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1,3-Diaminopropan-2-ol Sulfonamides as potent and selective inhibitors of the glycine transporter type 1

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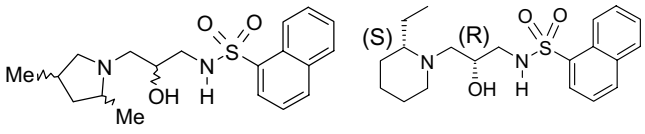
Abstract—High throughput screening led to the discovery of a novel series of 1,3-diaminopropan-2-ol sulfonamides as selective GlyT-1 inhibitors. Structure–activity relationships of this novel series and optimisation of the initial hit that led to the identification of (**2**), a potent and selective GlyT-1 inhibitor, are also presented.

Molecular cloning has revealed the existence in mammalian brains of two classes of glycine transporters, termed GlyT-1 and GlyT-2. GlyT-1 is found predominantly in the forebrain and its distribution corresponds to that of glutaminergic pathways and NMDA receptors.[1] Molecular cloning has further revealed the existence of three variants of GlyT-1, termed GlyT-la, GlyT-1b and GlyT-1c,[2] each of which displays a unique distribution in the brain and peripheral tissues. GlyT-2, in contrast, is found predominantly in the brain stem and spinal cord, and its distribution corresponds closely to that of strychnine-sensitive glycine receptors.[3] Another distinguishing feature of glycine transport mediated by GlyT-2 is that it is not inhibited by sarcosine, as is the case for glycine transport mediated by GlyT-1. These data are consistent with the view that, by regulating the synaptic levels of glycine, GlyT-1 and GlyT-2 selectively influence the activity of NMDA receptors and strychnine-sensitive glycine receptors, respectively.

NMDA receptors are critically involved in memory and learning[4] and, furthermore, decreased function of NMDA-mediated neurotransmission appears to underlie, or contribute to, the symptoms of schizophrenia.[5] Thus, agents that inhibit GlyT-1 and thereby increase glycine activation of NMDA receptors may be useful as novel anti-psychotics and anti-dementia agents, and to treat other diseases in which cognitive processes are impaired, such as attention deficit disorders and organic brain syndromes.

High throughput screening of our in-house compound collection (measuring inhibition of [^{3}H]glycine uptake in HEK293 cells stably transfected with hGlyT-1c)[6,7] identified the 2,4-dimethylpyrrolidine derivative (**1**) (Fig. 1), a mixture of four diastereoisomers.[8] Compound (**1**) has good inhibitory activity against hGlyT-1c (pIC_{50} 6.1) and good selectivity over hGlyT-2 ($pIC_{50} < 5.0$). In this communication, we describe the optimisation of the 1,3-diaminopropan-2-ol derivative (**1**) leading to the identification of the substituted piperidine (**2**). Compound (**2**) is a potent and selective GlyT-1c inhibitor and a valuable tool compound for investigating the scientific rationale for the use of GlyT-1 inhibitors in



(1)
pIC_{50} 6.1 (hGlyT-1c),
<5.0 (hGlyT-2)

(2)
pIC_{50} 7.0 (hGlyT-1c),
<5.0 (hGlyT-2)

Figure 1. Structures of HTS hit (**1**) and optimised analogue (**2**).

Keywords: GlyT-1; Schizophrenia; NMDA, Transporter; 1,3-Diaminopropan-2-ol.
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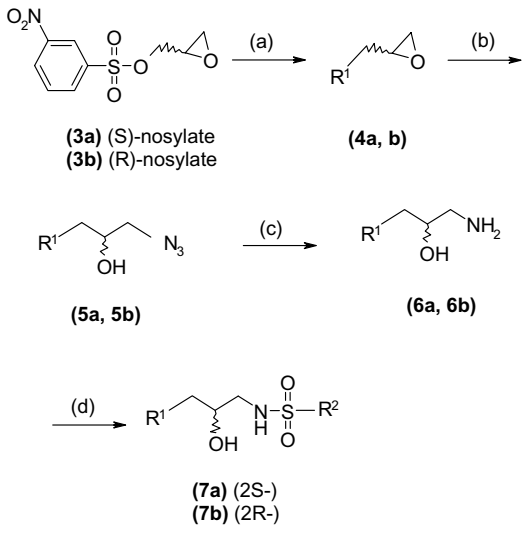
the treatment of schizophrenia. Structure–activity relationships of this novel series of Gly-1 inhibitors are also presented.

1,3-Diaminopropan-2-ols (**6**) were prepared by the previously reported procedure[9] (Scheme 1). Both (*S*) and (*R*) glycidyl nosylates (**3a**) and (**3b**) were reacted with substituted secondary amines[10] affording chiral epoxides (**4a** and **4b**). Epoxide ring-opening was achieved using lithium azide (20% aq soln) to give the hydroxyazides (**5a** and **5b**), which were hydrogenated at atmospheric pressure in the presence of Pearlmans catalyst to afford the 1,3-diaminopropan-2-ols (**6a** and **6b**). The sulfonamides (**7**) were prepared by reaction of (**6**) with sulfonyl chlorides in the presence of Amberlyst IRA 93 resin.

The optimal stereochemistry around the hydroxyl group was first investigated by preparing the two possible 2-hydroxy isomers of 2,4-dimethylpyrrolidine (**1a** and **1b**) and 2-methylpyrrolidine (**8a** and **8b**) from the commercially available (*S*)- and (*R*)-glycidyl nosylates, respectively. In both cases activity resided mainly with the (2*R*)-isomer (Table 1). In subsequent optimisation only the preferred (2*R*)-hydroxyl isomer was used.



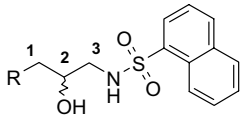
Scheme 1. Reagents and conditions: (a) Amine R^1H,[10] KH/THF, rt, argon; (b) 20% aq LiN_3, THF, 75 °C; (c) $H_2/Pd(OH)_2$, MeOH, atmospheric pressure, rt; (d) R^2-SO_2-Cl, DCM, Amberlyst IRA 93.

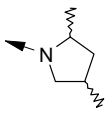
We next turned our attention to substitution in the pyrrolidine ring (Table 2). All compounds were prepared as a mixture of isomers and separated by HPLC.[11] Substitution at the ortho position of the heterocycle is required for good affinity. Compounds with isopropyl (**9**) or *tert* butyl (**10**) groups are optimal with potency decreasing for the cyclopropyl (**11**), ethyl (**12**), methyl (**8**), or the unsubstituted (**13**) analogues. Compounds substituted with 2-(methyl)-propyl (**14**) or cyclohexyl (**15**) substitutions are detrimental suggesting that larger groups are not preferred.

We then investigated ring size by replacing the pyrrolidine ring with a piperidine (Table 3). Whilst most comparable analogues were equipotent, trends are not mirrored. Ethyl substitution (**2**) was identified as the best group for activity in the piperidine series. The 2-alkyl diastereoisomers of pyrrolidine (Table 2) and piperidine analogues (**2**), (**8**–**12**), (**14**), (**15**) and (**21**) were separated by HPLC.[11] Both isomers have affinity for GlyT-1c but the (2*S*)-alkyl-(2*R*)-hydroxy stereoisomer was shown to be the favoured[12] isomer. Small alkyl substitution at the 3 position of the piperidine does not offer any advantage. The most potent isomers of the dimethyl and monomethyl pyrrolidine derivatives (**1**) and (**8**), respectively, are equipotent. Alicyclic analogues (**16**) and (**17**) are active but potency decreases a little with respect to similar cyclic analogues.

We then examined the SAR of the aromatic sulfonamide fragment. A diverse set of 50 monocyclic, bicyclic, aryl and heteroaryl sulfonamides (**7**) (keeping the 2,4-dimethyl pyrrolidine group as constant) were prepared by parallel synthesis.[7,13] SAR around this position (Table 4) is tight with 1-naphthyl substituent, present in the original HTS hit (**1**), being optimal. 2-Naphthyl analogue (**24**) and isosteric replacements of naphthyl ring such as dichlorophenyl (**25**) are active

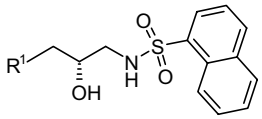
Table 1. Optimal stereochemistry of C-2 hydroxyl group

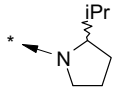
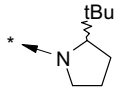
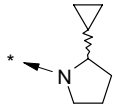
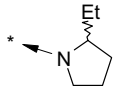
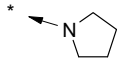
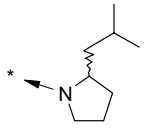
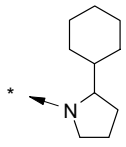
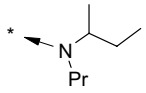
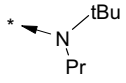


Compound	R	Isomer	GlyT-1c (pIC_{50})[a]
1a		2*S*	5.1
1b		2*R*	6.1
8a		2*S*	4.9
8b		2*R*	6.0

[a] Mean of at least three determinations with standard deviation of <±0.3.

Table 2. Inhibitory activity of 1-pyrrolidine analogues (**9**–**17**)



Compound	R^1	GlyT-1c (pIC_{50})[a]			Isomer A retention time (run time in min)[b]	Isomer B retention time (run time in min)[b]
		Isomer		Mixture		
		A	B	A + B		
9		6.0	6.7	—	9.71 (16)	12.78 (16)
10		5.1	6.7	—	24.59 (35)	27.32 (35)
11		5.8	6.3	—	20.76 (32)	26.05 (32)
12		5.9	5.8	—	19.53 (35)	29.66 (35)
13		—	—	5.5		
14		5.2	5.6	—	12.70 (18)	14.25 (18)
15		5.2	5.2	—	19.75 (30)	24.44 (30)
16		—	—	5.9		
17		—	—	6.0		

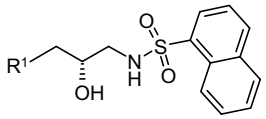
[a] Mean of at least three determinations with standard deviation of $<\pm 0.3$.
[b] HPLC retention time using the analytical protocol described in the notes.[11]

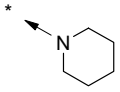
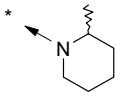
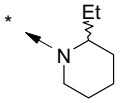
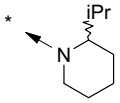
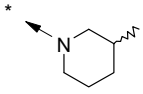
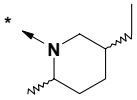
but less potent. Similarly, substituted aryl or heteroaryl sulfonamide analogues with ortho substitution, such as compounds (**26**), (**27**) and (**28**), show reduced inhibitory activity.

Optimisation of the HTS hit (**1**) culminated in the identification of the (2*S*)-ethylpiperidine derivative (**2**) GlyT-1c (pIC_{50} 7.0). This compound demonstrated high intrinsic clearance in both rat and human microsomes (CLi 8.0 mg/ml/g for both species) and significant affinity for CYP2D6 (1.2 μM). After oral administration of 5 mg/kg (free base) in rats, (**2**) showed poor oral bioavailability (4%).[14] However, bioavailability after subcutaneous administration (5 mg/kg in rats) was very high (95%), with a moderate half-life ($t_{1/2}$ = 0.9 h) and brain to plasma AUC ratio of 0.4:1 (C_{max} 564 ng/ml, AUC_{0-inf} 1731 h ng/ml, brain level 1 h postdose 564 ng/ml). With this PK profile, diaminopropan-2-ol (**2**) represents a valuable tool compound for validating the rationale for the use of GlyT-1 inhibitors in the treatment of schizophrenia.

The results of these studies together with the optimisation of PK parameters of this novel series of GlyT-1 inhibitors will be the subject of a later paper.

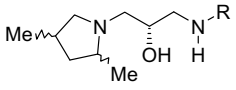
Table 3. Inhibitory activity of 1-piperidine analogues (**18**–**23**)



Compound	R^1	GlyT-1c (pIC_{50})[a]			Isomer A retention time (run time in min)[c]	Isomer B retention time (run time in min)[c]
		Isomer		Mixture		
		A	B	A + B		
18		—	—	5.5		
19		—	—	6.5		
20 and **2**		5.1	7.0[b]	—	27.04 (40)	30.63 (40)
21		5.4	6.2	—	20.69 (40)	22.71 (40)
22		—	—	5.4		
23		—	—	6.0		

[a] Mean of at least three determinations with standard deviation of $<\pm 0.3$.
[b] This isomer was shown to correspond to the *N*-{(2*R*)-3-[(2*S*)-2-ethyl-1-piperidinyl]-2-hydroxypropyl}-1-naphthalenesulfonamide diastereoisomer.
[c] HPLC retention time using the analytical protocol described in the notes.[11]

Table 4. Modifications of the arylsulfonamide group



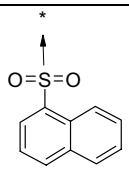
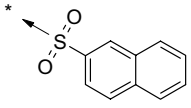
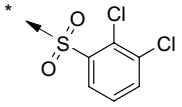
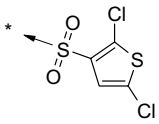
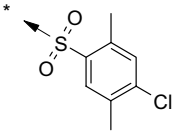
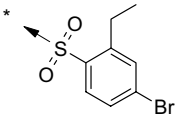
Compound[a]	R	GlyT-1c (pIC_{50})[b]
1b		6.1
24		5.4
25		5.6
26		5.5

Table 4 (*continued*)

Compound[a]	R	GlyT-1c (pIC_{50})[b]
27		5.5
28		5.5

[a] Compounds are diastereoisomeric mixture of 2,4-dimethylpyrrolidines.
[b] Mean of at least three determinations with standard deviation of <±0.3.

Acknowledgments

We thank Matthew Sanders for providing analytical support with separating the diastereoisomers and Peter Eddershaw for providing DMPK data.

References and notes

1. Smith, K. E.; Borden, L. A.; Hartig, P. R.; Branchek, T.; Weinshank, R. L. *Neuron* **1992**, *8*, 927.
2. Kim, K. M.; Kingsmore, S. F.; Han, H.; Yang-Feng, T. L.; Godinot, N.; Seldin, M. F.; Caron, M. G.; Giros, B. *Mol. Pharmacol.* **1994**, *45*, 608.
3. (a) Liu, Q. R.; Lopez-Corcuera, B.; Mandiyan, S.; Nelson, H.; Nelson, N. *J. Biol. Chem.* **1993**, *268*, 22802; (b) Jursky, F.; Nelson, N. *J. Neurochem.* **1995**, *64*, 1026.
4. Rison, R. A.; Staunton, P. K. *Neurosci. Biobehav. Rev.* **1995**, *19*, 533.
5. Olney, J. W.; Farber, N. B. *Arch. Gen. Psychiatry* **1995**, *52*, 998.
6. Herdon, H. J.; Godfrey, F. M.; Brown, A. M.; Coulton, S.; Evans, J. R.; Cairns, W. J. *Neuropharmacology* **2001**, *41*, 88.
7. Coulton, S.; Hadley, M. S.; Herdon, H. J.; Jin, J.; Joiner, G. J.; Porter, R. A.; Rahman, S. S. WO Patent 03/055478 A1, 2003.
8. Pyrrolidine derivative (**1**) is an isomeric mixture of four diastereoisomers–activity resides predominantly with one isomer as confirmed by testing the four diastereoisomers separated by HPLC.
9. Dhanoa, D. S.; Parsons, W. H.; Greenlee, W. J.; Patchett, A. A. *Tetrahedron Lett.* **1992**, *33*, 1725.
10. The non-commercially available alkyl pyrrolidines and piperidines required for the synthesis of compounds (**11**), (**12**), (**13**), (**17**) and (**21**) were prepared using the following literature methods: (a) De Jong, M.; Wibaut, J. P. *Recl. Trav. Chim. Pays-Bas* **1930**, *49*, 237; (b) Mundy, B. P.; Lipkowitz, K. B.; Lee, M.; Larson, B. R. *J. Org. Chem.* **1974**, *39*, 1963; (c) Bortnick, N.; Luskin, L. S.; Hurwitz, M. D.; Craig, W. E.; Exner, L. J.; Mirza, J. *J. Am. Chem. Soc.* **1956**, *78*, 4039.
11. Diastereoisomers were separated by HPLC using the following protocol: samples were dissolved in EtOH and run isocratically on Rainin preparative HPLC equipment, eluting with *n*-hexane:HiPerSolv EtOH:AnalaR TEA (90:10:0.25 v/v pre-mixed) mobile phase, on Chiralpak AS stationary phase (250 mm × 20 mm id). Flow rate 20 mL min^{-1}, ambient temperature, detection was by UV absorbance at 290 nm.
12. The absolute stereochemistry of (*N*-{(2*R*)-3-[(2*S*)-2-ethyl-1-piperidinyl]-2-hydroxypropyl}-1-naphthalenesulfonamide) (**2**) was determined by unambiguous synthesis from (*S*)-2-ethylpiperidine (Cymerman, J. C.; Pinder A. R. *J. Org. Chem.*, **1971**, 36, 3648.) and (*S*)-glycidyl nosylate, using afore-mentioned literature procedures. Optical rotation: (**2**) $[\alpha]_D^{20}$ +25.70 (*c* 0.3% in MeOH) and (*N*-{(2*R*)-3-[(2*R*)-2-ethyl-1-piperidinyl]-2-hydroxypropyl}-1-naphthalenesulfonamide)(**20**) $[\alpha]_D^{20}$ −9.5° (*c* 0.3% in MeOH).
13. *General procedure for array synthesis*: A solution of (*S*)-1-amino-3-(2,4-dimethylpyrrolidin-1-yl)propan-2-ol (**6a**, R^1 = 2,4-dimethyl pyrrolidin-1-yl) (800 mg; 4.65 mmol) in anhydrous dichloromethane (38 ml) was prepared, and aliquots (0.5 ml; 0.06 mmol) were added to solutions of 50 sulfonyl chlorides (0.075 mmol each) dissolved in anhydrous dichloromethane (1 ml each). Triethylamine (0.021 ml; 0.15 mmol) was added to each solution, which was shaken overnight at ambient temperature. The reaction mixtures were shaken with polymer-bound tris amine (~45 mg) for 3 h, then filtered and purified by preparative HPLC to afford the sulfonamides (**7**) as the trifluoroacetate salts.
14. PK data for (**2**) after i.v. administration (1 mg/kg; rat), CLp 18 ml/min/kg; $t_{1/2}$ = 1.0 h, plasma AUC_{0-inf} 952 h ng/ml, brain AUC_{0-inf} 587 h ng/ml.