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Synthesis and characterization of 1,3-dihydro-benzo[*b*][1,4]diazepin-2-one derivatives: Part 4. In vivo active potent and selective non-competitive metabotropic glutamate receptor 2/3 antagonists

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ABSTRACT

This study completes a series of papers devoted to the characterization of the non-competitive mGluR2/3 antagonist properties of 1,3-dihydro-benzo[*b*][1,4]diazepin-2-one derivatives with particular emphasis on derivatizations compatible with brain penetration and in vivo activity. Especially the compounds bearing a *para*-pyridine consistently showed in vivo activity in rat behavioral models after oral administration, for example, blockade of the mGluR2/3 agonist LY354740-induced hypoactivity and improvement of a working memory deficit induced either by LY354740 or scopolamine in the delayed match to position task (DMTP). Moreover, combination studies with a cholinesterase inhibitor show apparent synergistic effects on working memory impairment induced by scopolamine.

The eight subtypes of the metabotropic glutamate receptor family are classified into three groups according to their sequence homology, pharmacology and second messenger coupling.[1] While group I receptors (mGluR1 and 5) are positively coupled to phospholipase C, group II (mGluR2 and 3) and group III (mGluR4, 6, 7 and 8) receptors are negatively coupled to the activity of adenyl cyclase(s). Selective ligands for the different mGluRs are currently in development for different indications. The therapeutic potential of mGluR2/3 antagonists as antidepressants and cognitive enhancers has been related in particular to the neurogenetic properties of these compounds, to the control on glutamatergic function in cortical and hippocampal regions and to the modulation of cholinergic and monoaminergic systems, respectively.[2–4]

We previously reported on the discovery of the random screening hit **1** (Fig. 1), its characterization as a non-competitive antagonist at both recombinant mGluR2/3 and native mGluR2 (reversal of LY354740-mediated inhibition of fEPSPs in the rat dentate gyrus) and the lead optimization program to obtain compounds like **4**. They are orally active, brain penetrating and also exhibit in vivo activity demonstrated by the dose-dependent blockade of the LY354740-induced hypolocomotion in mice.[5]

This Letter summarizes the results obtained when replacing the 1-imidazolyl and 1,2,3-triazolyl moieties in the 3′-position with other heterocycles as well as further efforts to optimize physicochemical properties to obtain drug-like derivatives. The regioselective synthesis of unsymmetrically 7,8-substituted 1,3-dihydro-benzo[*b*][1,4]diazepin-2-ones was readily achieved by simple condensation of mono Boc protected 1,2-phenylenediamines **5** and *tert*-butyl β-ketoesters **6** in refluxing toluene leading to the intermediate β-ketoamides and treatment with TFA effected deprotection as well as concomitant cyclization yielding the desired 1,3-dihydro-benzo[*b*][1,4]diazepin-2-ones **7** (Scheme 1).[6,7,12]

As previously described the pharmacological properties of these compounds were consistent with a mechanism of non-competitive antagonism at both mGluR2 and mGluR3[5,6] demonstrated by partial inhibition of the binding of the selective agonist [^{3}H]-LY354740 to rat mGluR2, full blockade of the effect of LY354740, (1*S*,3*R*)-ACPD and L-glutamate in both GTPγ35S and cAMP assays and concentration-dependent inhibition of the glutamate-induced GIRK

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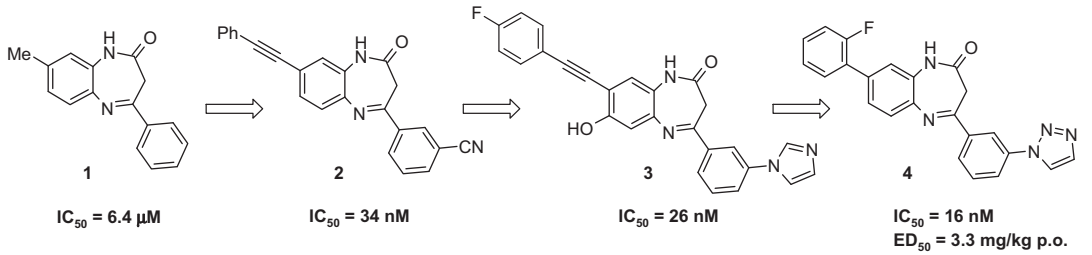
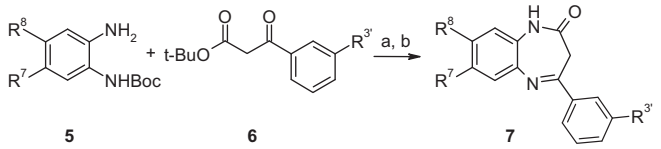


Figure 1. Development of the random screening hit **1** into compounds, like, for example, **2**, **3** and **4**, with low nanomolar IC_{50} values in binding inhibition studies carried out with the mGluR2/3 agonist [^{3}H]-LY354740 in membranes expressing recombinant rat mGluR2. The last step represented by **4** led to in vivo activity in mice behavioral models (ED_{50} blockade of LY354740-induced hypolocomotion).[5]



Scheme 1. Regioselective synthesis of unsymmetrically 7,8-substituted 1,3-dihydro-benzo[*b*][1,4]diazepin-2-ones **7**. Reagents and conditions: (a) toluene, reflux; (b) TFA [optional anisole], DCM, rt.

currents. Table 1 contains IC_{50} values calculated for each compound in affinity studies (partial displacement of 10 nM [^{3}H]-LY354740, recombinant rat mGluR2) and cell based assays: concentration-dependent antagonism of the effect of the mGluR2/3 agonist (1*S*,3*R*)-ACPD (10 μM-EC_{90}) on intracellular cAMP levels in cells permanently expressing recombinant rat mGluR2 (cells stimulated with Forskolin 10 μM).[5]

In our efforts to develop more drug-like mGluR2/3 antagonists we sought to further reduce their lipophilicity (**2**: *c* log *P* 4.86; calculated $\log(c_{octanol}/c_{water})$; **3**: *c* log *P* 4.85; **4**: *c* log *P* 4.82).[8] With regard to the left part of compounds **7** the best compromise between lipophilicity and activity has been found by combination of a trifluoromethyl group in 8-position and a simple methyl group in 7-position (Table 1). Our main focus in this study was the search for the optimal heterocycle in the 3′-position. While the 1-imidazole or the 1,2,3-triazole group produced highly potent compounds (**7a**, **7b**), they either suffered from strong cytochrome P450 3A4 isoenzyme inhibition (**7a**: IC_{50} <0.1 μM) or lack of in vivo activity (**7b**). The in-depth evaluation of a series of five-membered heterocycles (e.g., **7a**–**g**) revealed that very potent compounds could be obtained, but only at the expense of high lipophilicity, as shown for the isoxazole **7c** (*c* log *P* 5.00). The more polar isomeric 1,2,4-triazole **7d** (*c* log *P* 3.69) lost its activity in the cAMP assay, while oxazole **7e** and pyrazole **7f** were overall far less potent.

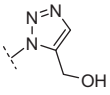
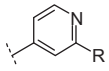
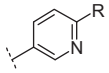
Incorporation of six-membered heterocycles, especially the *m*- and *p*-pyridine (**7h**, **7z**) led also to very active compounds, whereas *o*-pyridines (**7y**) as well as pyridazines (**7ah**, **7ai**), pyrimidines (**7aj**, **7ak**) or pyrazines (**7al**) were all less effective. In order to avoid the drug–drug interaction (DDI) potential shielding of the *p*-pyridine nitrogen by *ortho*-substitution was necessary to block its ability of binding to CYP450 3A4 isoenzyme (**7h**: IC_{50} ~0.2 μM; **7z**: IC_{50} 1.8 μM). Electron deficient substituents, like cyano or trifluoromethyl (**7k**, **l**), resulted in less active compounds. Most effectively and without significant increase of lipophilicity proved to be a simple 2-methyl group or a 2,6-dimethyl substitution (CYP450 3A4 IC_{50} 1.9 μM (**7i**), 4.8 μM (**7am**)). As a benefit the concomitant increase of basicity (**7h**: pK_a 5.4; **7i**: pK_a 5.9; **7am**: pK_a 6.2), enhanced the solubility (thermodynamic solubility at pH 3: **7h** ~5 mg/L; **7i** 45 mg/L; **7am** 64 mg/L) and led to overall improvement of physico-chemical properties. It is noteworthy, that all relevant compounds of this structural class, including **7i** and **7am**, showed medium to high permeability in the parallel artificial membrane permeability assay (PAMPA). Unfortunately the addition of small alkyl substituents on the *m*-pyridine did not result in such preferred profile for compounds (**7aa**–**ad**), therefore making this subseries finally less attractive. Neither the incorporation of hydroxylated residues (**7g**, **7r**, **7u** and **7ap**) nor attachment of remotely (**7u**) or directly joined basic moieties (**7w**, **7x**, **7af** and **7ag**) to the 5- or 6-membered heterocycles resulted in improved compounds. In summary, we were only able to identify highly potent moieties in combination with quite high lipophilicity. Nevertheless we could keep the ligand-lipophilicity efficiency LLE (LLE = p(IC_{50}) − *c*log*P*)[9] of the also functionally most active compounds almost constant (**7i**: LLE 2.87; **7am**: LLE 2.67) (Table 1).

The antagonistic effect of potent group II mGluR antagonists (representative compounds listed in Table 2) has been also characterized on Glutamate-stimulated G protein-coupled inwardly rectifying potassium channel (GIRK) currents for rat and human mGluR2 and rat mGluR3, respectively. There is no clear discrimination capacity between mGlu2 and mGlu3 for any of the listed antagonists. Interestingly **7am** (RO4491533) exhibits a very slow on-rate probably due to a very high affinity for the allosteric site of the mGlu2 receptor (Fig. 2).

Despite their high lipophilicity but due to their good permeability (BCS class II) the most interesting compounds **7i** and **7am** (**7i**: *c* log *P* 5.53; **7am**: *c* log *P* 6.03) were quite suitable for in vivo evaluation, since they revealed low clearance in rat liver microsomes (**7i**: 0.8 mL/min/kg, MAB 98%; **7am**: 4.7 mL/min/kg, MAB 88%). The rat pharmacokinetic profile of **7am** has been determined after 2.5 mg/kg iv administration ($n = 2$ rats) and showed a long terminal half life ($T_{1/2}$ 12.8 ± 1.2 h), high volume of distribution (V_{ss} 5.8 ± 0.2 L/kg) and low clearance (CL 5.7 ± 0.4 mL/min/kg). The bioavailability (F 52 ± 15%) was acceptable after oral administration (10 mg/kg po, $n = 2$ rats).[10] The observed brain/plasma ratio was 1.4. The selectivity for mGluR2/3 of the series of compounds **7** versus other metabotropic and ionotropic Glutamate receptors (e.g., NMDAR, AMPAR and mGluR4/5/8) as well as the specificity versus other receptors (e.g., GABARs, Adenosine A1R and Orphanin R) was tested in vitro using recombinant systems and in all cases no effect could be demonstrated at a concentration <1 μM.

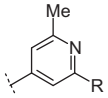
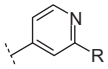
Compound **7am**'s in vivo antagonistic properties after administration per os by gavage in rats were shown (Fig. 3) to be consistent with the in vivo exposure and the brain penetration data. The mGluR2/3 agonist LY354740 produces a dose-dependent decrease of horizontal activity after subcutaneous administration (10 mg/kg, 30 min prior to testing) in rats. The experimental conditions of this test have been previously validated for the contribution of mGluR2 using mGluR2 null mutant mice.[3,11] The po administration of **7am** 180 min prior to the mGluR2/3 agonist (10 mg/kg s.c.) was able to significantly block the hypoactivity caused by the administration of LY354740. It should be noted that **7am** did not cause a significant increase in locomotor activity when administered alone. The

Table 1
Structure–activity relationship data related to the new 1,3-dihydro-benzo[*b*][1,4]diazepin-2-ones **7** described in this study

Compound	$R^{3'}$		R^8	R^7	*c* log *P*	Rat mGluR2 [^{3}H]-LY354740 binding[a] IC_{50} (μM)	Rat mGluR2 (1*S*,3*R*)-ACPD inhibition of Forskolin stimulated cAMP[b] IC_{50} (μM)	LLE = p(IC_{50} of [^{3}H]-LY354740 binding)—*c* log *P*
1	CN		Me	H	3.29	6400	nt	−1.10
2	CN		Ph-C≡C–	H	4.86	0.034	0.017	2.61
3			4-F–C_6H_4–C≡C–	HO	4.85	0.026	0.011	2.74
4			2-F–C_6H_4–	H	4.82	0.012	0.027	3.1
7a			F_3C–	Me	4.57	0.012	0.019	3.35
7b			F_3C–	Me	4.36	0.009	0.039	3.69
7c			F_3C–	Me	5	0.005	0.009	3.3
7d			F_3C–	Me	3.69	0.008	0.075	4.41
7e			F_3C–	H	4.19	0.35	nt	2.27
7f			F_3C–	H	4.36	0.039	0.19	3.05
7g			F_3C–	Me	3.33	0.12	nt	3.59
7h		R= H	F_3C–	Me	5.03	0.004	0.011	3.37
7i		Me	F_3C–	Me	5.53	0.004	0.004	2.87
7j		Et	F_3C–	Me	6.06	0.008	0.005	2.04
7k		CN	F_3C–	Me	4.85	0.012	0.018	3.07
7l		CF_3	F_3C–	Me	6.05	0.066	nt	1.13
7m		*c*-Propyl	F_3C–	Me	5.97	0.01	0.006	2.03
7n		*i*-Propyl	F_3C–	Me	6.46	0.004	0.01	1.94
7o		*c*-Pentyl	F_3C–	Me	7.09	0.01	0.007	0.91
7p		Ph	F_3C–	Me	7.13	0.118	nt	−0.20
7q		CH_2Ph	F_3C–	Me	7.1	0.016	0.005	0.7
7r		CH_2OH	F_3C–	Me	4.44	0.013	0.018	3.45
7s		CH_2OMe	F_3C–	Me	4.83	0.013	0.006	3.06
7t		CMe_2OH	F_3C–	Me	4.7	0.04	0.014	2.7
7u		CH_2NMe_2	F_3C–	Me	4.86	0.274	nt	1.7
7v		OMe	F_3C–	Me	5.84	0.013	0.016	2.05
7w		1-Pyrrolidinyl	F_3C–	Me	5.86	0.059	nt	1.37
7x		4-Morpholinyl	F_3C–	Me	5.04	0.029	nt	2.5
7y			F_3C–	Me	5.24	0.026	0.03	2.35
7z		R= H	F_3C–	Me	5.03	0.002	0.003	3.67
7aa		Me	F_3C–	Me	5.53	0.013	0.005	2.36
7ab		Et	F_3C–	Me	6.06	0.009	0.018	1.99
7ac		*c*-Propyl	F_3C–	Me	5.97	0.006	0.02	2.25
7ad		*i*-Propyl	F_3C–	Me	6.46	0.01	0.01	1.54
7ae		OMe	F_3C–	Me	5.84	0.005	0.01	2.46
7af		NH_2	F_3C–	Me	4.71	0.014	0.16	3.14
7ag		NMe_2	F_3C–	Me	5.74	0.086	nt	1.33
7ah			F_3C–	Me	3.82	0.018	0.072	3.92
7ai			F_3C–	Me	4.03	0.128	nt	2.86
7aj			F_3C–	Me	4.27	0.006	0.05	3.95

(*continued on next page*)

Table 1 (*continued*)

Compound	$R^{3'}$		R^8	R^7	*c* log *P*	Rat mGluR2 [^{3}H]-LY354740 binding[a] IC_{50} (μM)	Rat mGluR2 (1*S*,3*R*)-ACPD inhibition of Forskolin stimulated cAMP[b] IC_{50} (μM)	LLE = p(IC_{50} of [^{3}H]-LY354740 binding)—*c* log *P*
7ak			F_3C–	Me	4.06	0.023	0.048	3.58
7al			F_3C–	Me	4.27	0.02	0.016	3.43
7am		R= Me	F_3C–	Me	6.03	0.002	0.003	2.67
7an		Et	F_3C–	Me	6.56	0.002	0.004	2.14
7ao		*c*-Propyl	F_3C–	Me	6.47	0.002	0.004	2.23
7ap		CH_2OH	F_3C–	Me	4.94	0.014	0.015	2.91
7aq		CH_2OMe	F_3C–	Me	5.33	0.008	0.005	2.77
7ar			F_3C–	F_3C–	6.57	0.007	0.007	1.58
7as		R= H	F_3C–	H	4.53	0.01	0.026	3.47
7at		H	F_3C–	OEt	5.11	0.004	0.01	3.29
7au		H	Cl	H	4.17	0.008	0.003	3.93
7av		Me	Cl	Cl	5.35	0.004	0.002	3.05
7aw		Me	F_3C–	H	5.03	0.018	0.036	2.71
7ax		Me	F_3C–	OEt	5.61	0.006	0.008	2.61

$R^{3'}$, R^7 and R^8 refer to the positions of R's in Scheme 1.
nt, not tested.
[a] Values are means of at least two independent experiments.
[b] Values are means of three independent experiments.

Table 2
IC_{50} values for GIRK current inhibition by selected compounds in CHO cells expressing mGluR2 and mGluR3 receptors

Compound	Rat mGluR2 GIRK inhibition IC_{50}[a] (μM)	Rat mGluR3 GIRK inhibition IC_{50}[a] (μM)	Human mGluR2 GIRK inhibition IC_{50}[a] (μM)
3	0.024	nt	nt
4	0.011	0.033	nt
7i	0.013	0.014	0.041
7am	<0.01	<0.01	0.014
7as	0.101	0.029	0.052
7at	0.008	0.006	0.038
7au	nt	nt	0.010
7av	nt	0.030	0.007
7aw	nt	0.017	0.025
7ax	nt	0.003	0.015

[a] Values are means of 3–5 independent experiments, (nt = not tested).

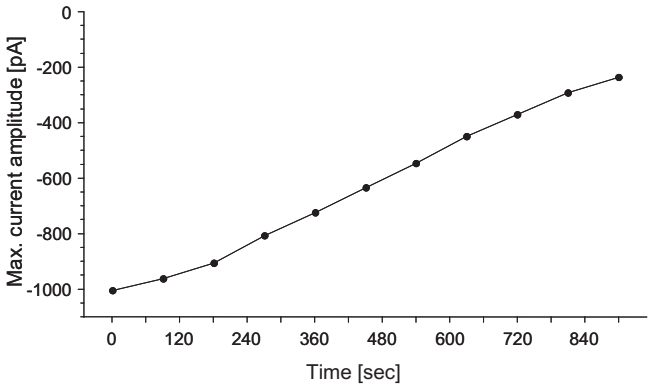


Figure 2a. Time course of **7am**-induced inhibition of GIRK currents in a cell expressing rat mGluR2. Glutamate (1 μM) was applied in the presence of 10 nM **7am**. The compound showed very slow on-rate kinetics. The block was almost complete but only after 15 min application.

in vivo data related to **7am** have been presented in poster format by Knoflach et al.[4c] and in patents;[12] a successive poster publication from Campo et al.[4d] is also referring to the same compound **7am** (RO4491533).

The mGluR2/3 agonist LY354740 produces a dose-dependent impairment of working memory in the delayed match to position (DMTP) task in rats, but does not have an effect on parameters of task performance such as missed trials and latencies to respond.[3] Compound **7am** dose-dependently reversed the mGluR2/3 agonist-induced impairment of working memory, with partial reversal at 3 mg/kg po and full reversal at 10 mg/kg po (Fig. 4a, % total correct choices). It has been shown in both rats and monkeys that LY354740 impairs working memory, however, in humans there are no reports to date that mGluR2/3 agonists impair cognition. Moreover, it has been shown that LY354740 has a trend to reduce the impairing effects of ketamine in the continuous performance test in healthy human volunteers.[13] The direct translation of these effects from rodents to humans is still under discussion.[14]

However, we have also shown that compound **7am** partially but significantly reversed a scopolamine-induced working memory impairment in the DMTP task at 3 mg/kg po (Fig. 4b). Interestingly when sub-threshold doses of **7am** and donepezil (Aricept®) were co-administered they showed an apparent synergistic effect versus the scopolamine-induced working memory deficit in the DMTP task in rats (Fig. 4c and d).[11,12b] Interestingly, compound **7am** also exhibits mild antidepressant-like activity in the mouse forced swim test after oral administration in a consistent range of doses.[4d]

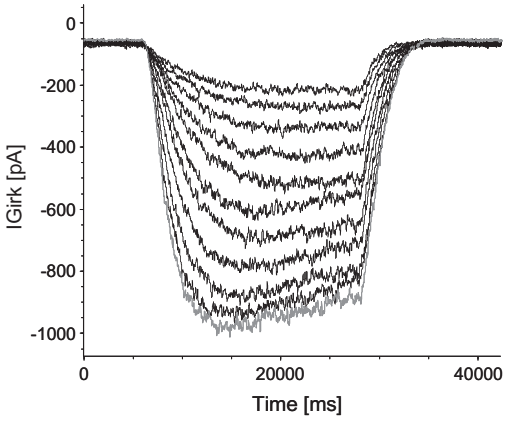


Figure 2b. Superimposed glutamate-induced currents in the absence and presence of **7am**, recorded at 90 s intervals in a representative human mGluR2 expressing cell. The gray current trace is a control response to 1 μM L-glutamate, the black currents were recorded in the presence of 10 nM **7am**.

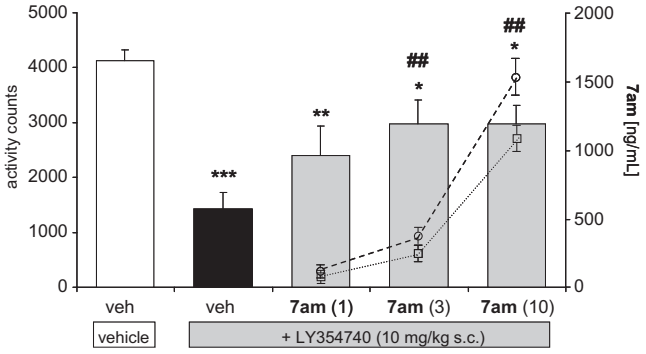


Figure 3. Spontaneous locomotor activity in rats (total horizontal activity counts in 30 min): reversal of LY354740-induced (10 mg/kg s.c., ptt 30 min) hypoactivity by pretreatment with compound **7am**. Dose response assessment of **7am** suspension prepared in 0.3% Tween 80 v/v saline (at 1, 3 and 10 mg/kg po, ptt 180 min). ($n = 8$ rats/group; statistics: $p < 0.01$; $^{*}p < 0.05$, $^{***}p < 0.001$ vs veh. + veh.; $\#\#p < 0.01$ vs veh. + LY354740). Plasma (□) and brain (○) levels for **7am** (approx. 210 min post administration) are also reported. Brain/plasma ratio remains constant (B/P ~1.4) at all doses.

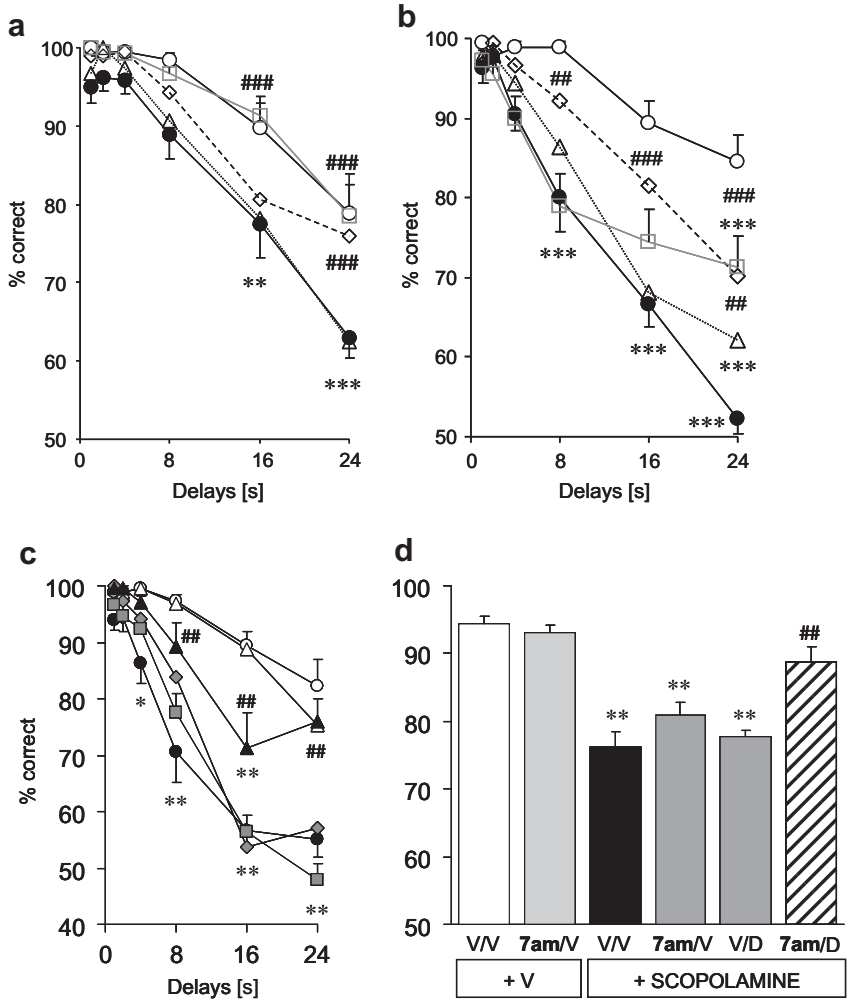


Figure 4. (a) Effect of **7am** (1, 3, 10 mg/kg po, ptt 180 min) versus mGluR2/3 agonist (LY354740: 6 mg/kg ip)-induced working memory impairment in the delayed match to position (DMTP) task in rats. (b). Effect of **7am** (1, 3, 10 mg/kg po, ptt 180 min) versus scopolamine (0.06 mg/kg s.c.)-induced working memory impairment in the DMTP task in rats. (c) Combination of sub-threshold doses of **7am** (1 mg/kg po) and donepezil (1 mg/kg po) significantly reversed the scopolamine (0.06 mg/kg s.c.)-induced working memory impairment in the DMTP task. Data are presented as mean correct responses ± SEM. Percent correct responses across delay intervals: (a) vehicle (○); LY354740 (●); **7am** at (1 mg/kg po) (△), (3 mg/kg po) (◇) and (10 mg/kg po) (□) versus LY354740 ($n = 12$ rats); (**b**) vehicle (○); scopolamine (●); **7am** at (1 mg/kg po) (△), (3 mg/kg po) (◇) and (10 mg/kg po) (□) versus scopolamine ($n = 12$ rats). (c) Vehicle (○); scopolamine (0.06 mg/kg s.c.) (●); **7am** (1 mg/kg po, ptt 180 min) versus scopolamine (0.06 mg/kg s.c.) (♦); donepezil (1 mg/kg po, ptt 35 min) versus scopolamine (0.06 mg/kg s.c.) (■); **7am** (1 mg/kg po, ptt 180 min) plus donepezil (1 mg/kg po, ptt 35 min) versus scopolamine (0.06 mg/kg s.c.) (▲) ($n = 12$ rats). (d). Total percent correct responses collapsed across delays: V: vehicle; D: donepezil (1 mg/kg po, ptt 35 min); **7am** (1 mg/kg po, ptt 180 min); scopolamine (0.06 mg/kg s.c.) ($n = 12$ rats). Statistics: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus vehicle-treated group; $\#\#p < 0.01$, $\#\#\#p < 0.001$ versus LY354740 or scopolamine-treated group).

In addition, the in vivo active compounds described in this Letter are in general well tolerated and they do not cause behavioral disruption up to 30 mg/kg po in neurological assessment including rotarod and grip strength and on spontaneous locomotor activity.

In summary, with the unique combination of trifluoromethyl in 8-position and methyl in 7-position and the incorporation of a 2-methyl- or 2,6-dimethyl-substituted *para*-pyridine in the 3′-position we were able to develop a series of in vivo active 1,3-dihydro-benzo[*b*][1,4]diazepin-2-one derivatives with drug potential. This is shown by the capacity of these compounds to rescue the working memory impairment induced by either an mGluR2/3 agonist or a muscarinic antagonist in the DMTP task in rats. A more detailed description of the pharmacology of compounds **7am** and **7i** and their capacity to act as cognitive enhancers in animal models of aging and Alzheimer's disease will follow in due course.

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