New SPECT and PET Imaging Agents for Metabotropic Glutamate 2/3 Receptors in Schizophrenia

Lynne Gifillan[a], Sally Pimlott[b], Lutz Schweiger[c] and Andrew Sutherland[a]

[a]WestCHEM, Department of Chemistry, Joseph Black Building, University of Glasgow, Glasgow, G12 8QQ.

[b]West of Scotland Radionuclide Dispensary, University of Glasgow and North Glasgow University Hospital NHS Trust, Glasgow, G11 6NT.

[c]University of Aberdeen, School of Medical Sciences, John Mallard Scottish P.E.T. Centre, Foresterhill, Aberdeen, AB25 2ZD.

BACKGROUND

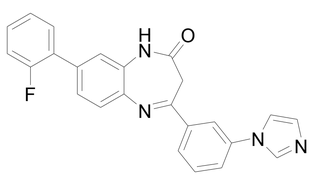
- Schizophrenia is a chronic and severe mental disorder that is thought to effect up to 1% of the population in developed countries.
- Currently, schizophrenia is treated by antipsychotic drugs which target dopamine receptors. However, more recent research has given rise to the glutamate hypothesis of schizophrenia, which suggests that schizophrenia is caused by irregularities in glutamate synaptic function.[1]
- Group II metabotropic glutamate receptors (mGluR2/3) have been shown to be of use in the treatment of schizophrenia as mGluR2/3 agonists have produced positive results in clinical trials.[2]
- It would be highly advantageous to be able to image these receptors as this would allow for a greater understanding of the role of mGluR2/3 in schizophrenia and would also be useful in evaluating new drugs *in vivo* and measuring treatment response.

AIMS AND OBJECTIVES

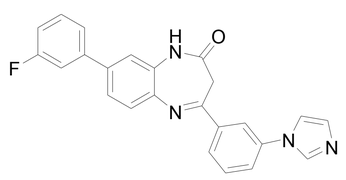
- This project aims to produce both SPECT and PET imaging agents for mGluR2/3.
- Another key objective of this project is the development of precursors which can be used for both SPECT and PET. Thus, potential radiotracers will also be designed and synthesised with multi-labelling sites .

PREVIOUS WORK

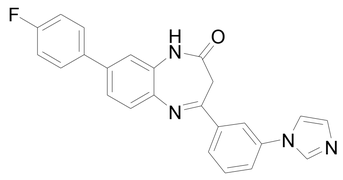
- Work carried out by Woltering and co-workers in 2008 identified a library of 1,3-dihydro-benzo[*b*][1,4]diazepin-2-ones that act as non-competitive antagonists of mGluR2/3 with low nanomolar affinity assessed by displacement of [3H]-LY354740 binding to rat mGluR2.[3]
- Compounds containing a halogenated phenyl group provide a good starting point for the development of SPECT imaging agents containing an ^{123}I radiolabel.



IC_{50} = 12 nM

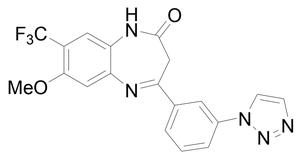


IC_{50} = 25 nM

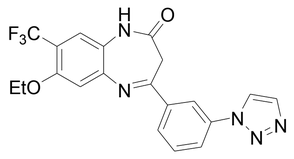


IC_{50} = 17 nM

- Compounds containing trifluoromethyl and alkoxy substituents are of potential use in the development of PET imaging agents containing either a ^{11}C or ^{18}F radiolabel incorporated in the alkoxy group.



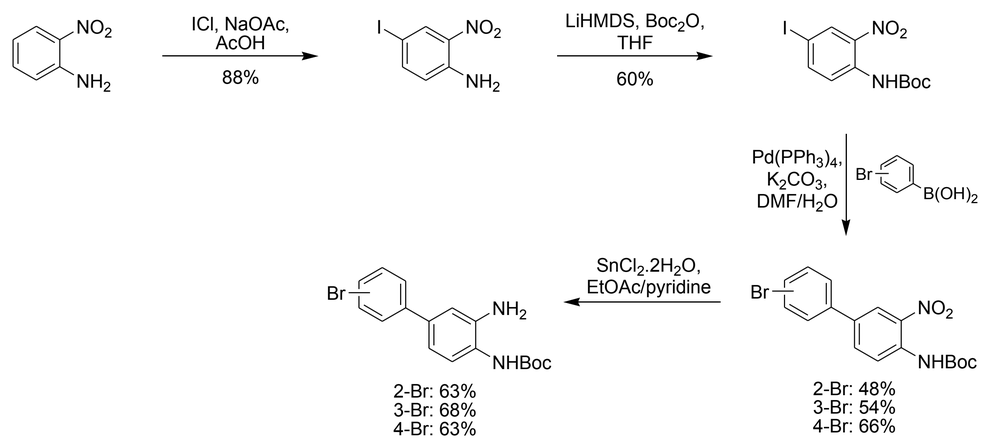
IC_{50} = 29 nM



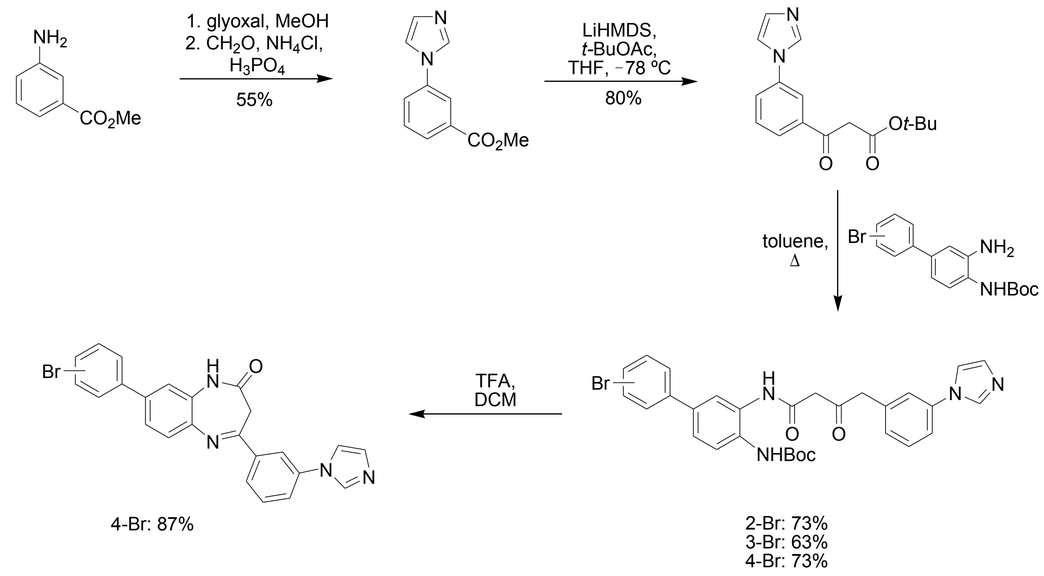
IC_{50} = 7 nM

SYNTHESIS OF SPECT COMPOUNDS

- The first stage of work on this project was the synthesis of a small library of benodiazapine-2-ones incorporating the late stage introduction of iodine.
- The 1,2-diaminobenzene fragments were synthesised by a four step procedure starting from commercially available 2-nitroaniline.

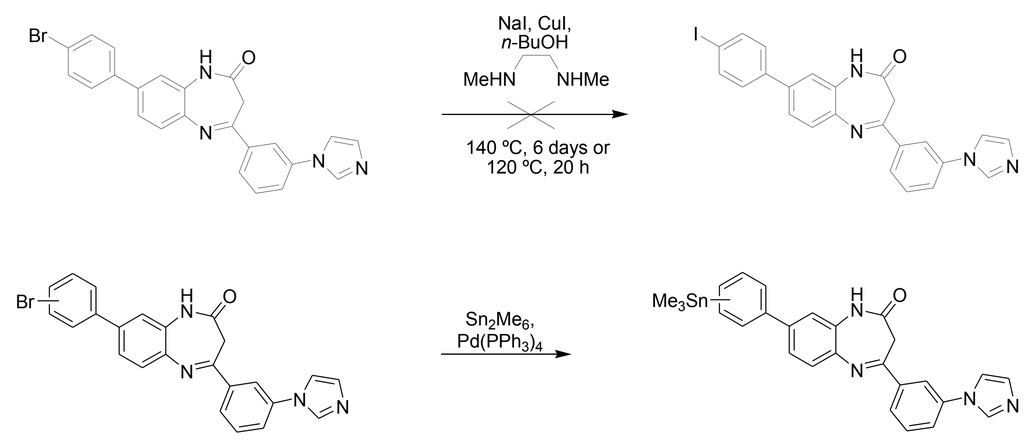


- The β-keto ester fragment was synthesised in two steps from methyl 3-aminobenzoate.
- The benzodiazapin-2-one core was then formed by the condensation of the 1,2-diaminobenzenes with the β-keto ester followed by treating with acid.



HALOGEN EXCHANGE

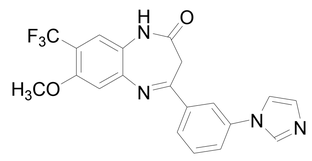
- Initial attempts to perform the final halogen exchange step using a copper catalysed reaction were unsuccessful.

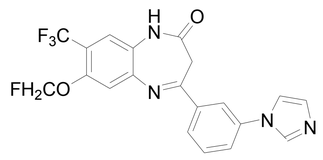


- A new approach has been proposed which involves first converting the aryl bromide to an aryl stannane before performing an oxidative iododestannylation reaction.
- This method could also be used to form the radiolabeled version using [I^{123}]NaI in the final step.

FUTURE WORK

- Upon successful completion of the halogen exchange step these compounds will undergo biological testing to determine their binding affinity with mGluR2/3.
- The most potent analogues will be radiolabeled and evaluated as potential radiotracers to be used in SPECT imaging of mGluR2/3.
- Work will commence on the synthesis of a small library of compounds to be evaluated as potential PET imaging agents following a synthesis which allows for the late stage inclusion of either a ^{11}C or ^{18}F radiolabel in the alkoxy substituent.





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ACKOWLEDGEMENTS

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