Contribution to the synthesis of positive allosteric modulators of AMPA receptors for potential use in the early diagnosis of neurodegenerative diseases.

Lesenfants, C. [a]; Goffin, E. [a]; Pirotte, B. [a]; Dammicco, S. [b]; Francotte, P. [a]

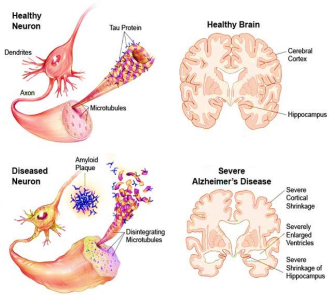
[a] *CIRM, Laboratoire de Chimie Pharmaceutique, University of Liège, Belgium;* [b] *CRC, Centre de Recherches du Cyclotron, University of Liège, Belgium.*

Alzheimer's Disease and AMPA Receptors

Alzheimer's Disease (AD) is the cause of 60-70% of dementia cases. Dementia is a syndrome marked by unnatural deterioration in cognitive function: memory, thought and behavior (Figure 1).[1]

The World Health Organization (WHO) estimated that 48 million people worldwide were suffering from dementia in 2015, with 75 million affected foreseen for 2030.[1]

It continues to be of major economic and social cost, as current treatments are limited and do not ultimately halt the progress of the disease.[2]



AMPA receptors (**AMPARs**) represent one of three sub-groups of ionotropic glutamate receptors and are found in the majority of fast central nervous system excitatory synapses.[3]

AMPARs are recognised for their involvement in **long-term potentiation** (LTP), linked to the processes of learning and memory. Indeed, their increased expression at synapses has been shown to reverse AD related memory and learning deficits.[4a,b]

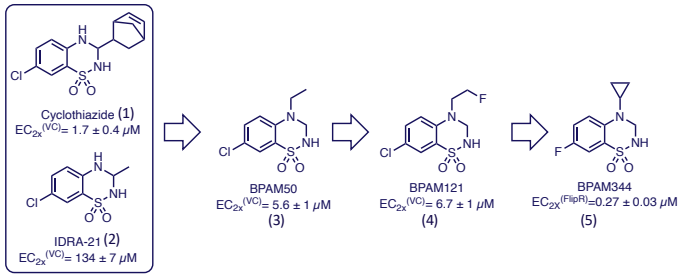
AMPARs represent a valid cognitive enhancer/neuroprotective target to combat AD.

AMPARpams Benzothiadiazine 1,1-dioxides

Of the many drug target methods available for AMPARs, AMPA positive allosteric modulators (AMPARpams) are of interest to counteract the symptomatic progress of AD.

AMPARpams are able to potentiate AMPA signals in the presence of glutamate, while without the endogenous transmitter they have no effect. This reduces possibility of neurotoxicity that plague AMPAR agonists.

Benzothiadiazine 1,1-dioxides (a class of AMPARpams based on the structure of two well-known AMPA potentiators: cyclothiazide and IDRA-21) have been a focal point of Pirotte group research. This led to the discovery of lead compounds BPAM50 (**3**), BPAM121 (**4**) and BPAM344 (**5**).[5a,b,c]



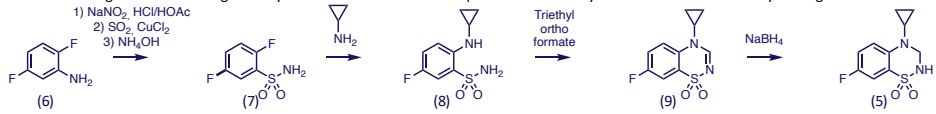
Synthesis of Cold and Hot BPAM344

Our goal is the preparation of radiolabelled AMPARpams such that *in vivo* positron emission tomography (PET) can be used to highlight where the benzothiadiazine 1,1-dioxide family bind within the brain. Amongst all the radionuclides that could be used, stands ^{18}F which has an interesting half life around 110 min. This half time is sufficient to complete reactions steps necessary to reach the radiolabelled pams and *in vivo* analyses.

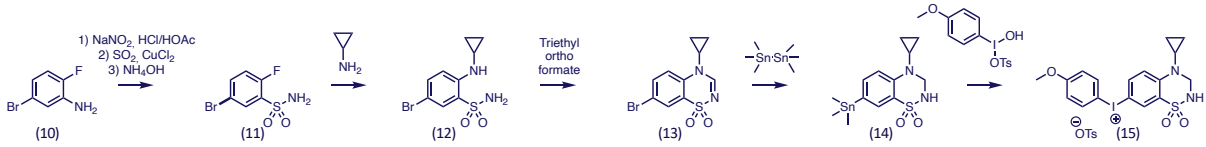
BPAM121 was first identified as a perfect candidate for radiolabeling investigations. As lead **BPAM121** already possessed an aliphatic fluorine atom, radiolabeling with ^{18}F did not pose a possible alteration in compound activity. This study was achieved in partnership with the CRC Cyclotron team (ULiège) and led to a publication. [6]

Considering its high potency, BPAM344 was also pointed as a good candidate. However, the ^{18}F-labelling experiments for this compound revealed much more challenging, as its fluorine atom is aromatic. Thanks to the recent advances in organic synthesis, this kind of reaction is now possible using an iodonium intermediate. The present work is focused on the preparation of the precursor which will be radiolabeled at the cyclotron.

Synthesis began from 2,5-difluoro-aniline (**6**) first reacting with nitrous acid in presence of SO_2 and $CuCl_2$, before addition of ammonia to afford the corresponding sulfonamide. Then, reaction with cyclopropylamine followed by the thiadiazine ring formation using triethyl orthoformate and subsequent reduction by means of sodium borohydride gave cold BPAM344.

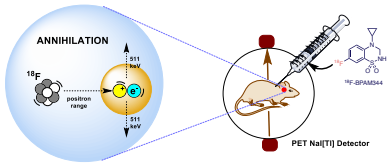


To reach ^{18}F-BPAM344, an iodonium precursor (**15**) was designed. After diazotization of the 5-bromo-2-fluoroaniline **10**, the resulting sulfonamide **11** reacted with cyclopropylamine. Cyclisation of compound **12** occurred as expected with triethylorthoformate. The bromine atom at the 7-position was substituted using hexamethylditin to afford **14** which was then converted into the iodonium precursor **15**.



Future Work: ^{18}F Labelling to Obtain ^{18}F-BPAM344

- Design and synthesis of compound **15** was successfully undertaken for ^{18}F labelling experiments, alongside resynthesis of cold reference sample of BPAM344.
- The ^{18}F substitution of compound **15** and obtention of ^{18}F-BPAM344 will be carried and optimized out at the ULiège Cyclotron Research Centre.
- Following optimization of the ^{18}F-BPAM344 synthesis, this compound will then be injected into mice and/or rats and PET scans carried out to achieve the aim to discover the pharmacological action of this family of potential AD active drug leads.



References

1.WHO, Dementia Fact Sheet, http://www.who.int/mediacentre/factsheets/fs362/en/ (Oct. 2021); 2. Alzheimer's Disease International, World Alzheimer Report 2020: Design, dignity, dementia: Dementia-related design and the built environment (2020) ; 3. S. F. Traynelis *et al., Pharmacol. Rev.*, **62**, **405-496** (2010) ; 4. a) J. Keifer, Z. Zheng, *Eur. J. Neurosci.*, **32**, 269-277 (2010); b) L. Gao *et al.*, J. Neurochem., **136**, 620-636 (2016) ; 5. a) P. Francotte *et al.*, *J. Med. Chem.*, **50**, 3153-3157 (2007); b) P. Francotte *et al.*, *J. Med. Chem.*, **53**, 1700-1711 (2010); c) A.B. Nørholm et al., J. Med. Chem., **56**, 8736–8745 (2013) ; 6. R. Ding *et al.*, *Molecules*, **16**, 5665-5673 (2011) ; 6. Manos-Turvey et al., *ChemMedChem*, **14**, 788-795 (2019).