# NODAGA- and DOTA-Flurpiridaz derivatives for Myocardial Perfusion Imaging with $^{68}$Ga

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**Introduction:** Myocardial perfusion imaging (MPI) is an important tool in the diagnosis of coronary heart disease. At the moment the SPECT-tracer [$^{99m}$Tc]Sestamibi is the gold standard in clinics. The suitability of [$^{18}$F]Flurpiridaz as a new MPI-agent has been shown already.[1] This radiolabeled pyridaben-derivative is an insecticide and acts as mitochondrial complex (MC) I inhibitor. The heart with its high energy demand exhibits a high amount of mitochondria because these membrane-enclosed organelles are the power house of cells. Thus a selective accumulation of [$^{18}$F]Flurpiridaz in the myocardium can be determined. Its uptake and tissue to non-target organ ratio is superior to [$^{99m}$Tc]Sestamibi.[2] The ideal behavior of [$^{18}$F]Flurpiridaz as MPI-agent prompts the development of a correspondent derivative for the generator-produced PET nuclide gallium-68 for easier availability. To the established chelators NODAGA and DOTA, a variety of pyridaben-derivatives have been attached as targeting vectors.

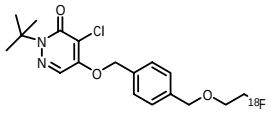

Figure 1: Structure of [$^{18}$F]Flurpiridaz

**Methods:** Several amino-pyridaben-derivatives with have been synthesized.[3] The chain length of the linker between chelator and insecticide varies. These compounds have been reacted with NODAGA-NHS and DOTA-NHS. The cold Ga-complexes have been made for all derivatives. Their affinity towards MC I has been tested. $^{68}$Ga-labeling in HEPES-buffer has been done. Optimization regarding pH, temperature and amount of precursor has been performed. Challenge experiments have been carried out.

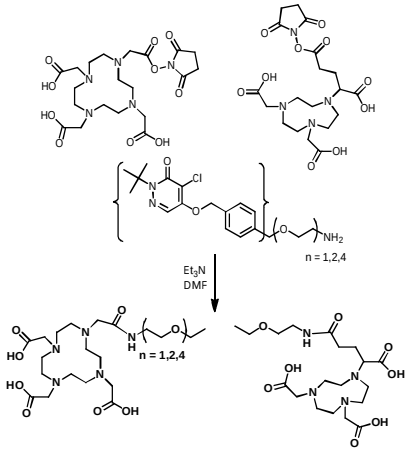


Figure 2: Reaction of DOTA-NHS and NODAGA-NHS esters with pyridaben derivatives

**Results:** Optimal pH for $^{68}$Ga-labeling:

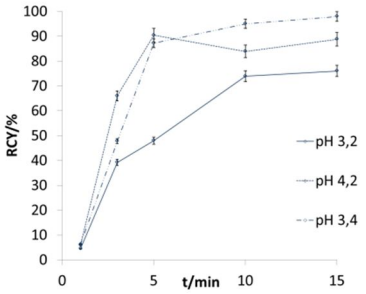


Figure 3**:** Effect of the pH on labeling yields (HEPES-buffer adjusted with 0.1 M NaOH; n=3)

All $^{68}$Ga-compounds are stable (RCY > 93 %) over 100 min in human serum, apotransferrin and 0.9% NaCl-solution. The $IC_{50}$ values for all compounds have been determined using the cold complexes. Applying the shake-flask method, the lipophilicity of all $^{68}$Ga-labeled structures has been defined.

| Tracer | LogD | $IC_{50}$ |
|---|---|---|
| DOTA_n=1 | -1,44 ± 0,06 | 17,4 µM |
| DOTA_n=2 | -1,86 ± 0,19 | 44,9 µM |
| DOTA_n=4 | -1,79 ± 0,07 | 33,1 µM |
| NODAGA_n=1 | -0,40 ± 0,09 | - |
| DOTA_aminoalkyl | -1,90 ± 0,34 | 6,9 µM |
| Flurpiridaz | 1,76 ± 0,12 | 4,6 nM |

Figure 4: Lipophilicities and $IC_{50}$ values for all tracers

**Summary:** Five new pyridaben-DOTA/NODAGA derivatives for MPI have been successfully synthesized. $^{68}$Ga-labeling has been proved with high yields and low amount of precursor. LogD and IC50 values have been determined.The low affinity of the compounds for MC I might be the consequence of their hydrophilic character. More lipophilic and additional positively charged derivatives could improve the binding affinity towards MC I.

## References

[1] Yu, M., et al., J. Nucl. Cardiol., 14, 789-798 (2007).
[2] Yalamanchili, P., et al., J. Nucl. Card., 14, 6, 782-788 (2007)
[3] Sawicki et al., Europ. J. Med. Chem., 43, 2768-2777 (2008)