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SYNTHESIS AND BIOLOGICAL ACTIVITY OF A SERIES OF 4-ARYL SUBSTITUTED BENZ[b]AZEPINES: ANTAGONISTS AT THE STRYCHNINE-INSENSITIVE GLYCINE SITE

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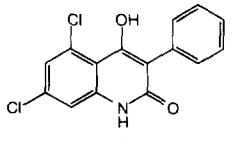
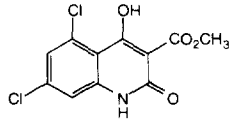
Abstract: A series of 4-arylbenz[b]azepine analogs were prepared and shown to act as antagonists at the strychnine-insensitive glycine receptor. The heteroaryl substituted benz[b]azepine derivative **11** also showed excellent *in vivo* activity.

The glycine site of the NMDA receptor complex has received considerable attention as a target for therapeutic intervention in neurological disorders.[1] Antagonists at this site have been proposed to have utility in treating a variety of disease states, such as cerebral ischemia, Parkinson's disease, and schizophrenia.[2] There are a variety of molecules known to interact at this receptor, with a large number being derived from either the kynurenic acid or quinoxaline framework. Attention has focused on building molecules within these series which contain extensions off the northeastern section of the compounds in an attempt to take advantage of a putative hydrophobic binding pocket in the glycine receptor.[3] For example, compounds **1** and **2** show increased affinity at the glycine site when compared with their parent compound **3**.[4,5] Recently, the benz[b]azepine **4a** was reported as a potent antagonist at the glycine receptor.[6] In this report, we describe a new series of compounds, 4-arylsubstituted benz[b]azepine derivatives, and describe their *in vitro* and *in vivo* profile.



1



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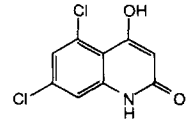
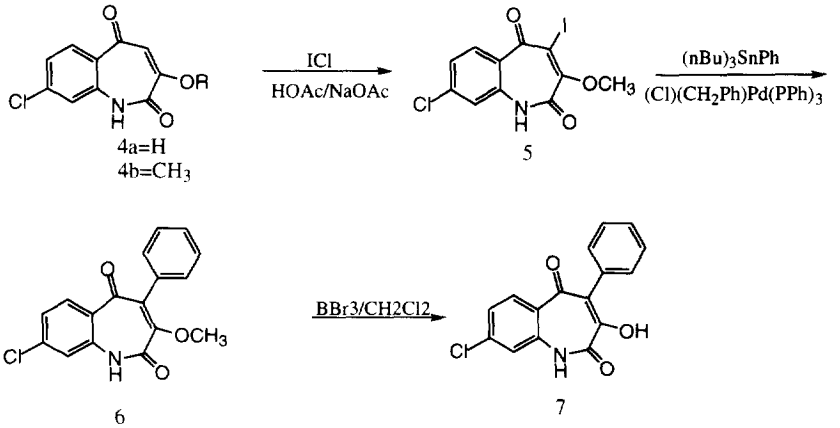


3

The substituted benz[b]azepines were prepared using the Stille cross-coupling reaction.[7,8] This route is exemplified with the preparation of the 4-phenylbenz[b]azepine

7 as illustrated in Scheme 1. As shown, the benz[b]azepine **4b** served as the starting material for the synthetic sequence. Reaction of this compound with a buffered solution of iodine monochloride afforded the iodinated species **5** in quantitative yield.[9] Upon treatment of the aryl halide with tributylphenyltin in the presence of a catalytic amount of benzylbis(triphenylphosphine)palladium(II), the 4-phenyl derivative was obtained in 80% yield. The compounds shown in Table 1 were prepared in a similar fashion, with comparable yields.

SCHEME 1



4a=H
4b=CH_3

5

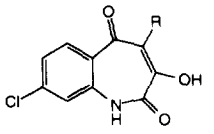
6

7

The benz[b]azepines listed in Table 1 were tested for their ability to displace [^{3}H]glycine as previously described.[10] The substrates which exhibited the best affinity for the receptor contained a heteroaryl substituent at the 4-position. In addition, the compounds were tested in the red nucleus assay, which delivers an *in vivo* functional measure of the effects of glycine antagonists. This electrophysiological screen measures a compound's effect on the NMDA receptor complex following administration by iv infusion, iv bolus or a combination of the two.[11] The most active compound in the series, the 2-pyridyl derivative **11**, showed weak binding at the glycine site, but excellent activity in this assay. There are several possible explanations for the excellent *in vivo* properties of this molecule when compared to the 3-pyridyl compound **10**. For example, it is possible that an intramolecular hydrogen bond exists in compound **11** that is not present in compound **10**. To explore this possibility, we performed *ab initio* calculations on these compounds.[12] The results are consistent with an intramolecular hydrogen bond existing in the 2-pyridyl but not the 3-pyridyl compound. The presence of this hydrogen bond may

also account for the high pKa of compound **11** (6.7) when compared to the value obtained for compound **10** (5.6). This in turn may facilitate the passage of compound **11** across the blood brain barrier causing an increase in *in vivo* potency. In summary, we have described a series of novel, 4-substituted benz[b]azepines. Unlike other series of glycine antagonists, addition of substituents onto the northeastern portion of these molecules did not increase *in vitro* activity. However, several compounds within this series do show potent *in vivo* activity. Further development of this series may be useful for the treatment of a variety of neurological disorders such as cerebral ischemia or Parkinson's disease.

TABLE 1



Compound	R	IC_{50}	Red Nucleus[a]
7	Ph	0.38	9.4
8	4-$CH_3$0Ph	0.57	9.9
9	4-HOPh	0.57	NT
10	3-pyridyl	0.19	Inactive
11	2-pyridyl	1.1	1.7
12	2-furanyl	0.21	5.0
13	2-thienyl	0.63	5.6
14	3-thienyl	0.59	NT
15	2-(3-CH_3O)pyridyl	0.82	2.8

a: Compounds tested utilizing an i.v. infusion

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12. *Ab Initio* calculations were performed at the 3-21G*//3-21G* level.

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