Cognitive deficits are trait markers in schizophrenia and the improvement of these dysfunctions has been considered as a new frontier of treatment in this disease. A current model for the patophysiology of schizophrenia states that N-methyl-D-aspartate receptor (NMDAR) hypofunction leads to a dysregulation of gamma-amino butyric acid (GABA) fast-spiking interneurons, consequently disinhibiting pyramidal glutamatergic output and disturbing signal-to-noise ratio. In this way, the modulation of the glutamate activity might constitute a highly promising target for future therapeutic interventions of this disease. In the present review, we discuss key regulatory elements for glutamatergic neurotransmission and provide new insights into their potential role in developing pharmacological treatments. Also, we emphasize the role of certain chemical families as potential sources of new lead compounds with affinity for metabotropic glutamate receptors (mGluRs) with cognitive enhancing properties.