Synthesis of Two Novel Fluorinated Rexinoids

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The purpose of this research is to synthesize two novel retinoids for future testing regarding receptor efficacy.

Background

- 1999 - FDA approves Bexarotene, a retinoid, as a therapeutic regimen for Cutaneous T-Cell Lymphoma
- As a retinoid, Bexarotene induced the apoptosis cutaneous T-cell lymphoma cells within pre-clinical *in vitro* and *in vivo* studies (Querfeld, 2006)
- 2012 - Correlation between Retinoid X Receptors (RXR) and Alzheimer's Disease (AD) via induction of two receptors that play a key role in the transcription of apolipoprotein, one of the greatest risk factors for developing AD. Bexarotene showed:
  - Clearance of beta-amyloid plaques, the primary cause of neurodegenerative symptoms in AD
  - Regression of social, cognitive, and sensory deficits (Cramer, 2012)
- Replicative studies were not able to achieve the same results, but all studies found cognitive improvements
- Replicative studies used “unconventional formulations of bexarotene” (Tousi, 2015)
- Different analogs of Bexarotene have been hypothesized to induce RXR with differing levels of efficacy.

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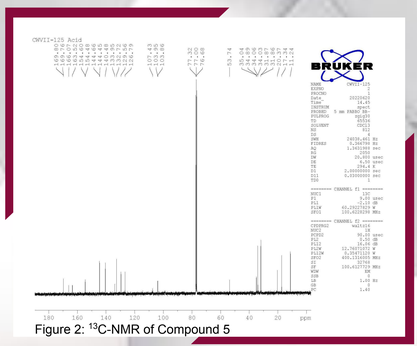


Figure 2: ^{13}C-NMR of Compound 5

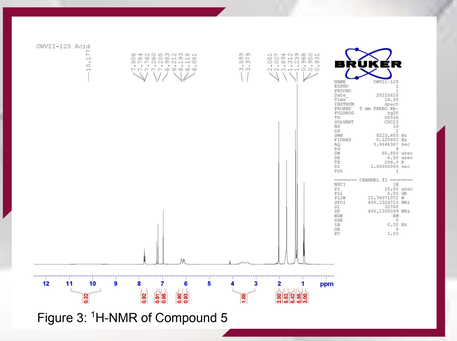
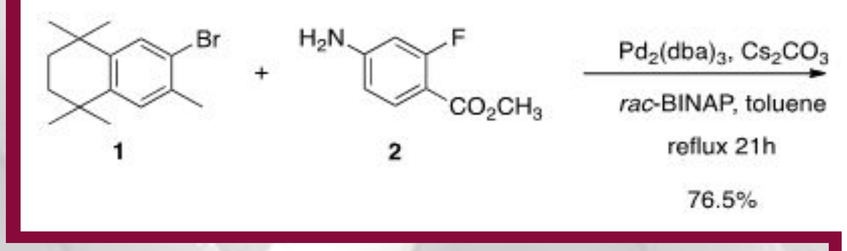


Figure 3: ^{1}H-NMR of Compound 5



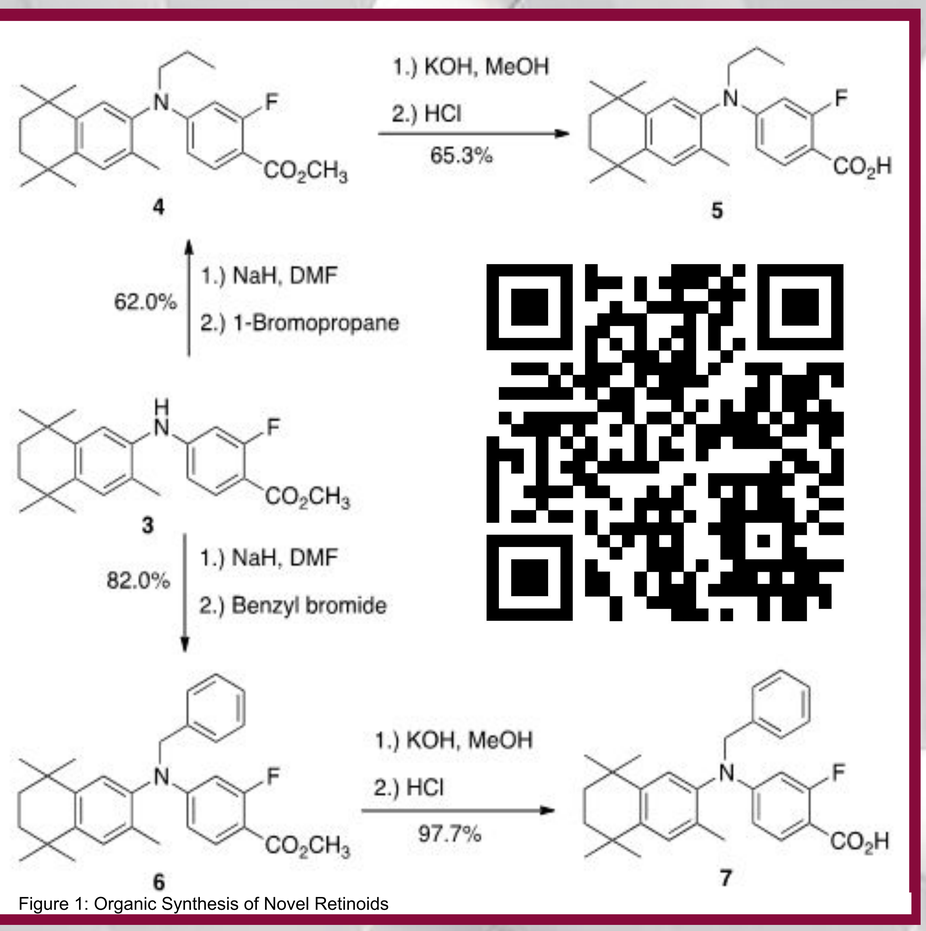


Figure 1: Organic Synthesis of Novel Retinoids

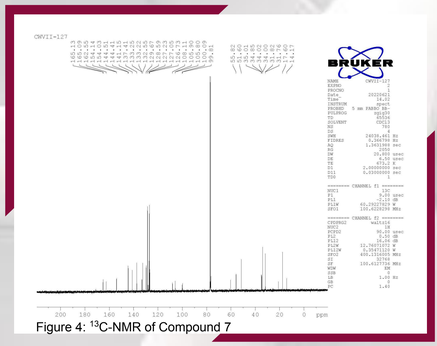


Figure 4: ^{13}C-NMR of Compound 7

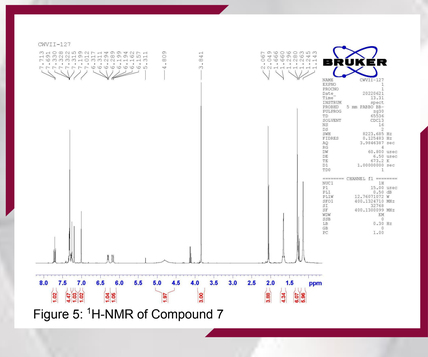


Figure 5: ^{1}H-NMR of Compound 7

Conclusion/Future Research

Final products were successfully obtained, achieving nearly a gram of each, which is found to be consistent with previous trials of similar research. ^{1}H-NMR and ^{13}C-NMR were utilized throughout the synthesis as confirmatory tests of the molecular structure. In the future, these synthesized compounds will be tested in yeast 2-hybrid assays in order to test the efficacy of binding to RXR receptors when compared to previously tested retinoids/rexinoids. These future studies can also help elucidate the mechanism of action of the retinoids/rexinoids in treating and managing AD.

References

Cramer, P. E., Cirrito, J. R., Wesson, D. W., Lee, C. Y., Karlo, J. C., Zinn, A. E., Casali, B. T., Restivo, J. L., Goebel, W. D., James, M. J., Brunden, K. R., Wilson, D. A., & Landreth, G. E. (2012). ApoE-directed therapeutics rapidly clear β-amyloid and reverse deficits in AD mouse models. *Science (New York, N.Y.)*, *335*(6075), 1503–1506. https://doi.org/10.1126/science.1217697

Querfeld, C., Nagelli, L. V., Rosen, S. T., Kuzel, T. M., & Guitart, J. (2006). Bexarotene in the treatment of cutaneous T-cell lymphoma. *Expert opinion on pharmacotherapy*, *7*(7), 907–915. https://doi.org/10.1517/14656566.7.7.907

Tousi B. (2015). The emerging role of bexarotene in the treatment of Alzheimer's disease: current evidence. *Neuropsychiatric disease and treatment*, *11*, 311–315. https://doi.org/10.2147/NDT.S61309