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Novel GlyT1 inhibitor chemotypes by scaffold hopping. Part 2: Development of a [3.3.0]-based series and other piperidine bioisosteres

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ABSTRACT

This Letter describes the development and SAR of a novel series of GlyT1 inhibitors derived from a scaffold hopping approach, in lieu of an HTS campaign, which provided intellectual property position. Members within this new [3.3.0]-based series displayed excellent GlyT1 potency, selectivity, free fraction, and modest CNS penetration. Moreover, enantioselective GlyT1 inhibition was observed, within this novel series and a number of other piperidine bioisosteric cores.

Scaffold hopping has emerged as an attractive approach to rapidly access new chemical space and enable fast-follower programs without the need for expensive and time-consuming HTS campaigns.[1–4] As the negative symptom cluster in schizophrenia remains a critical unmet medical need,[5–7] and GlyT1 inhibition has been shown to be affective toward negative symptoms in Phase II clicnial trials,[8–14] we initiated scaffold hopping efforts to expediently develop novel GlyT1 inhibitors within a crowded intellectual property (IP) space. In a recent Letter, we reported on our preliminary scaffold hopping exercise (Fig. 1) employing GlyT1 inhibitors from Merck and Pfizer, **1** and **2**, respectively, that generated a novel, patented series exemplified by **3**.[15] Notably, **3** was a potent GlyT1 inhibitor with an exceptional DMPK profile, high CNS penetration and robust efficacy in preclinical models of schizophrenia.[15]

Based on work from our labs with $mGlu_1$ NAMs, and the ability of [3.3.0] systems, such as the octahydropyrrolo[3,4-*c*]pyrrole, to effectively mimic piperazines,[16] we focused our attention on the potential bioisoteric replacement of the [3.1.0] system of **2** and **3**, as well as the piperidine of **1**, with a [3.3.0] system, an octahydrocyclopenta[*c*]pyrrole, **5**, and effectively scaffold hop from analogs **4** (Fig. 2). If successful at maintaining GlyT1 inhibitory activity, this

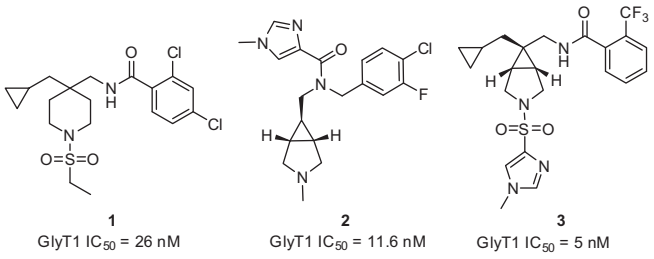

Figure 1. Reported GlyT1 inhibitors **1** (Merck) and **2** (Pfizer), and the novel series **3** (VU0240391), derived from scaffold hopping.

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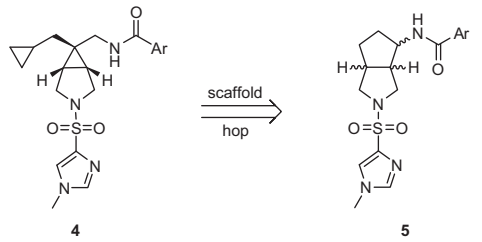
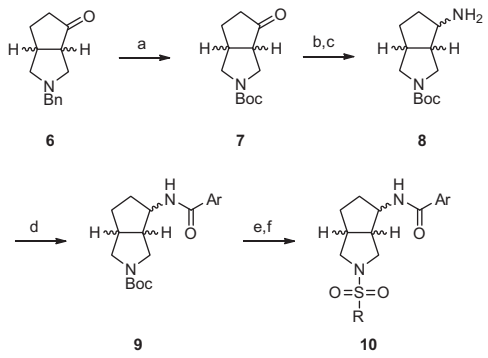


Figure 2. Envisioned scaffold hopping from the novel series **4** to a [3.3.0]-core, an octahydrocyclopenta[*c*]pyrrole, **5** .



Scheme 1. Reagents and conditions: (a) Boc_2O, $Pd(OH)_2/C$, H_2 (50 psi), EtOH, rt; (b) NH_2OH, MeOH, 100 °C; (c) 'Raney' Ni, H_2 (50 psi), rt; (d) ArCOCl, DIEPA, CH_2Cl_2, 0 °C; (e) 4 N HCl/dioxane, rt; (f) RSO_2Cl, DIEPA, CH_2Cl_2, rt. Overall yields range from 10–34%.

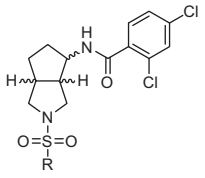
would represent a major strucutral change, eliminating the pendant cyclopropylmethyl moeity while introducing an additional chiral center (providing an opportunity for enantioselective activity).

Synthetically, analogs **10** were initially prepared as racemates via a six step route that proceeded in ~22% overall yield (Scheme 1). Commercial racemic, 90% *cis*-benzylhexahydrocyclopenta[*c*]pyrrol-4(2*H*)-one **6** was subjected to hydrogenation conditions to deprotect the benyl moiety in the presence of Boc_2O to provide **7**. Conversion of the ketone to the oxime, followed by 'Raney' nickel reduction generated the racemic primary amine **8**, which was subsequently acylated with a variety of benzoyl chlorides to deliver analogs **9**. Finally, the Boc moiety was removed with HCl, and the secondary pyrrolidine nitrogen capped with various sulfonyl chlorides to afford analogs **10**.

Initially, we held the 2,4-dichlorobenzamide constant and surveyed a wide-range of sulfonamides in analogs **11** (Table 1). Unlike the piperdine **1** and [3.1.0] series **3**, few sulfonamide moieties were tolerated. Ethyl (**11a**) and propyl congeners (**11b**) that were very potent in the piperidine series **1**, afforded inactive compounds (GlyT1 IC_{50} > 10 μM). Aryl and heteroaryl analogs, such as **11d**–**11f**, were also devoid of GlyT1 activity. Only the *N*-methyl imidazole (**11g**) and the *N*-methyl triazole (**11h**) derivative were active,[15] both displayed low nanomolar potency (GlyT1 IC_{50}s of 25 nM and 15 nM, respectively) and were selective versus GlyT2 (IC_{50} > 30 - μM). Based on the disposition previously noted for the *N*-methyl imidazole sulfonamide in **3**, we prepared a second library held the *N*-methyl imidazole sulfonamide moiety constant, and surveyed a broader range of amides in analogs **12** (Table 2).

The SAR was far more shallow than in the case of **3**,[15] with the 2,4-dichlorobenzamide (**11g**/**12a**) possessing optimal potency. Other analogs such as the 2-triflouromethylbenzamide (**12b**) and the 2-chlorobenzamide (**12c**) were respectable, with GlyT1 IC_{50}s of 112 ± 6 nM and 115 ± 18 nM, respectively. The vast majority of other substitution patterns afforded a considerable loss in potency (GlyT1 IC_{50}s from 631 nM to 10 μM), as did a cyclohexyl amide congener **12l** (GlyT1 IC_{50} = 617 nM). To ensure that the major structural change in scaffold hopping from **1** to **3** to **12** did not alter the competitive mechanism of action of GlyT1 inhibition, we evaluated the affect of **12b** on enzyme kinetics of [^{14}C]-glycine transport. As shown in an Eadie–Hoffstee plot (Fig. 3), this [3.3.0] series, represented by **12b**, competitively inhibits the enzyme kinetics of [^{14}C]-glycine transport. Thus, this series is competitive

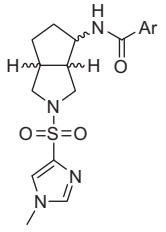
Table 1
Structures and activities of analogs **11**



Compound	R	GlyT1 IC_{50}[a] (μM)	GlyT2 IC_{50}[a] (μM)
11a		>10	>30
11b		>10	>30
11c		>10	>30
11d		>10	>30
11e		>10	>30
11f		>10	>30
11g		0.025	>30
11h		0.015	>30

[a] IC_{50}s represent single determinations performed in duplicate.

Table 2
Structures and activities of analogs **12**



Compound	R	GlyT1 IC_{50}[a] (μM)	GlyT2 IC_{50}[a] (μM)
12a (**11g**)	2,4-diClPh	25	>30
12b	2-CF_3PH	112[b]	>30
12c	2-ClPh	115[b]	>30
12d	2,4-diFPh	926	>30
12e	2,6-diFPh	631	>30
12f	2-FPh	1815	>30
12g	3-FPh	>10,000	>30
12h	4-FPh	2215	>30
12i	3,4-diFPh	1569	>30
12j	4-ClPh	1029	>30
12k	3,4-diClPh	891	>30
12l		617	>30

[a] IC_{50}s represent single determinations performed in duplicate.
[b] The average of four determinations performed in duplicate.