

- The NanoTek Microfluidic Synthesis System is a modular microfluidic chemistry system with the ability to combine both microscale and macroscale process steps. Modular components give the user maximum flexibility for both discovery and clinical applications.

Preparation of [F-18]Altanserin using the NanoTek® LF

Introduction

In this application note, we describe the use of the NanoTek LF in Discovery Mode to determine the best conditions for the preparation of altanserin¹, a 5HT_{2A} serotonin receptor binding agent.

Equipment

NanoTek LF System
Version 1.3.2 Control Software
Reactor: 2 m X 100 µm

RadioTLC System:

Bioscan AR-2000

[F-18]Altanserin Analysis:

Silica TLC plates
90% acetonitrile/water mobile phase

Reagents:

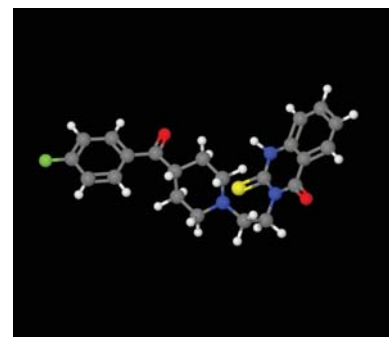
Nitro-altanserin (ABX)
Dimethyl sulfoxide, anhydrous (Acros)
Acetonitrile, anhydrous (Acros)

Results and Discussion

The optimum conditions for altanserin synthesis were determined by running the Nanotek LF in the Discovery Mode and varying precursor concentration, reaction temperature, and reactor residence time (varying flow rate).

The radiosynthesis of altanserin was optimized by determining conditions that maximized radiochemical yield when corrected for radiochemical decay². For radiotracers with longer half lives this effect does not have a major impact. However, for isotopes such as C-11 and F-18 this must be taken into account during the optimization process.

Reported methods for the radiosynthesis of [F-18]altanserin involve the nucleophilic substitution of the nitroprecursor of



altanserin with K[¹⁸F]/Kryptofix2.2.2 in dimethyl sulfoxide (up to 9 mg in 1 ml of DMSO) at 135 °C for 30 minutes or under microwave (150W) for 5 minutes, followed by SepPak and high-performance liquid chromatography (HPLC) purification. Reported overall radiochemical yields ranged from 10-26% at end of synthesis (EOS)^{3,4,5}. Overall synthesis times including HPLC purification varied from 90–114 minutes with high radiochemical purity.

Optimizing reaction conditions using the NanoTek LF involved changing precursor concentration, reaction temperature and reactor flow rate. The NanoTek was setup using the standard Discovery Mode plumbing (see Figure 1). The results of these experiments are shown in Table 1.

Table 1: Radiochemical purity of altanserin under test conditions

Precursor Concentration (mg/ml)	Temperature °C	Residence Time (min)	% Radiochemical Purity
5.0	180	0.79	29.3
5.0	200	0.79	50.7
5.0	220	0.79	38.2
5.0	220	3.14	86.7
10.0	90	0.79	0.0
10.0	100	0.79	0.0
10.0	120	0.79	0.6
10.0	120	0.79	0.0
10.0	120	0.79	0.0
10.0	140	0.79	9.7
10.0	140	0.79	9.7
10.0	180	0.79	40.6
11.8	220	0.52	47.1
11.8	160	0.79	13.4
11.8	200	0.79	47.0
11.8	200	0.79	58.2
11.8	220	0.79	59.5
11.8	200	1.05	60.6

Conclusions

The NanoTek LF system is capable of preparing the serotonin imaging agent in high yield compared to reported literature. The highest radiochemical purity determined in these experiments was >80% at a 5 $\mu\text{l}/\text{min}$ flow rate, however these conditions do not produce the highest yield of final product since the overall processing time is longer than operating at a flow rate of 20 $\mu\text{l}/\text{min}$ in batch mode. A typical radiotlc chromatogram is shown in Figure 2.

Overall the best yields of ~50% overall were obtained using 200-220 $^{\circ}\text{C}$ at 20 $\mu\text{l}/\text{min}$. These are almost double those currently reported in literature. The amount of precursor could also be reduced by almost half of that reported in literature.

References

¹Kam Leung, 3-[2-[4-(4-[¹⁸F]Fluorobenzoyl)-1-piperidyl]ethyl]-2-sulfanyl-3H-quinazolin-4-one. [¹⁸F]Altanserin. In: Molecular Imaging and Contrast Agent Database (MICAD) [database online]. Bethesda (MD): National Library of Medicine (US), NCBI; 2004-2009. Available from: <http://micad.nih.gov>

²Since we are dealing with short-lived isotopes, the optimum conditions for a reaction may not be those that yield the highest radiochemical yield. Since the time it takes to flow the entire solution through the reactor increases with increased residence time (slower flow rates), the yields must be corrected for radiochemical decay when determining optimal conditions.

³Tan P.Z., Baldwin R.M., Soufer R., Garg P.K., Charney D.S., Innis R.B. A complete remote-control system for reliable preparation of [¹⁸F]altanserin. *Appl Radiat Isot.* 1999; 50(5):923-7

⁴Monclus M., Van Naemen J., Mulleneers E., Damhaut P., Luxen A., Goldman S. Automatic Synthesis of [¹⁸F]Altanserin, a Radiopharmaceutical for Positron Emission Tomographic Studies of the Serotonergic Type-2 Receptors. *Clin Positron Imaging.* 1998; 1(2):111-116

⁵Lemaire C., Cantineau R., Guillaume M., Plenevaux A., Christiaens L. Fluorine-18-altanserin: a radioligand for the study of serotonin receptors with PET: radiolabeling and in vivo biologic behavior in rats. *J Nucl Med.* 1991; 32(12):2266-72.

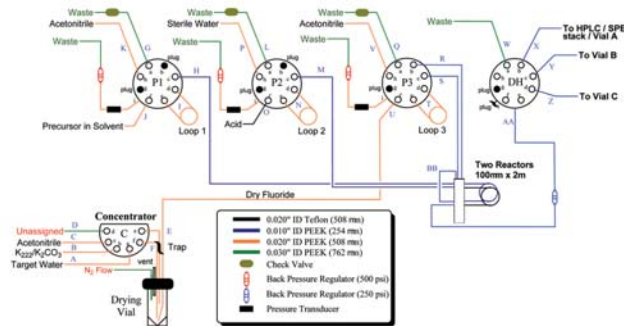


Figure 1: Flow path used for altanserin experiments in Discovery Mode.

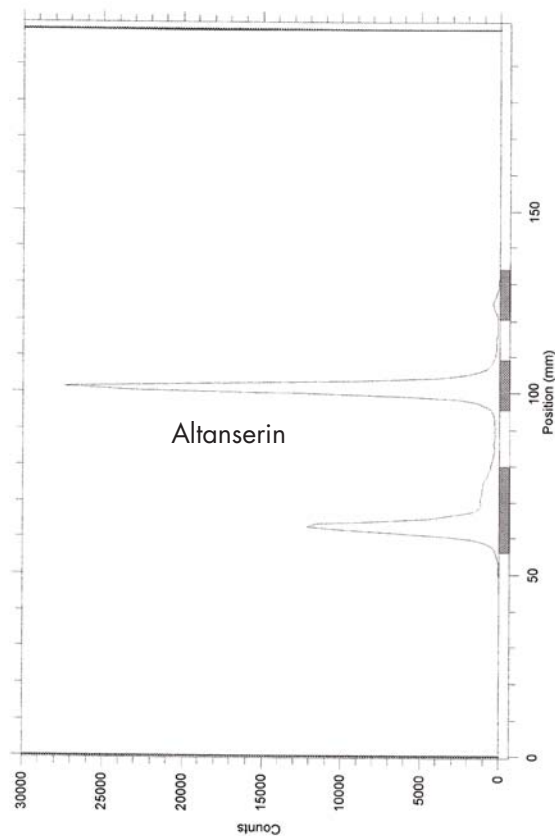


Figure 2: Radiotlc of altanserin reaction. This chromatogram was obtained at a reactor temperature of 200 $^{\circ}\text{C}$, and a flow rate through a 100 x 2 m reactor of 20 $\mu\text{l}/\text{min}$.