Bioorganic & Medicinal Chemistry Letters 19 (2009) 1492–1495

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of GlyT1 inhibitors with improved pharmacokinetic properties

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ARTICLE INFO

Article history:
Received 24 November 2008
Revised 6 January 2009
Accepted 7 January 2009
Available online 10 January 2009

Keywords:
GlyT1
Schizophrenia
NMDA pharmacokinetics
Cassette dosing

ABSTRACT

Glycine transporter 1 (GlyT1) represents a novel target for the treatment of schizophrenia via the potentiation of glutamatergic NMDA receptors. The discovery of 4,4-disubstituted piperidine inhibitors of GlyT1 which exhibit improved pharmacokinetic properties, including oral bioavailability, is discussed.

Mounting evidence suggests that the long established dopamine hyperfunction model[1] for schizophrenia may inadequately account for the symptoms of this widespread disease.[2,3] Although both typical and atypical antipsychotics target dopamine receptors and address the positive symptoms of schizophrenia (hallucinations, paranoia, and other delusions), negative symptoms (blunted affect, withdrawal) and cognitive deficits are not satisfactorily addressed with these treatments. A growing body of evidence[4] indicates that hypofunction of *N*-methyl-D-aspartate (NMDA) glutamatergic receptors may contribute to the etiology of the disease, yet direct agonists of NMDA receptors are neurotoxic.[5] Glycine transporter 1 (GlyT1) has emerged as a promising alternative target due to existing reports of its potentiation of NMDA receptor activity by modulating the local concentrations of the NMDA co-agonist glycine.[6]

Recently, we disclosed potent and selective inhibitors of GlyT1 based on a 4,4-disubstituted piperidine lead structure. Exemplified by **1** and **2** (Fig. 1), these compounds exhibit potent (<10 nM), selective (versus GlyT2, taurine transporter) inhibition of GlyT1 and selectively elevate glycine levels in rat prefrontal cortex.[7,8]

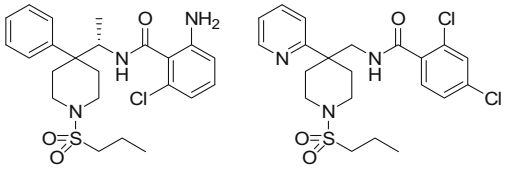

Figure 1. 4,4-Disubstituted piperidine GlyT1 inhibitors.

Furthermore, **1** significantly enhances prepulse inhibition in DBA/2J mice without impairing basal startle amplitude indicating an antipsychotic effect without sedation.[7]

While **1** and **2** were effective in animal models after being dosed subcutaneously, they exhibit poor pharmacokinetic properties including low bioavailability. In addition to optimizing these properties to enable oral dosing, a further objective was developing compounds which demonstrate high transporter occupancy in vivo. Herein we report the achievement of these goals employing an iterative analogue library approach.

A variety of strategies were pursued in order to improve the properties of **1** and **2**, including modification of the piperidine C4 substituent and substitution of the piperidine *N*-sulfonamide. Aryl group replacements were prepared according to the route described in Scheme 1a. Quenching the lithium anion of nitrile **3** with a variety of electrophiles (alkyl halides, epoxides), followed by Ra-

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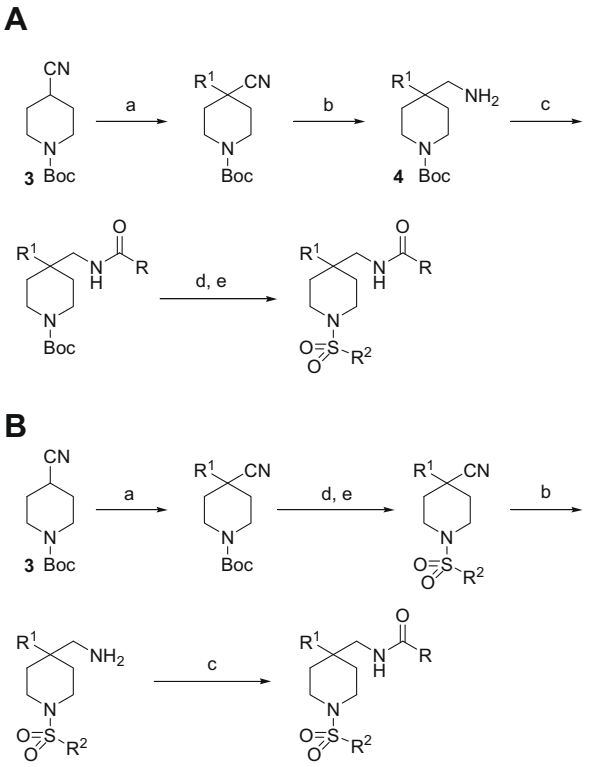
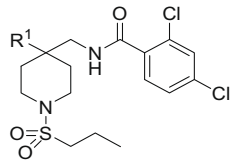
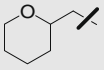
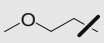
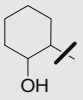
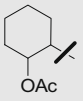
doi:10.1016/j.bmcl.2009.01.015



Scheme 1. Reagents and conditions: (a) LHMDS, THF, 25 °C, then electrophile R^1–X; (b) H_2, Raney Ni; (c) carboxylic acid, PS-DCC, HOBt, CH_2Cl_2, 25 °C; (d) 4 M HCl/dioxane; (e) sulfonyl chloride, *i*-Pr_2NEt, 25 °C.

Table 1
Piperidine 4-position replacements



Compound	R^1	GlyT1 IC_{50}, nM[a]	GlyT2 IC_{50}, nM[a]	TauT IC_{50}, nM[a]
5		2.9	>30,000	>30,000
6		26.5	>30,000	>30,000
7		2.8	>30,000	>30,000
8		17.7	nd[b]	nd
9		38.1	nd	nd
10		30.0	>30,000	>30,000

[a] Values are means of at least three experiments.
[b] Not determined.

ney Ni-catalyzed reduction provided mono-Boc protected diamine **4**. Acylation (PS-DCC, HOBt, or carboxylic acid chloride), acidic deprotection of the Boc group, and sulfonamide formation furnished the GlyT1 inhibitors listed in Table 1. Alternatively, the sequence could be modified (Scheme 1b) such that amide formation furnished the final products. Use of both routes enabled the facile generation of both amide and sulfonamide libraries; >300 analogues were prepared according to this procedure and selected data are presented in Table 1.[9]

Generally, replacement of the aryl group was well tolerated, with tetrahydropyran (**5**) and hydroxyl (**7**) functionality providing potency equivalent to **1** and **2**. These substitutions had no effect on selectivity versus GlyT2 and taurine transporter (TauT)—no activity was observed at micromolar concentrations. This level of selectivity (>30,000-fold) is notable among non-sarcosine derived GlyT1 inhibitors.[10] Despite the variety of structures incorporated at the piperidine C4 position and the removal of likely sites of metabolism (aromatic oxidation and *N*-oxide formation), compounds in Table 1 exhibited uniformly poor pharmacokinetic properties (dog Cl > 15 mL/min/kg, $t_{1/2}$ < 2 h).

Evaluation of propylsulfonamide modifications was therefore undertaken; a focused sulfonamide library was prepared according to Scheme 1 and results are shown in Table 2. Metabolite profiling of **2** indicated that oxidation occurs on the propyl chain, and potential metabolite **11** lost 20-fold in potency. The corresponding fluoride (**12**), while only 2× less potent than **2**, demonstrated poor pharmacokinetics. Alkyl sulfonamides (**13–17**) were 10- to 50-fold less potent than **2**, with the truncation and extension of the straight alkyl chain by even a single methylene unit having a significant negative effect (**14** and **15**, respectively). Sulfamide (**18**) and trifluorinated alkyl chains (**19** and **20**) were poorly tolerated.

Although the truncated alkyl sulfonamides (**13**, **14**, and **16**) lose potency versus **1** and **2**, they constitute a breakthrough in terms of pharmacokinetic properties (Table 2). These compounds exhibit low clearance (<2 mL/min/kg) and long half lives (>7.5 h) in dogs.

The data cited in Table 2 were generated in a series of dog iv cassette experiments, which was an attractive strategy due to the number of compounds in the library for which pharmacokinetic evaluation was desired.[11] Although there are myriad potential complications associated with dosing in cassette format,[12] within this structural series we noted excellent agreement between iv clearance values determined via cassette and single dose experiments. This strong correlation led to a high degree of confidence in these data, and cassettes were followed with single dose experiments evaluating promising compounds. Based on the dramatic improvement in dog clearance afforded by the shortened alkyl sulfonamides, efforts were focused on enhancing potency with these groups in place.

Previous experience gained during the development of **1** suggested that incorporation of a chiral (*S*) methyl group alpha to the amide nitrogen could confer increases in potency up to 10-fold.[7] The methylated analogue of **14** was therefore prepared according to Scheme 2. Following incorporation of the 2-pyridyl group via a nucleophilic aromatic substitution reaction, the methyl group was installed through Grignard addition (MeMgBr, 25 °C) and reduction ($NaBH_4$) of the resulting imine. Following resolution using chiral chromatography, acylation of the amine, piperidine *N*-Boc deprotection, and sulfonamide formation provided optically pure **21**.[13] Gratifyingly, **21** exhibited improved GlyT1 potency (11 nM) while maintaining complete selectivity versus GlyT2 and TauT; this analogue was not a substrate for human or rat P-glycoprotein (PgP) and displayed excellent passive permeability (37×10^{-6} cm/s).[14] Moreover, **21** retained a favorable dog pharmacokinetic profile (see Fig. 3 and Table 3). Data contained in Fig. 3