Key research objectives: Comparison of the antipsychotic potential of 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) and olanzapine on three independent levels – behavioural, molecular and neurochemical – using animal models of schizophrenia.

The results will provide answers to the following questions: Does administration of 1MeTIQ to healthy rats improve their memory and the speed of learning? Is 1MeTIQ capable of reducing (if so, to what extent) or eliminating cognitive deficits induced by NMDA receptor antagonists? Does 1MeTIQ show affinity for L-type calcium channels and does it have influence on their density in the rat brain?

Schizophrenia is a serious chronic neuropsychiatric disorder that is characterized by three different types of symptoms: positive (such as hallucinations), negative (social withdrawal) and cognitive disruptions [Elvevag and Goldberg 2000]. Currently available antipsychotic drugs efficiently alleviate positive symptoms but their influence on reducing negative symptoms and cognitive impairments remains insufficient [Carpenter and Koenig 2008]. Thus, considerable research effort is exerted in searching for drugs with higher efficacy in relieving negative symptoms and cognitive deficits associated with schizophrenia. This research topic was selected as there is an urgent need to develop new, more efficient pharmacotherapies for schizophrenia since the negative symptoms as well as disrupted cognitive functions are directly associated with patients' social functioning, independent living skills and the quality of life. Both dopamine agonists (e.g. amphetamine) and non-competitive NMDA antagonists (e.g. PCP and ketamine) can induce psychosis, negative symptoms and cognitive deficits related to schizophrenia [Neill et al. 2010]. Due to producing aforementioned effects, NMDA antagonists are used to mimic schizophrenia in rodents. Olanzapine is an atypical antipsychotic that blocks 5-HT_{2a}, D_2, muscarinic and histamine receptors [Bymaster et al. 1999]. Olanzapine improves some cognitive functions, such as executive functions, but fails to produce positive effects in case of working memory or visual memory [Cuesta et al. 2001].

Our previous research results provided evidence that 1MeTIQ exerts modulatory effects in many neurotransmission systems (dopaminergic, serotonergic, noradrenergic and glutamatergic) in the rat brain. This compound has a strong impact on the dopaminergic system – it shows antioxidant properties (suppressing free radical production) and acts as a free radical scavenger [Ankiewicz-Michaluk et al. 2001; 2003]. Moreover, 1MeTIQ reduces excitotoxicity induced by glutamate and MK-801 (NMDA receptor antagonist) [Antkiewicz-Michaluk et al. 2006; Kuszczyk et al. 2010]. Therefore, 1MeTIQ influences the dopaminergic and glutamatergic systems in the brain, which are both implicated in schizophrenia [Seeman 1987; Stone et al. 2007; Kristiansen et al. 2007]. The variety of modulatory, mild effects produced by 1MeTIQ involving few neurotransmission systems in the mammalian brain raise hope that it will be used in clinical treatment in the future. 1MeTIQ may prove to have more beneficial effects than classical neuroleptics which induce EPS and clozapine which causes marked sedation.

The project was designed adopting a comprehensive approach, as the research will include a wide range of modern behavioural tests, that will allow to obtain detailed assessment of the influence of the tested substance on various types of memory and the learning process in animals. Complementing behavioural tests with biochemical and radiological studies will provide a complete picture of the changes occurring the brain after administering NMDA antagonists and 1MeTIQ. *In vivo* microdialysis experiments will enable us to measure changes in neurotransmitter release into the extracellular space in living animals in real time.

The research included in the project represents the first attempt to assess the antipsychotic potential of 1MeTIQ.