6 receptors potency. However, changes in styrene configuration from (*Z*)-**3**(1) to (*E*)-**3**(1) led to a 10-fold reduction in the potency of the compound to block H_1 receptors. The nature of the aryl substituent also does not seem to have significant effect on H_1 receptor affinity in the series of **4**(2–6) and **4**(7–11).

Specificity profiles were determined for the most potent compounds, 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles (*Z*)-**3**(2), **4**(2),and **4**(3), using a panel of 31 therapeutic targets, including GPCRs, ion channels, and transporters, by their ability to displace radio-labeled ligands of these targets (Fig. 2 (data shown only for (*Z*)-**3**(2))).

The specificity profiles showed that the new 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **3** and **4** display a rather broad spectra of

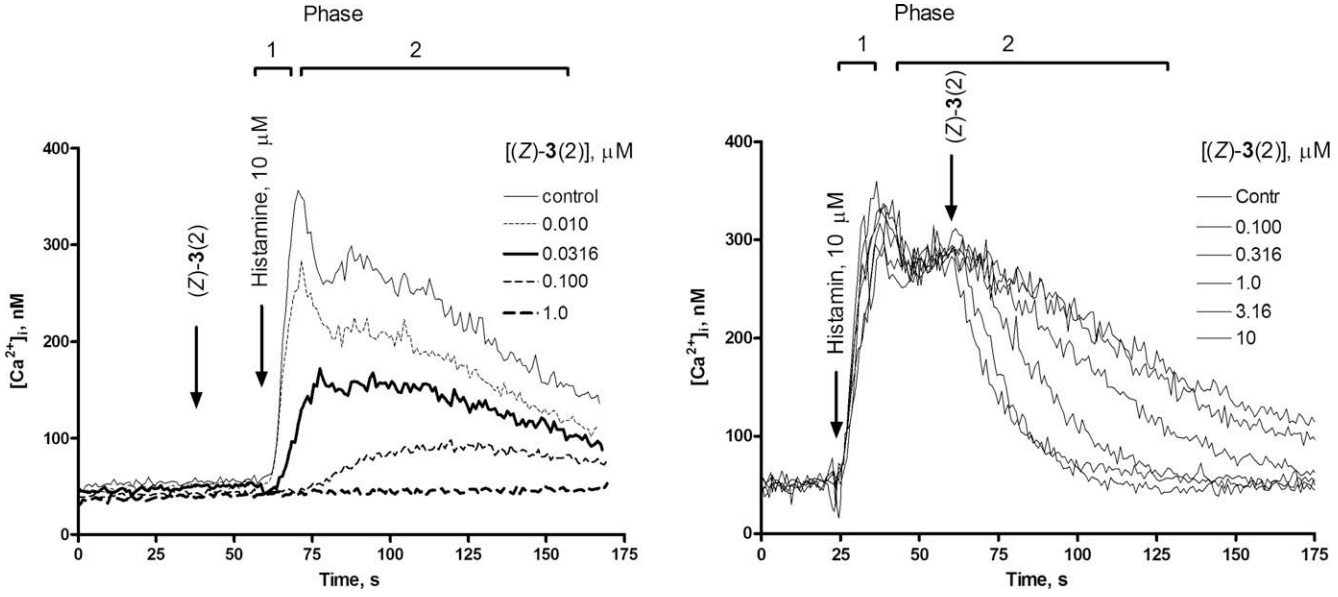

Figure 1. Effect of (*Z*)-**3**(2) on histamine-induced $[Ca^{2+}]_i$ temporal profile in SK-N-SH cells. (A) (*Z*)-**3**(2) was added 15 s before histamine. (B) (*Z*)-**3**(2) was added 30 s after histamine. Typical data is shown.

Table 2
The ability of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **3**, **4** to block the activity of histamine H_1 receptors in cell-based assays

Compds	R^1	R^2	Ar (HetAr)	IC_{50} (μM)			
				Compd **3**		Compd **4**	
				Phase 1	Phase 2	Phase 1	Phase 2
Dimebolin	Me	H	2-Me–Py-5			0.158	1.58
(*Z*)-**3**(1)	H	H	Ph	0.033	0.181		
(*E*)-**3**(1)	H	H	Ph	0.345	2.13		
(*Z*)-**3**(2), **4**(2)	Me	H	Ph	0.07	0.154	0.04	0.146
4(3)	Me	H	4-Me–C_6H_4			0.112	
4(4)	Me	H	4-F–C_6H_4			0.030	
4(5)	Me	H	4-CF_3–C_6H_4			0.098	
4(6)	Me	H	4-MeO–C_6H_4			0.066	
4(7)	F	H	Ph			0.04	0.131
4(8)	F	H	4-F–C_6H_4			0.031	
4(10)	F	H	4-CF_3–C_6H_4			0.035	
4(11)	F	H	4-MeO–C_6H_4			0.032	
4(12)	CF_3	H	Ph			0.068	
4(13)	MeO	H	Ph			0.104	

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

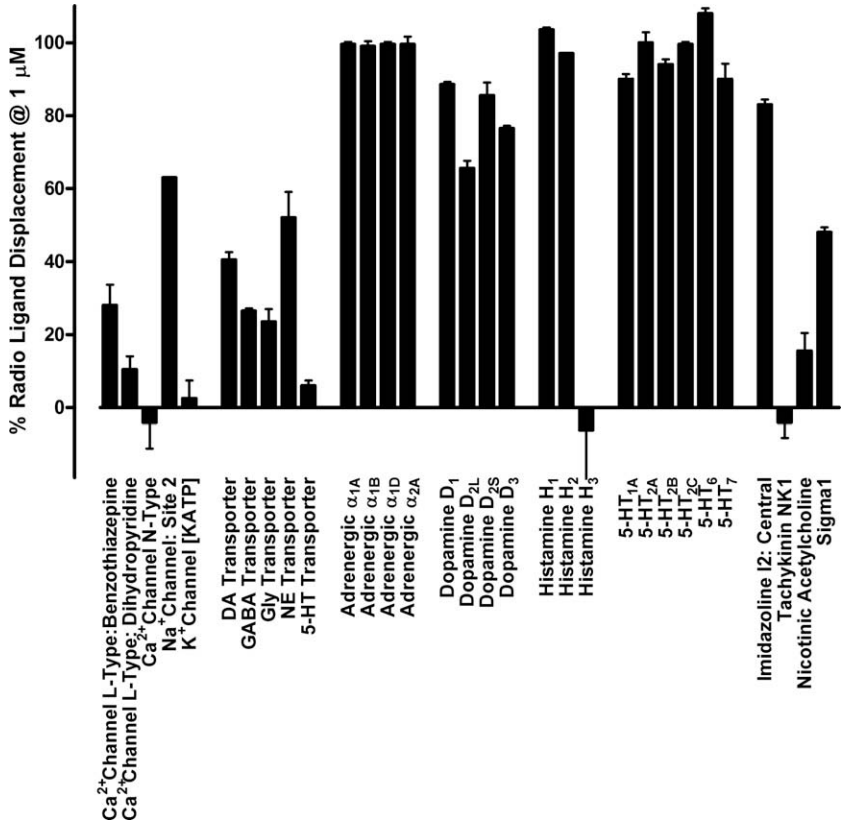

Figure 2. Target-specific profile determined for 2,8-dimethyl-5-((Z)-styryl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole, (*Z*)-**3**(2). Displacement of corresponding radio-labeled ligand was measured at the compound concentration of 1 μM. Shown is a typical experiment performed in duplicates, where the radio labeled ligand displacement values ± SD are presented.

potential pharmacological activities including adrenergic (α_{1A}, α_{1B}, α_{1D}, α_{2A}), dopaminergic (D_1, D_{2L}, D_{2S}, D_3), histaminergic (H_1 and H_2), serotonergic (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, 5-HT_7) as well as some other receptors and ion channel targets. The specificity profiles of these newly synthesized derivatives of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles are very similar to the dimebolin profile that we have previously published.[6]

Binding analysis of the tested compounds measured by concentration-dependent displacement of radio-labeled ligands (Table 3) showed that like dimebolin, *Z*-**3**(2), **4**(2), and **4**(3) exhibit highest affinity to 5-HT_7 and lowest one to dopamine D_{2S} receptors with some variability in potency rank orders for other receptors. The affinity rank orders are for dimebolin: 5-HT_7 > 5-HT_6 ⩾ adrenergic α_{1A} = 5-HT_{2A} = 5-HT_{2C} = adrenergic α_{2A} > dopamine D_{2S}; *Z*-**3**(2): 5-HT_7 = adrenergic α_{2A} ⩾ 5-HT_{2C} = 5-HT_6 ⩾ 5-HT_{2A} = adrenergic α_{1A} > dopamine D_{2S}; **4**(2): 5-HT_7 > 5-HT_{2C} = 5-HT_6 = 5-HT_{2A} = adrenergic α_{2A} > adrenergic α_{1A} > dopamine D_{2S}; and **4**(3): 5-HT_7 > adrenergic α_{2A} = 5-HT_{2A} = 5-HT_{2C} = 5-HT_6 > adrenergic α_{1A}.

The novel compounds demonstrate much higher affinity to all of the receptors studied, *Z*-**3**(2) having approximately two orders

Table 3
Affinity, pK_i, of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles, *Z*-**3**(2), **4**(2), and **4**(3), to selected GPCR receptors as measured by competition with radio-labeled ligands ($n = 2$)

Target	pK_i			
	Dimebolin	(*Z*)-**3**(2)	**4**(2)	**4**(3)
Adrenergic α_{1A}	7.22	8.85	7.72	8.15
Adrenergic α_{2A}	6.96	9.62	8.70	9.09
Dopamine D_{2S}	6.20	7.46	7.07	
Serotonin 5-HT_{2A}	7.21	9.00	8.70	8.96
Serotonin 5-HT_{2C}	7.12	9.32	8.92	8.80
Serotonin 5-HT_6	7.47	9.21	8.70	8.62
Serotonin 5-HT_7	8.10	9.68	9.60	9.41

of magnitude higher affinity to adrenergic α_{2A}, 5-HT_{2C}, 5-HT_{2A}, and 5-HT_6 than dimebolin.

The affinities of the three novel derivatives and Dimebon towards different receptors correlate very well. The Pearson correlation coefficients (r) between *Z*-**3**(2) and the other three compounds were better than 0.98 and regression coefficients were 2.357 ± 0.1987 for **4**(2), 33.33 ± 1.595 for **4**(3), and 16.60 ± 1.123 for dimebolin.

In summary, we have described syntheses and biological evaluations of novel small-molecule 5-styryl and 5-phenethyl-substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indoles, which possess activities to a broad spectrum of therapeutic targets characteristic for dimebolin but with substantially higher affinities. In general, steric orientation of 5-styryl substitution plays an important role in the affinity of the molecules to 5-HT_6 and H_1 receptors. The most promising molecule, 2,8-dimethyl-5-[(*Z*)-2-phenylvinyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole, has the highest affinity among other derivatives in a majority of the receptors.

Supplementary data

Supplementary data (description of compound syntheses and biological assay methods) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.11.037.

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