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An octahydro-cyclopenta[*c*]pyrrole series of inhibitors of the type 1 glycine transporter

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ABSTRACT

We describe a novel series of inhibitors of the type 1 glycine transporter (GlyT1) as an approach to relieving the glutamatergic deficit that is thought to underlie schizophrenia. Synthesis and SAR follow-up of a series of octahydro-cyclopenta[*c*]pyrrole derivatives afforded potent in vitro inhibition of GlyT1 as well as in vivo activity in elevating CSF glycine. We also found that a 3-*O*(c-pentyl), 4-F substituent may serve as a surrogate for the widely used 3-trifluoromethoxy group, suggesting its application as an isostere for future medicinal chemistry studies.

Glycine performs a critical role as a regulator of the activity of the major excitatory CNS neurotransmitter glutamate. Binding to the regulatory NR1 subunit of the NMDA receptor for glutamate, glycine controls the 'gain' of the receptor, and in the process regulates a post-synaptic event mediated by NMDA transmission: LTP, or long-term potentiation, which in turn regulates memory, executive function, and affect.[1] These three aspects of glutamatergic transmission are key deficits of patients suffering from schizophrenia, leading to the hypothesis that NMDA hypofunction underlies the etiology of the disease.[2] Elevating glycine levels by blocking its re-uptake would restore NMDA function and potentially relieve many, if not most, of the symptoms of schizophrenia.[3]

One approach to elevating glycine levels is inhibition of the type 1 glycine transporter (GlyT1), which controls glycine uptake in the vicinity of NMDA synapses.[4] We have previously reported our efforts to discover novel GlyT1 inhibitors. Our first approach was based on the structure of the prototypical GlyT1 inhibitor (*R*)-N[3-(4′fluorophenyl)-3-(4′phenylphenoxy)propyl]-sarcosine, designated ALX 5407, (racemic form named NFPS) **1**,[5] (Fig. 1) and resulted in the compound **2**, (*R*)-N[3-phenyl-3-(4′-(4-toluoyl)-phenoxy)-propyl]sarcosine ((*R*)-NPTS).[6] Radiolabeled (*R*)-NPTS served as a radioligand for a binding assay to help discover our first structurally novel GlyT1 inhibitor series exemplified by compound **3**.[7] This series, however, was plagued with high clearance and affinity for the HERG-encoded I_{Kr} potassium channel, a source of potential cardiovascular toxicity, and hence was not pursued further. A subsequent high-throughput screen identified compound **4** as a promising lead based on its potent in vitro GlyT1 inhibition and in vivo activity in elevating CSF glycine levels, as reported previously and outlined in Table 1.[8]

As a follow up to compound **4**, we selected a template variation based on the octahydro-cyclopenta[*c*]pyrrole system found in the known compound **5**.[9] This compound had potential sites for derivatization analogous to those in compound **4**, and incorporated one

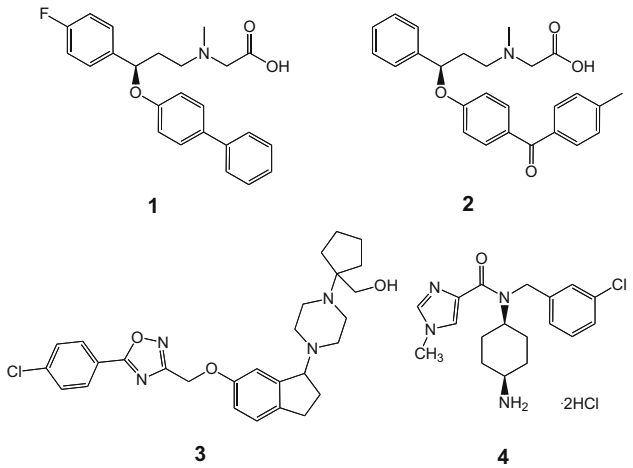

Figure 1. GlyT1 inhibitors.

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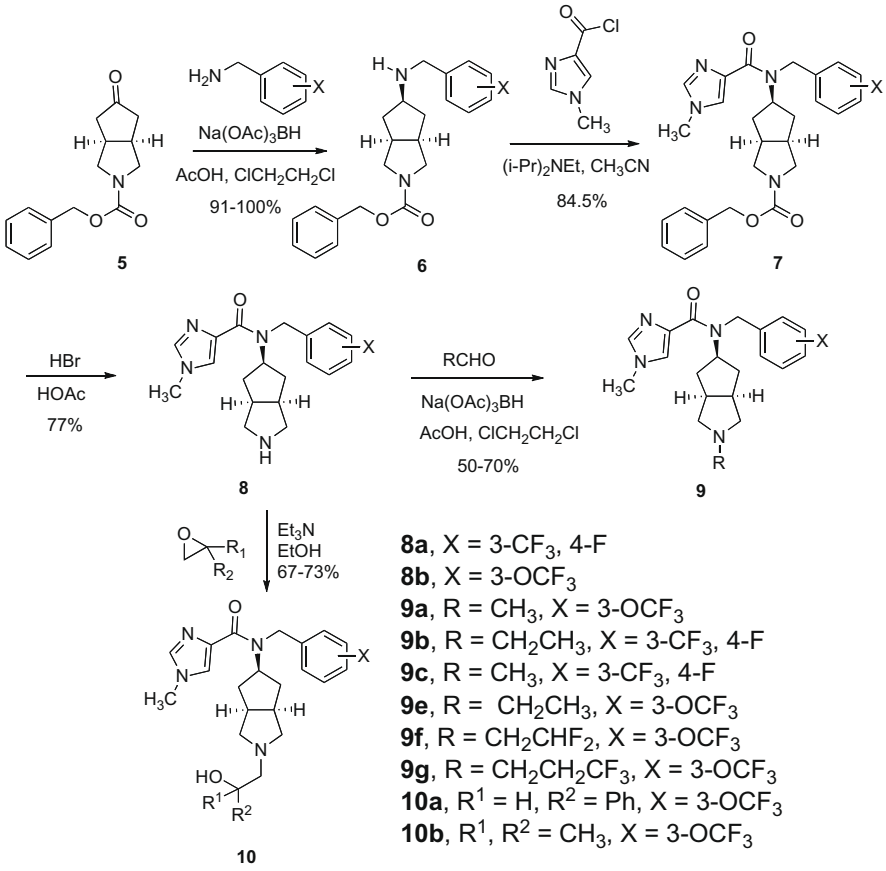
Table 1
Data for GlyT1 Inhibitors

Compound No.	GlyTl K_i (nM)	GlyT2 IC_{50}	Rat CSF glycine	hMic $t_{1/2}$ min	MDCK AB_C	MDR ratio	Dofetilide K_i	HERG IC_{50} (nM)	CYPZD6 IC_{50} nM	CYP3A4 IC50 nM	*c* log *P*	Polar area	Motwt
4	1.79 (1.59–2.01, $n = 68$)	1150	3.79 (2.17–7.41)	>120	0.5	1.50	3760	65,600	>10,000	>10,000	1.75	64.15	347
8a	1.71	4200 (3720–4740, $n = 2$)	249% @ 10	>120	2 1	ND	3310	4330	>10,000	>10,000	1.95	50.16	410.4
8b	1.98	1170	219% @ 10	50	1.1	ND	1650	13,200	>10,000	>10,000	1.95	59.39	408.4
8c	2.44	2270	NT	>111	0.2	1.90	>4760	NT	>10,000	>10,000	2.4	59.39	426.53
8d	3.96	2210	NT	>120	2.2	5.26	ND	NT	>10,000	>10,000	1.68	59.39	382.5
8c	5.3	>10,000	NT	>120	0.262	2.65	ND	NT	>10,000	>10,000	2.31	59.39	408.54
8f	>641	NT	NT	>120	0.291	2.52	ND	NT	>10,000	>10,000	2.05	68.62	438.57
9a	2.5	6250	240% @ 1	30.5	21.5	1.64	2560	NT	7100	>10,000	2.4	50.6	422.45
9b	2.64 (2.00–3.48, $n = 5$)	>3450 (18.9–6,30,000 $n = 3$)	0.91	>120	14.5	1.91	4500	1540	1800	5000	2.92	41.37	438.4
9c	2.90 (1.07–7.83, $n = 5$)	>7290 (2650–20,100, $n = 4$)	0.58	>120	13	2.07	2100	1720	>10,000	>10,000	2.4	41.37	424.4
9d	3.76	>10,000	181% @ 1	78.1	10.4	2.80	4910	NT	>10,000	>10,000	2.84	50.6	440.56
9e	3.82	3000	NT	10	30	1.54	2110	NT	1100	>10,000	2.93	50.6	436.48
9f	4.44 (0.277–71.0, $n = 2$)	>10,000	NT	<3.2	45.8	0.80	>5190	NT	1300	7900	2.8	50.6	472.46
9g	10.5	3020 (1950–4700, $n = 2$)	NT	<3.2	25.9	1.00	4530	NT	100	8700	3	50.6	504.47
10a	2.79	3880	NT	8.19	8.1	3.17	177	NT	1700	>10,000	3.27	70.83	528.57
10b	5.74	8870	217% @ 10	7.06	17.7	2.50	3810	NT	1100	>10,000	2.4	70.83	480.53
14	26.9	NT	NT	>120	0.2	1.02	>4590	NT	>10,000	8200	1.95	50.16	410.4

NT—not tested; GlyT1 K_i values are given in nM units, with standard error of the mean and number of determinations indicated in parentheses. GlyT2 IC_{50} values are given in nM units. Both GlyT1 and GlyT2 values were determined as previously described in Refs. 6,7 CSF Glycine ED200 values represent the dose that doubles endogenous (baseline) levels of glycine in rat csf following subcutaneous administration of a test compound at a 90 min time point, with 95% confidence limits in parentheses. hMic $t_{1/2}$—compound half-life in human microsomes given in minutes. MDCK_AB_C—apparent permeability through MDCK cell membranes in units of 10–6 cm/s, corrected for background, at an initial concentration of 2 μM. MDR ratio is MDR_C_BA_AB divided by MDCK_C_BA_AB, where the ratio of permeation in the BA direction divided by the AB direction in MDR over-expressing cells is compared with the value in MDCK cells not over-expressing MDR. Dofetilide K_i values are given in nM units for displacement of radiolabeled dofetilide from HERG I_{Kr} channels expressed in HEK293 cells. HERG IC_{50} values given in nM units for block of HERG current in patch clamp measurement. *c* Log *P*, Polar area (calculated topological polar surface area), and Mol wt (molecular weight).

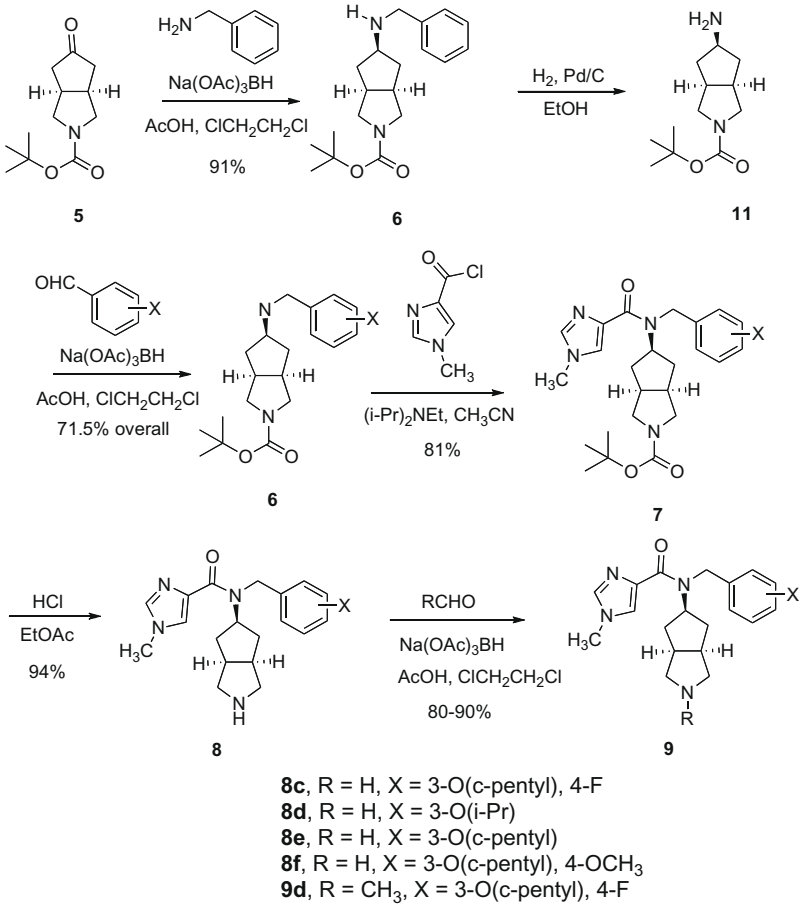


Scheme 1. Preparation of compounds **8**–**10**.

of the nitrogens into a five-membered ring. In addition, we hoped its increased lipophilicity would address the poor permeability of **4**, indicated by its MDCK_C_AB value of 0.5 (where a value >10 denotes good permeability to facilitate brain penetration). We began by attaching the requisite benzylamine and imidazole amide functions as shown in Scheme 1. We chose benzylamines substituted in the meta-position as in **4**. In some cases, the synthesis required addition of an appropriately substituted aldehyde to the 5-amino-(octahydro-cyclopenta[*c*]pyrrole) ring system, as shown in Scheme 2. We focused on 3-alkoxy-substituted benzylamines to enable expansion of the SAR. The initial N–H compounds, **8**, generated by deblocking compounds **7**, have potent GlyT1 inhibitory activity, as well as good selectivity over the type 2 glycine transporter (GlyT2), as shown in Table 1. In order to achieve this potent GlyT1 inhibitory activity, electron-withdrawing substituents are favored, but not required. For example, addition of a fluorine at position 4 to the 3-*O*(c-pentyl) compound **8e** to afford compound **8c** improves GlyT1 affinity. Addition of a 4-methoxy substituent, as in compound **8f**, on the other hand, abolishes activity. We prepared the endo isomer, compound **14**, in low yield from the minor isomer formed in the first two steps in Scheme 1, as shown in Scheme 3, and found it to be far less active than the exo isomer **8a**.

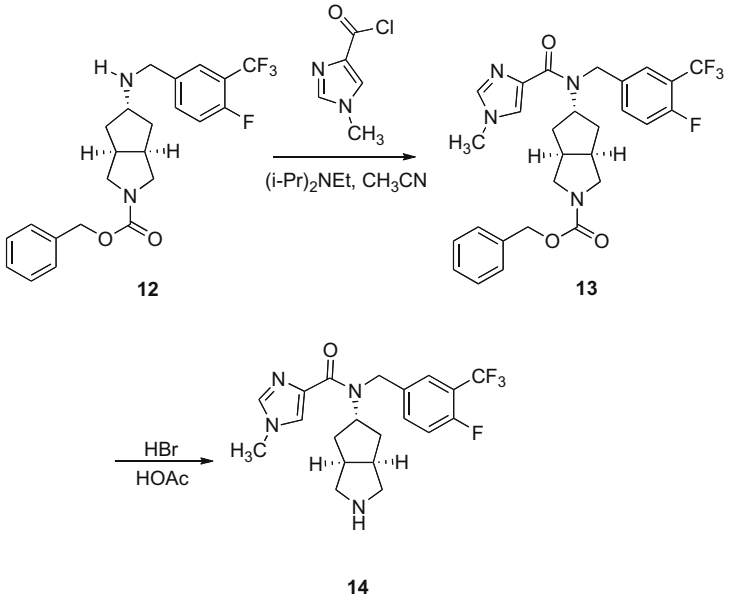
Compounds **8a–f**, however, are poorly permeable through MDCK cell membranes (MDCK_C_AB values <2.5). The two most potent compounds reported here, **8a** and **8b**, show only modest in vivo activity in elevating CSF glycine, giving an estimated ED200 dose, the dose required to double CSF glycine, of a little under 10 mg/kg administered subcutaneously (sc). CSF glycine levels are a measure of glycine that spills over from the CNS compartment upon GlyT1 block at NMDA synapses. In order to achieve clinically relevant doses, we sought compounds with ED200 values less than 1 mg/kg sc. The Pgp transporter, which effluxes drug from the brain compartment, plays only a limited role with these compounds, as indicated by MDR ratios generally less than three as shown in Table 1. In addition, compounds **8a–f** show good stability in the presence of human microsomes (hMic $t_{1/2}$ generally >100 min), and weak inhibition of the HERG-encoded I_{Kr} potassium channel or cytochrome P450 2D6 or 3A4.

Addition of an alkyl group to the ring nitrogen via reductive amination afforded much better MDCK_C_AB values (generally >10), leading to an improvement in in vivo efficacy. For example, compound **9a** shows over 200% elevation of CSF glycine at a dose of 1 mg/kg sc, and compounds **9b** and **9c** show ED200 values of 0.91 and 0.58 mg/kg sc, meeting the goal we had set for this activity. This improvement came at the cost of increased HERG-encoded I_{Kr} block for compounds **9b** and **9c**, and inhibition of cytochrome P450 2D6 and 3A4 for **9b**. Compound **9d**, with the larger *O*-cyclopentyl substituent, reversed this trend, but showed weaker CSF glycine elevation. We tried to decrease I_{Kr} block by reducing the basicity of the ring nitrogen using fluorine substitution, in compounds **9f** and **9g**. While this modification achieved reduced I_{Kr} block, and increased permeability in MDCK cells, it resulted in catastrophic loss of microsomal stability and increased inhibition of cytochrome P450 2D6 and 3A4. Finally, we tried addition of an alcohol substituent by reaction of the N–H compound with an epoxide, expecting decreased basicity and increased polarity to reduce I_{Kr} block. These expectations were unfulfilled, however, in that compound **10a** shows potent binding to I_{Kr}, possibly due to the phenyl ring in proximity to the basic ring nitrogen. Compound **10b** shows only modest activity in elevating CSF glycine, and both compounds show instability in the presence of human microsomes and inhibition of cytochrome P450 2D6.



8c, R = H, X = 3-O(c-pentyl), 4-F
8d, R = H, X = 3-O(i-Pr)
8e, R = H, X = 3-O(c-pentyl)
8f, R = H, X = 3-O(c-pentyl), 4-OCH_3
9d, R = CH_3, X = 3-O(c-pentyl), 4-F

Scheme 2. Preparation of compounds **8**–**9**.



Scheme 3. Preparation of compound **14**.

In summary, compound **9d** represents the best balance of properties in this series, although its in vivo activity in elevating CSF glycine is somewhat less than desired. It also demonstrates that 3-*O*(c-pentyl), 4-F may serve as a surrogate for the 3-trifluoromethoxy group, a substituent widely used by medicinal chemists. It only affords a modest addition of molecular weight (18 mass units) and lipophilicity (0.44 *c* Log *P* units). In the case of compounds **9a** and **9d**, there is a modest decrease in MDCK cell perme-

ability and an increase in MDR ratio. While these results may vary in particular cases, it nonetheless may serve as an isostere for the trifluoromethoxy group for future medicinal chemistry studies.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.12.071.

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