

Date of submission:  
Project title:

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## SINAPSE PhD Project Proposal Template for PhDs starting in 2009

SINAPSE Centre (i.e. primary university to which this studentship will be attached\*):

University of Glasgow

First supervisor: contact details

Name: Andrew Sutherland  
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Second supervisor: contact details

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Speciality of first supervisor:

Chemistry

Speciality of second supervisor:

Radiochemistry, Imaging

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### PROJECT

Title:

New SPECT And PET Imaging Agents For Metabotropic Glutamate 2/3 Receptors In Schizophrenia

Planned start date (month/year):

October 2009

Likely background of suitable student (eg. Neuroscience, MR Physics, Chemistry, Psychology) and essential skills required prior to starting this PhD:

This proposal requires a student with a chemistry degree and some background training in medicinal chemistry. Practical experience in a synthetic laboratory along with the ability to purify and characterise compounds are all essential skills.

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\*usually this would be the university in which the first supervisor is based.

**Summary of proposed project (approximately 200 words):**

Schizophrenia is a devastating illness that can affect as much as 1% of the population in developed countries. Antipsychotic drugs that target the dopamine receptor have been developed, however, these do not treat all the symptoms and have significant side effects. There is now evidence for glutamatergic dysfunction in schizophrenia and thus, the development of metabotropic glutamate Glu2/3 (mGlu2/3) receptor agonists could overcome the limitations of existing treatments [1]. To exploit mGlu2/3 for the treatment of schizophrenia, biomarkers to probe glutamatergic transmission are urgently needed. The aim of this project is to develop new imaging agents for the mGlu2/3 site that could be used to evaluate novel glutamatergic drugs in vivo and measure treatment response. Moreover, we plan to design and synthesise a high affinity precursor with multi-labelling positions that could be used for either PET or SPECT imaging. The SPECT studies involved with this project will be carried out in collaboration with Dr Sally Pimlott from the Glasgow Neuroimaging Research Group. The project will begin with the multi-step synthesis of a small library of novel diazepam-2-ones, compounds with structural motifs known to have affinity with mGlu2/3 [2]. Following biological evaluation of these, the most potent analogue with multi-labelling positions will be selected for development as both a PET and SPECT tracer. Successful tracers will then be used to study and develop a better understanding of glutamatergic transmission in schizophrenia.

**Key references (up to five):**

1. C. M. Adler, A. K. Malhotra, I. Elman, T. Goldberg, M. Egan, D. Pickar and A. Breier, Comparison of Ketamine-Induced Thought Disorder In Healthy Volunteers And Thought Disorder In Schizophrenia, *Am. J. Psychiatry*, 1999, **156**, 1646-1649.
2. T. J. Woltering, J. Wichmann, E. Goetschi, G. Adam, J. N. C. Kew, F. Knoflach, T. M. Ballard, J. Huwyler, V. Mutel and S. Gatti, Synthesis And Characterisation of 1,3-Dihydrobenzo[b][1,4]diazepin-2-one Derivatives: Part 3. New Potent Non-competitive Metabotropic Glutamate Receptor 2/3 Antagonists, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2725-2729.

**In what way does this PhD proposal meet the SINAPSE criteria as described in the call for proposals? (100 words)**

This is a multidisciplinary project that brings together a variety of imaging expertise such as chemists, clinical physicists and neuroscientists at two centres of the SINAPSE network. Furthermore, the student working on this project will gain experience in a number of key disciplines, which are fundamental for developing a career in neuroimaging. This proposal addresses a key objective of SINAPSE, the development of novel radiotracers as tools for neuroimaging. In particular, this work will generate a precursor that can be used for either PET or SPECT imaging of schizophrenia.

**Please state the name of the local SINAPSE Centre Lead with whom you have discussed this project (Leads are listed on the Call for Proposals, applications submitted without prior discussion will not be considered.):**

Donald Hadley