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Viewpoint

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# ACS Chemical Neuroscience Molecule Spotlight on RG1678

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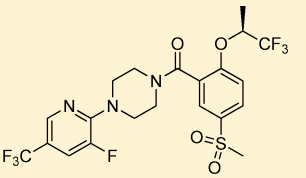
**ABSTRACT:** RG1678 is a glycine transporter-1 inhibitor currently in Phase III trials for the treatment of the negative symptoms of schizophrenia and is being developed by Roche (in combination with Chugai). Recent Phase II data shows that RG1678 is effective in reducing the negative symptoms when given in combination with second generation antipsychotics.




RG1678
A novel GLYT1 Inhibitor

**KEYWORDS:** *Schizophrenia, negative symptoms, RG1678, glycine transporter-1 inhibitor, GlyT1*

Schizophrenia (SZ) is a devastating disease afflicting nearly 1% of the adult population worldwide. The disease causes a significant burden on the medical community with some estimates as high as $60+ billion per year in direct/indirect costs and >$20 billion in direct costs for the healthcare industry (2002 numbers).[1] The staggering costs of this disease are primarily due to the fact that those affected begin early in their life and thus carry this burden throughout their lives. SZ is equally distributed between men and women, with an earlier onset in males. Although there has been significant progress for the treatment of SZ, the current therapies only treat the positive symptoms (hallucinations/delusions) associated with the disease. Unfortunately, the negative symptoms which are associated with disruptions in normal emotions/behaviors, lack of pleasure in everyday life, and poor personal and social functioning are poorly treated with the mainstay treatment options. A new paradigm for treatment of SZ which has emerged is the evidence that hypofunction of *N*-methyl-D-aspartate (NMDA) receptor function plays a role in the pathophysiology of SZ.[2] Thus, restoration of normal NMDA function could represent a novel mechanism for the treatment of SZ. One approach is to elevate the levels of extracellular glycine by inhibition of the glycine transporter-1 (GlyT1), which is coexpressed with the NMDA receptor, thereby enhancing NMDA receptor function and normalizing glutamate neurotransmission.

There has been significant research into the discovery of novel GlyT1 inhibitors for clinical applications.[3] One of the most advanced GlyT1 inhibitors being assessed in clinical studies is RG1678, a novel compound from Roche (Genentech). Roche has recently published a detailed report on the SAR and medicinal chemistry effort directed toward RG1678.[4] The preclinical research started with compound **9**, which progressed to **42**, and finally to RG1678 (Figure 1). All three compounds show excellent potency against GlyT1 with >100-fold selectivity versus GlyT2. However, the initial compound **9** showed significant off-target activity against the hERG channel (600 nM, 37-fold selectivity). The hERG profile could be improved by substituting the cyclopropylmethyl group with the 2-trifluoropropyl group in **42** (hERG: 1.2 $\mu$M, 57-fold selectivity); however, the brain/plasma ratio as assessed in a mouse was dramatically reduced. Finally, both of these parameters could be improved by substituting the cyano group with a trifluoromethyl and separation of the enantiomers leading to RG1678 (hERG: 17 $\mu$M, >500-fold selectivity).[4] RG1678 represents a novel and selective GlyT1 inhibitor that exhibits excellent pharmacokinetic and efficacy profiles in preclinical animal models.

In late 2010, Roche (Genentech) announced results from an 8-week, phase II clinical study of RG1678.[5] The study was a multicenter, randomized, double-blind, parallel group consisting of 323 patients comparing to placebo, where the patients received three dose regimens of RG1678 (10, 30, and 60 mg) in addition to a second generation antipsychotic. Efficacy was measured in a primary end-point (change from baseline at week 8 in the negative symptom factor) as assessed by PANSS (Positive and Negative Syndrome Scale) and a secondary end point as an improvement in negative symptoms in the CGI (Clinical Global Impression) and in the PSP scale (Personal and Social Performance). RG1678 showed statistically significant improvement in both primary (10 and 30 mg groups) and secondary end points (CGI, 10 mg; PSP, 10 mg, trending toward improvement). The 60 mg dose did not show any improvement in either end point. The safety profile for RG1678 was favorable with all three doses being well tolerated. There was a noted dose-dependent reduction in hemoglobin; however, this was not considered clinically relevant. There was an increase in patient study withdrawal due to adverse events from the placebo and 10 mg dose (1%) to the 30 mg dose (9%) and 60 mg dose (10%). However, overall withdrawal due to any reason was similar between all groups.[5]

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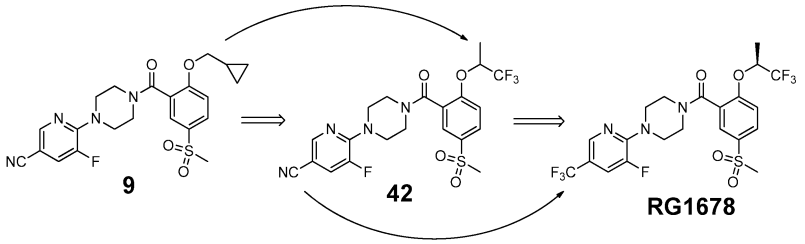


| Cmpd | hGlyT1 (nM) | hGlyT2 (μM) | hERG (μM) | B/P mouse |
|---|---|---|---|---|
| **9** | 16 | >30 | 0.60 | 0.1 |
| **42** | 21 | >30 | 1.2 | 0.04 |
| **RG1678** | 30 | >30 | 17 | 0.5 |

**Figure 1.**

The positive results for RG1678 could mark a significant turning point in the treatment of SZ, as this compound would allow a first-in-class treatment option for the negative symptoms, which are frequent problems with SZ patients. The pivotal phase III trial has commenced, and the entire SZ community will be waiting for this promising molecule to deliver a potentially disease changing treatment in patients.

## AUTHOR INFORMATION

### Notes

The authors declare no competing financial interest.

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