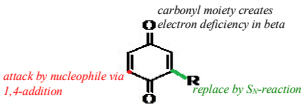
[^{18}F]-Labeled quinones as imaging tools for proteins

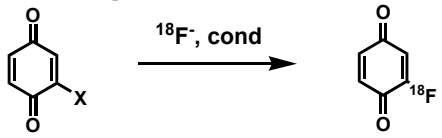
D.E. Borchmann[2], E.J. Millings[3], J.M. Hooker[1], J.S. Fowler[1]
[1]Brookhaven National Laboratory, NY, USA, [2]Johannes Gutenberg-Universität, Mainz, Germany, [3]Suffolk County Community College, NY, USA

Introduction

Tracking protein location and gaining insight into protein function is crucial for better understanding of diseases and metabolism. Imaging agents, however, should not significantly change the protein's three-dimensional structure and its function. Hence our aim was to develop a small (commercially available) precursor molecule to be labeled with fluorine-18 which can easily be attached to a protein's side group (lysine or cysteine). Substituted quinones can be labeled by substitution reactions and attached to proteins via Michael addition.



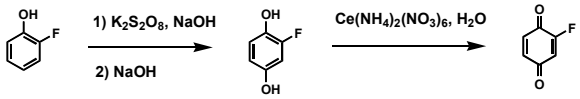
Scheme 1: quinone characteristics



Scheme 2: substitution reaction

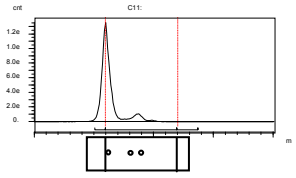
Results and discussion

As a start-up, "cold" 2-fluoro-1,4-benzoquinone was synthesized in a two-step synthesis (by Elizabeth Millings, fellow student) from *o*-fluorophenol via the 2-fluoro-1,4-hydroquinone (see scheme 1). This molecule served as a standard for TLC and HPLC in the "hot" reactions and as a tool to simulate the peptide or protein interactions with molecules like *N*-acetyl-cysteamine. These reactions were always successful, although isolation of the product still seems to be challenging.



Scheme 3: synthesis of 2-fluoro-1,4-benzoquinone

In the "hot" reaction, commercially available quinones were screened, like 2-chloro-1,4-benzoquinone (CBQ), 2,5-dichloro-1,4-benzoquinone (DCBQ) or 2,3,5,6-tetrachloro-1,4-benzoquinone (TCBQ). Especially TCBQ showed promising results, though it is not a good precursor (α,β-unsaturated carbonyl system already "blocked" by the four chloro substituents) and results were not reproducible.

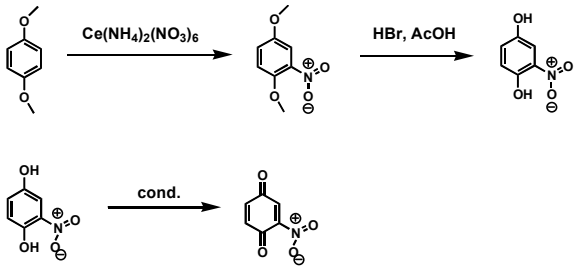


Scheme 4: typical radio-TLC of S_N-reaction

In the following, quinones with better leaving groups were synthesized, such as 2-bromo-1,4-benzoquinone (BBQ), 2-iodo-1,4-benzoquinone (IBQ) and 2-nitro-1,4-benzoquinone (NBQ).

BBQ and IBQ could not provide significantly better radiochemical yields. The reaction with IBQ did not even lead to the desired product.

NBQ could not be tested "hot", because the precursor synthesis always failed in the oxidation step from hydroquinone to quinone. We assume that NBQ is too strong an oxidizing agent and thus has to be used in a one-pot reaction, if at all, which leads to the problem of purification.



Scheme 5: synthesic route to 2-nitro-1,4-benzoquinone

Conclusions

[^{18}F]-2-fluoro-1,4-benzoquinone was synthesized successfully, which is an enhancement to older radioactive labeling agents in so far that only one step is necessary and that the precursor is commercially available.
Yields still have to be improved or a better precursor molecule has to be found.

References

[1] Cai, W., Zhang, X., Wu, Y., Chen, X.; *J. Nuclear Medicine* 2006, 47 (7), 1172-1180
[2] Knalves, *J. Am. Chem. Soc.* 1934, 56, 670
[3] Mason, D.E., Liebler, D.C.; *Chem. Res. Tox.* 2000, 13 (10), 976-982
[4] Carlson, B.W., Miller, L.L.; J. *Am. Chem. Soc.* 1985, 107 (2), 479-485

Acknowledgements

Thanks go to my mentor Dr. J. Hooker, to my fellow student E.J. Millings, who introduced me to the project and to [^{18}F]-labeling basics, to Dr. J. Fowler and the imaging group and to Prof. Dr. F. Rösch and the DAAD.