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Synthesis and biological evaluation of novel γ-carboline analogues of Dimebon as potent 5-HT$_6$ receptor antagonists

Alexandre V. Ivachtchenko [a,b,*], Eugene B. Frolov [b], Oleg D. Mitkin [b], Volodymyr M. Kysil [b], Alexander V. Khvat [b], Ilya M. Okun [b,c], Sergey E. Tkachenko [b,c]

[a] Department of Organic Chemistry, Chemical Diversity Research Institute, 114401 Khimki, Moscow Reg., Russia
[b] ChemDiv, Inc., 6605 Nancy Ridge Drive, San Diego, CA 92121, USA
[c] Department of Molecular Biology and High-Throughput Screening, Chemical Diversity Research Institute, 114401 Khimki, Moscow Reg., Russia

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ABSTRACT

Synthesis, biological evaluation and structure–activity relationships for a series of novel γ-carboline analogues of Dimebon™ are described. Among the studied compounds, γ-carbolines **3***{8}* and **3**{*14*} have been identified as potent small molecule antagonists of histamine H$_1$ (IC$_{50}$ = 0.1 μM) and serotonin 5-HT$_6$ (IC$_{50}$ = 0.37 μM) receptors, respectively.

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During the last 60 years γ-carbolines (2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles) have been attracting a huge interest from scientists due to a relatively broad spectrum of their biological activity.[1–6] In particular, they have rightly been described as promising antihistamine[1] and local anaesthetic agents[2] as well as serotonin release inhibitors.[3] They were also shown to have antidepressant[4] and antiinflammatory[1,5] activity. In addition, some compounds containing the title Core fragment were found to have enhanced neuroleptic activity.[6]

Among several different groups of γ-carboline derivatives Dimebon **I** (Fig. 1) (initially named—Dimebolin, 2,8-dimethyl-5-[2-(6-methylpyridin-3-yl)ethyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole dihydrochloride) originally synthesized in 1961 by Alexey N. Kost (Professor D. Sc.) and colleagues[7] is the most famous drug-compound within this group. It is being currently evaluated in advanced clinical trials as promising small molecule drug-candidate for the treatment of various neurodegenerative disorders,[8] including Alzheimer[9] and Huntington[10] diseases as well as different types of schizophrenia[11], etc.[12,13] In the cerebellum cell culture Dimebon protects neurons against the neurotoxic action of β-amyloids (EC$_{50}$ = 25 μM).[14] Since 1983, Dimebon has been using in Russia as promising antihistamine agent.[15] It was also shown that Dimebon effectively blocked the L-type calcium channel activity with an IC$_{50}$ of 57 μM.[16] Based on various in vivo studies, it can also be regarded as promising therapeutic agent effectively suppressed NMDA receptors (ED$_{50}$ = 42 mg/kg),[17] a weak cholinesterase inhibitor (IC$_{50}$ = 45 μM (AChE) and IC$_{50}$ = 7.9 μM (BuChE))[18] as well as an inhibitor of the mitochondrial permeability transition pores.[19]

Finally, a recent clinical study of Dimebon performed by Medivation has revealed a novel mechanism of action ascribed to this compound directly related to mitochondrial signaling route.[20] However, a clear understanding towards the common mechanism of its pharmacological action has not been achieved yet.

Recently, in 2008, we have convincingly shown that Dimebon has a much wider scope of prospective therapeutic applications. Currently, it can be reasonably regarded as promising drug-compound active against several types of Adrenoceptors (α_{1A}, α_{1B}, α_{1D}, α_{2A}), Dopamine (D1, D2L, D2S, D3), Histamine (H$_1$, H$_2$), Serotonin (5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$, 5-HT$_6$, 5-HT$_7$) receptors and other GPCR classes.[21] For example, as a therapeutic agent that inhibits histamine H$_1$ activity Dimebon has been widely used for the treatment of allergy for just more than 20 years. Therefore, due to the remarkably broad spectrum of physiological activity as well as a very complex mechanism of action, Dimebon can be profitably viewed as an excellent example of drug-compound within the specific group of 'magic shotguns'.[22] Among the activities just listed the antagonistic potency of Dimebone against serotonin 5-HT$_6$

* Corresponding author. Tel.: +1 858 794 4860; fax: +1 858 794 4931.
E-mail address: av@chemdiv.com (A.V. Ivachtchenko).

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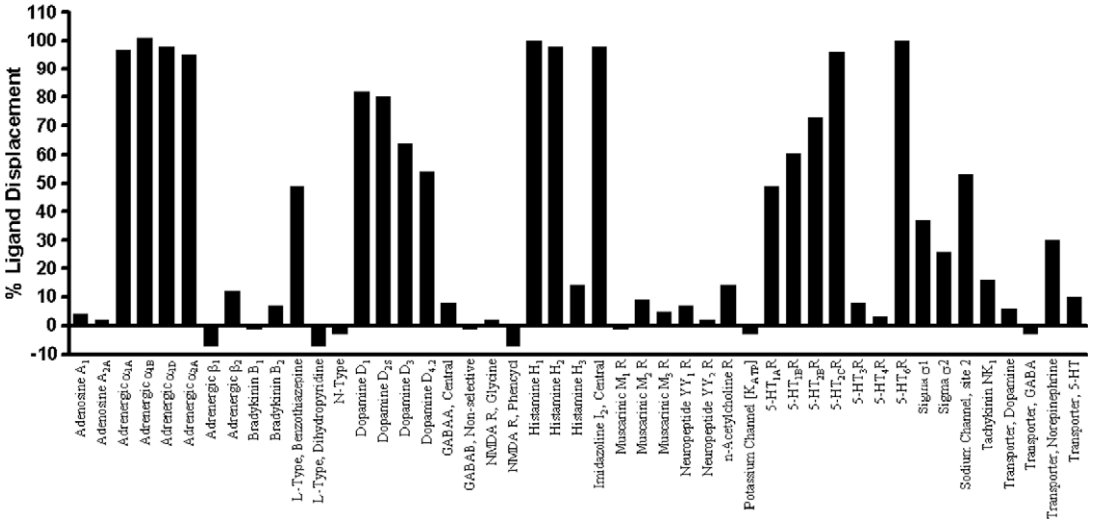
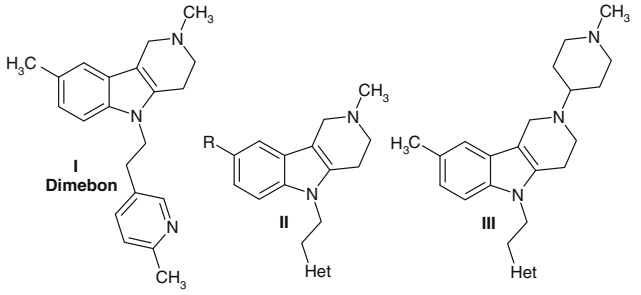


Figure 1. Target-specific profile determined for Dimebon **3**{*1*}.

receptors can be directly related to beneficial cognitive effects. It is well documented that in mammalians this type of serotonin receptors is thoroughly embedded in CNS and the related signaling cascades are deeply implicated in processes of information perception, learning and memory formation.[23] It has also been shown that serotonin 5-HT_6 receptors regulate several neurotransmitter pathways including cholinergic, noradrenergic, glutamatergic and dopaminergic systems.[24] Thus, taking into account both the fundamental role of this signal transduction system in regular cognitive processes as well as their dysfunction caused by neurodegenerative disorders, it is therefore becoming evidently clear that serotonin 5-HT_6 receptors represent extremely attractive target for the development of novel small molecule therapeutics for the treatment of various neurodegenerative disorders.[25]

In this Letter, we describe synthesis, biological evaluation and structure–activity relationships for a series of novel small molecule histamine H_1 and serotonin 5-HT_6 receptor antagonists having general formula **II** and **III**, which represent unique analogs of the 'template' molecule Dimebon **I**.

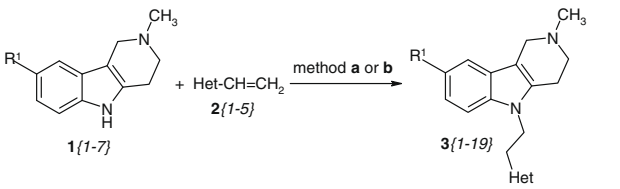


In turn, the overall aim of this work lies in comparative study of the synthesized analogs against serotonin 5-HT_6 and histamine H_1 receptors in vitro. In the initial stages of our work we have synthesized Dimebon **I** as well as its novel analogues which contain the core fragments **II** and **III**.

It was shown that in the presence of metallic sodium 5- and 8-unsubstituted 2-alkyl-γ-carbolines can be easily converted into the corresponding 5-substituted γ-carbolines by their reaction with 2- and 4-vinyl pyridines.[26] It should also be noted that the use of aprotic solvents, for example DMSO, in this reaction leads to increased activation of γ-carboline anions formed in the presence of sodium or sodium hydride that, in turns, results in their reaction with 3-vinyl pyridines becomes possible due to relatively weak polarization of the vinyl bond.[26] Thus, we have used this strategy for the preparation of both the known compounds **3**{*1,2,8,13*}.[27] as well as novel derivatives of Dimebon **3**{*3-9,9-12,14-19*} (Schemes 1 and 2, Table 1).

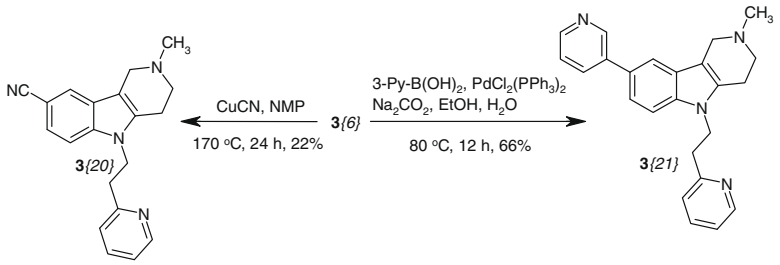
According to the approach depicted in Scheme 1, the target compounds **3**{*1-19*} can be readily obtained by two different ways. The first method (**a**) based on the reaction of the initial γ-carboline **1** with vinyl pyridine **2** in DMSO in the presence of Na/EtONa or NaH. The second one (method **b**) is the reaction between these reagents in the two-phase system— DMSO/KOH/$(Bu_4N)_2SO_4$. The reaction was performed successfully in accordance with the modified method described by Kost[26] there dry DMSO as well as catalyst—Na/NaH were jointly used to synthesize similar compounds. During the experimental procedure we have been observing that the alternative reaction has been proceeding much smoothly results in a fewer amount of side and oil products as well as much better yields. It should also be remarked that under the applied conditions the reaction with 4-vinyl pyridine **2**{*4*} has proceeded more readily (4–8 h, 40 °C) as compared to the reaction with 2-vinyl pyridine **2**{*1*} and it was far more tangible for 3-vinyl pyridines **2**{*2,3*}. Therefore, a complete conversion of the initial reactants was found to be most readily achieved only using more severe conditions (12–24 h, 80 °C).

2-Methyl-5-(2-pyridin-2-ylethyl)-8-cyano- **3**{*20*} and 2-methyl-8-pyridin-3-yl-5-(2-pyridin-2-ylethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole **3**{*21*} were obtained in 22% and 66% yield, respectively, from the corresponding 8-bromo-γ-carboline **3**{*6*} which



1{*1-7*}: R¹ = H {*1*}, Me {*2*}, F {*3*}, Br {*4*}, CF_3 {*5*}, CO_2H {*6*}, MeO {*7*}
2{*1-5*}: Het = 2-Py {*1*}, 3-Py {*2*}, 6-Me-3-Py {*3*}, 4-Py {*4*}, pyrazin-2-yl {*5*}

Scheme 1.



Scheme 2.

Table 1
The ability of γ-carbolines **3**{*1-24*} to block the activity of histamine H_1 and 5-HT_6 receptors in cell-based assays

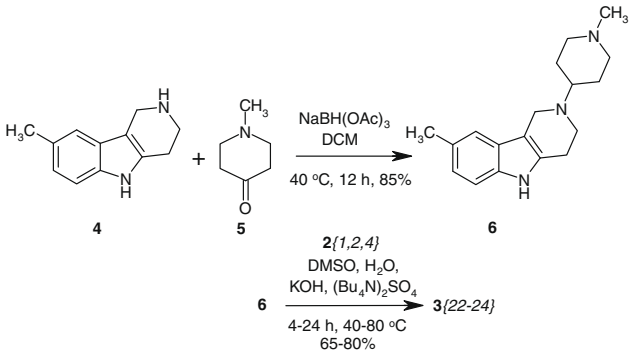
Compounds				Receptors		
				IC_{50} (μM)		
No.	Het	R^1	R^2	Histamine H_1		5-HT_6
				Phase-1	Phase-2	
3{*1*}	6-Me-Py-3	Me	Me	0.16	1.58	0.89
3{*2*}	2-Py	H	Me	1.82	0.93	15.75
3{*3*}	2-Py	Me	Me	0.50	10.0	0.86
3{*4*}	2-Py	MeO	Me	4.67	nd*	8.36
3{*5*}	2-Py	F	Me	0.94	0.61	2.98
3{*6*}	2-Py	Br	Me	0.12	nd	1.04
3{*7*}	2-Py	CF_3	Me	0.56	1.59	1.59
3{*8*}	3-Py	H	Me	0.10	0.41	5.99
3{*9*}	3-Py	Me	Me	0.50	3.16	0.44
3{*10*}	3-Py	F	Me	0.65	0.93	>10
3{*11*}	3-Py	CF_3	Me	>10	Nd	5.80
3{*12*}	6-Me-Py-3	F	Me	0.11	0.73	10.69
3{*13*}	4-Py	H	Me	0.12	0.50	8.91
3{*14*}	4-Py	Me	Me	0.16	3.98	0.37
3{*15*}	4-Py	MeO	Me	0.39	nd	4.34
3{*16*}	4-Py	F	Me	0.12	0.47	3.24
3{*17*}	4-Py	CF_3	Me	0.22	nd	6.40
3{*18*}	4-Py	CO_2H	Me	>10	nd	>10
3{*19*}	Pyrazin-2-yl	Me	Me	0.32	7.94	2.06
3{*20*}	2-Py	CN	Me	1.29	nd	7.47
3{*21*}	2-Py	3-Py	Me	7.16	nd	43.20
3{*22*}	2-Py	Me	*N*-Me-piperidin-4-yl	>10	nd	Inactive
3{*23*}	3-Py	Me	*N*-Me-piperidin-4-yl	2.79	nd	Inactive
3{*24*}	4-Py	Me	*N*-Me-piperidin-4-yl	7.57	nd	Inactive

* nd—'Not detected'.

have previously been prepared (Scheme 2). Thus, the reaction of compound **3**{*6*} with CuCN in *N*-methylpyrrolidone (NMP) at 170 °C for 24 h led to the first compound **3**{*20*}, while the reaction between **3**{*6*} and 3-pyridylboronic acid in aq. EtOH at 80 °C for 12 h yielded the second one in the presence of Pd-based catalyst.

N-Methyl 4-[8-methyl-5-(2-pyridine-ethyl)-1,3,4,5-tetrahydro-2*H*-pyrido[4,3-*b*]indol-2-yl]piperidines **3**{*22-24*} were obtained by the reaction between *N*-methylpiperidin-4-one **5** and γ-carboline **4** followed by *N*-arylation of the obtained intermediate **6** with various vinyl pyridines **2**{*1,2,4*} (Scheme 3). Thus, the initial components **4** and **5** have reacted in DCM at 40 °C also in the presence of sodium triacetoxyborohydride. Twenty hours later reductive amination has led to the formation of the intermediate product **6** (yield 85%). The latter was then easily converted into the target compounds **3**{*22-24*} by the reaction with vinyl pyridines **2**{*1,2,4*} in aq DMSO in the presence of NaOH/$(Bu_4N)_2SO_4$. The reaction had been progressively proceeding at 40 °C for 12 h, and the final products were formed in high yields (65–80%).

All the synthesized compounds were sufficiently characterized by ^{1}H NMR, LCMS and HR-MS spectral data. Satisfactory analytical data consistent with the shown molecular structures were obtained for all compounds (see Supplementary data).



Scheme 3.

All the synthesized γ-carbolines **3**{*1-24*} have then been tested on their ability to block Ca-dependent signaling cascades induced by histamine H_1 receptors in SK-N-SH cells. The inner concentration of unbound Ca^{2+} was measured using Ca-sensitive dye—Fura-2.[28] After activation of the histamine H_1 receptors a dramatic increase in [Ca^{2+}] along the kinetic curve exhibiting changes in Ca^{2+} concentration in the cell cytoplasm was observed (phase-I) followed by a

gradual decrease (phase-II). During phase-I, the release of Ca^{2+} ions from intracellular stores[29] was registered, whereas phase-II was accompanied by two oppositely directed processes: extruding Ca^{2+} from the cytoplasm and their penetration into neurons from the cytoplasm through the store-dependent calcium channels.[30]

To estimate the effects of the synthesized γ-carbolines towards calcium flows maintained by histamine H_1 receptors corresponding experiments were performed in two different ways: (a) the tested compounds were added to a mixture to be analyzed previous to histamine treatment, then the intensity of phase-I has been cautiously estimated; (b) compounds were added to a mixture immediately after histamine treatment, then the velocity of cytosolic calcium ion concentration falling in phase-II was determined. The obtained data that reflects the observed activity of compounds which have been tested during experimental procedures, exhibited in IC_{50} values, is thoroughly summarized in Table 1.

As clearly shown in Table 1, modifications in the structures of the obtained γ-carbolines **3**{*1-24*} lead to significant differences in their ability to block the histamine-induced calcium flows in phase-I. In particular, the most active compounds **3**{*1,6,10,12-14,16,17*} have IC_{50} values of 100–200 nm, whereas compounds **3**{*2,4,11,18,20-24*} have been found to have much weaker activity ranged around 1.29 μM and IC_{50} > 10.0 μM. Compounds **3**{*3,5,7,9, 10,15,19*} were found to exhibit moderate activity.

It should be noted that within each group of compounds, 5-(2-pyridine-2-ylethyl)- **3**{*2-9*}, 5-(2-pyridine-3-ylethyl)- **3**{*1,8-12*} as well as 5-(2-pyridine-4-ylethyl)-γ-carbolines **3**{*13-18*} the observed activities are dramatically different by one or two orders of magnitude. The top activity was assigned for 8-unsubstituted derivatives **3**{*8,13*} as well as for 8-bromo- **3**{*6*}, 8-fluoro- **3**{*12,16*}, 8-methyl- **2**{*1,14*} as well as 8-trifluoromethyl- **3**{*17*} γ-carbolines (see Table 1). The corresponding values of IC_{50} are dispersed exponentially from 0.1 μM (for compound **3**{*8*}) up to 0.225 μM (for compound **3**{*17*}). The minimum activity was observed for 8-pyridine-3-yl- **3**{*9*} (IC_{50} = 7.16 μM), 8-trifluoromethyl- **3**{*11*} (IC_{50} > 10 μM) and 8-carboxy- **3**{*18*} (IC_{50} > 10 μM) γ-carbolines. It was found that within each group of the tested compounds the activity correlates with the nature of the substituent in position 8(C) of γ-carboline, but differently. Thus, within the group of 5-(2-pyridine-2-ylethyl)-γ-carbolines **3**{*2-9*} the highest inhibitory activity was observed for 8-bromo-γ-carboline **3**{*6*} (IC_{50} = 0.12 μM). Within the 5-(1-pyridine-3-ylethyl)- **3**{*1,8-12*} and 5-(1-pyridine-4-ylethyl)- **3**{*13-18*} γ-carboline series the highest activity was determined for 8-methyl- **3**{*1,14*}, 8-fluoro- **3**{*12,16*} and 8-unsubstituted γ-carbolines **3**{*8,13*}; the corresponding IC_{50} values were in the range of 0.10–0.16 μM. In turn, 8-unsubstituted γ-carbolines **3**{*2,3,5*} in the line of 5-(2-pyridine-4-ylethyl)-γ-carbolines **3**{*2-9*} were found to be significantly less active (IC_{50} = 1.82 μM, IC_{50} = 0.5 μM and 0.94 μM, respectively) than analogues **3**{*1,8,12-14,16*} described just above.

An interesting correlation across these three series has been observed in the case of 8-fluoromethyl-γ-carbolines **3**{*7,11,17*}. Thus, particularly amongst two groups of γ-carbolines which contain 5-(2-pyridine-2-ylethyl)- or 5-(2-pyridine-4-ylethyl)-fragment compounds **3**{*7,17*} have high values of activity (IC_{50} = 0.56 μM and IC_{50} = 0.22 μM, respectively), whereas within the 5-(2-pyridine-3-ylethyl)-γ-carboline series compound **3**{*11*} has relatively poor activity (IC_{50} > 10 μM).

The activity of 2,8-dimethyl-5-(2-pyrazine-2-ylethyl)-γ-carboline **3**{*19*} (IC_{50} = 0.32 μM) is strikingly similar to that observed for 5-(2-pyridine-ethyl)-containing analogues **3**{*3*} (IC_{50} = 0.5 μM), **3**{*9*} (IC_{50} = 0.5 μM) and **3**{*14*} (IC_{50} = 0.16 μM). And finally, among the series of 2-(1-methylpiperidine-4-yl)-γ-carbolines **3**{*22-24*} the most active compound was 5-(2-pyridine-3-ylethyl)-γ-carboline **3**{*23*} (IC_{50} = 2.79 μM), whereas 5-(2-pyridine-2-ylethyl)-γ-carboline **3**{*22*} was revealed to be relatively inactive.

The ability of γ-carboline derivatives to accelerate the decrease in intracellular Ca^{2+} rate after stimulation of the histamine H_1 receptors by histamine (Table 1, Phase-2) varied in the range of 0.41 μM to >10 μM and depended crucially on the nature of substituents used. In most cases their activity is 1.5–25 times lower as compared to the suppression of histamine H_1 receptors during Phase-I. One exception is 5-(2-pyridine-2-ylethyl)-γ-carbolines **3**{*2,5*}; their inhibitory potency against histamine H_1 receptors is, in turn, 1.5–2 times lower than required for the acceleration of Ca release from the cytoplasm.

To investigate the antagonistic potential of the synthesized Dimebon analogues **3**{*1-24*} towards 5-HT_6 receptors we have studied their inhibitory potency in HEK293 cells stimulated by serotonin. Under normal conditions, these cells continuously produce recombinant human serotonin 5-HT_6 receptors. Serotonin-dependent stimulation of these receptors led to enhanced production of intracellular cyclic AMP which, in turns, was used as a control indicator. Its level has been continuously monitored using LANCE technology.[31]

As shown in Table 1, the antagonistic activity of γ-carbolines **3**{*1-24*} highly depends on the nature of side substituents. The IC_{50} value was found to be very spread along the range of 0.37 μM (compound **3**{*14*}) to absolutely inactive compounds **3**{*22-24*}. Within the group of 5-(2-pyridine-2-yl)-γ-carbolines **3**{*2-9*} the most active compound was 2,8-dimethyl-γ-carboline **3**{*3*} (IC_{50} = 0.86 μM); its activity was remarkably close to that observed in a similar assay performed for Dimebon (IC_{50} = 0.89 μM). A slightly lower inhibitory potency, as compared to 8-methyl-γ-carboline **3**{*3*}, was detected for 8-bromo- **3**{*6*}, 8-trifluoromethyl- **3**{*7*} and 8-fluoro- **3**{*5*} γ-carbolines (IC_{50} = 1.04 μM, 1.59 μM and 2.98 μM, respectively). Among the compounds described a relatively poor activity was observed for 8-unsubstituted analogues, including compound **3**{*2*}, 8-methoxy- **3**{*4*}, 8-cyano- **3**{*8*} and 8-pyridine-3-yl- **3**{*9*} γ-carbolines (IC_{50} = >10 μM, 8.365 μM, 7.467 μM and >10 μM, respectively).

An analogous relationship between the antagonistic activity and nature of substituent in position 8(C) was observed for γ-carbolines **3**{*8-12*} and **3**{*13-18*}. Among these compounds 2,8-dimethyl-substituted γ-carbolines **3**{*9,14*} were the most active agents (IC_{50} = 0.44 μM and 0.37 μM, respectively). It should also be noted that the replacement of 5-pyridinyl-ethyl substituents by 5-pyrazinyl-ethyl analogues led to a significant decrease in their antagonistic potential. Thus, 2,8-dimethyl-5-(2-pyrazine-2-yl-methyl)-γ-carboline **3**{*19*} (IC_{50} = 2.06 μM) is 2.5–6 times less active as compared to 2,8-dimethyl-5-(2-pyridine-ylmethyl)-γ-carbolines **3**{*1,3,9,14*}.

In this work we have also estimated a target-specific profile of the synthesized compounds towards various receptors. The corresponding activity was determined by measuring the amount of radiolabeled ligands displaced by the testing γ-carbolines which was used in a concentration of 10 μM. A comparative study across the data obtained has revealed a distinctive relationship between 'fingerprint' spectra and pharmacological activity of the compounds which have been tested in cell-based assays. This observation can be neatly illustrated by the example of the Dimebon (Fig. 1) and γ-carboline dihydrochloride **3**{*3*} profiles (Fig. 2).

In summary, here we have described synthesis and activity of novel small-molecule analogues of Dimebon™. In particular, it was found that inhibitory activity of the synthesized γ-carbolines towards histamine H_1 and serotonin 5-HT_6 receptors is highly dependent on the substitutions on the core scaffold, radically at the 2-, 5- and 8-position. Thus, the compounds contained H, F, Br, CH_3 and CF_3 substituents in position 8(C) as well as 2-pyridine-3(4)-ylethyl fragments in position 5(*N*) have shown potent antagonistic activity against histamine H_1 receptors, whereas only 8-methyl-substituted derivatives were found to have promising

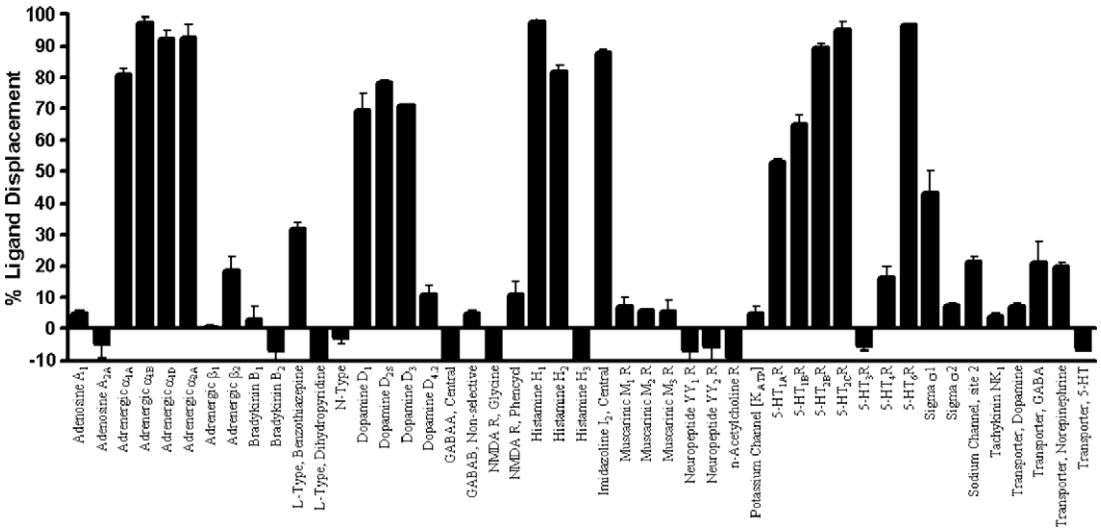


Figure 2. Target-specific profile determined for γ-carboline dihydrochloride **3**{*3*}. This compound was used in a concentration of 10 μM.

pharmacological potential towards serotonin 5-HT_6 receptors. It is also quite interesting that the introduction of other substituents in position 8(C) has led to a significant loss in activity. In turn, the nature of heterocyclic fragment anchored in position 5(*N*) of the γ-carboline scaffold has no significant impact on the activity of the tested compounds against 5-HT_6 receptors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.04.128.

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