Radiosynthesis of Novel Histamine H3 Tracers

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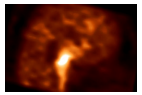
Background

PET/SPECT brain imaging can be used for: patient diagnosis and management of treatment, studying the pathology of neurological disorders and development of therapeutic treatments for neurological disorders.

The Glasgow Neuroimaging group has a strong track record in the development and use of novel SPECT tracers.

Likewise, the John Mallard PET Centre at Aberdeen has established a track record in the development of PET imaging agents.


The two groups are collaborating as part of a TMRC project to develop tracers for the histamine H3 receptor, to facilitate therapeutic drug development.

The H3 receptor is thought to be implicated in numerous neurological disorders including Alzheimer's Disease and ADHD. [1-4] Selective histamine H3 antagonists are currently being developed as novel treatments for these disorders.

Our target SPECT compounds (**1**, **2** and **3**) were identified from a library of compounds that have high affinity for the histamine H3 receptor.

Methods

Radiolabelling via electrophilic iododestannylation with chloramine-T
To a V-vial containing 10-80MBq of Na123I in 50µl of 0.05 M NaOH was added 20µl of 1M HCl, 0.3 mg of Precursor **1a**, **2a** or **3a** in 100 µl ethanol, and 50µl of 1 mg/ml chloramine-T solution. The reaction was mixed via vortex and incubated at room temperature for 5 min. The reaction mixture was analysed by HPLC and/or purified by preparative HPLC to determine the radiochemical yield.

Radiolabelling via electrophilic iododesilylation with chloramine-T
To a V-vial containing 10-80MBq of Na123I in 50µl of 0.05 M NaOH was added 0.3 mg of Precursor **1b**, **2b** or **3b** in 100µl glacial acetic acid, and 50µl of 5 mg/ml chloramine-T solution in glacial acetic acid. The reaction was mixed via vortex and incubated at 65˚C for 20-25 min. The reaction mixture was analysed by HPLC.

Table 1: Summary of radiolabelling reactions for the syntheses of Compounds **1,2,3**

Method of radioiodination	Precursor	Radiochemical Yield (%)	Isolated Radiochemical Yield (%)	Radiochemical purity (%)	Reaction time (mins)
Destannylation	**1a**	71.2 ± 10.1 (n=3)	47.9 ± 2.6 (n=3)	>98	5
	2a	79.5 ± 4.4 (n=4)	59.5 ± 5.5 (n=3)	>98	5
	3a	76.5 ± 4.8 (n=6)	50.5 ± 8.2 (n=3)	>99	5
Desilylation	**1b**	61.4 (n=1)			20
	2b	44.3 (n=1)			25
	3b	9.1 (n=1)			20

Results

The results of the radiolabelling reactions are summarised in Table 1. In all cases, the identity of the purified product was confirmed by co-elution with cold Compounds **1**, **2** and **3.**
The reconstituted 123I labelled compounds in saline solution have been shown to have radiochemical purity > 98% after 46hr of storage at room temperature (n=1 for each compound).

Conclusions

Radiochemical yields are higher and reaction times are shorter using the iododestannylation method. This method has been taken forward to produce tracer for *in vitro* evaluation.

Initial *in vitro* studies have commenced at the Wellcome Surgical Institute, Glasgow in order to confirm *in vitro* specificity and selectivity.

Further *in vivo* animal imaging studies, using our microSPECT (MollyQ 50 scanner), will determine *in vivo* uptake, biodistribution and binding kinetics.

Radiolabelling *via* Br/123I halogen exchange remains to be investigated.

References

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