Synthesis of Two Potent Rexinoids at the Gram Scale for In-Vivo Cancer Studies

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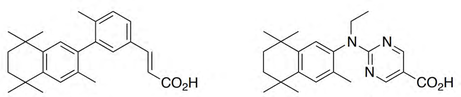
Introduction

Bexarotene is an antineoplastic agent approved by the U.S. Food and Drug Administration in late 1999 used to treat Cutaneous T Cell Lymphoma. It falls under a class of medications classified as Retinoids. Retinoids are drugs that are relatives of Vitamin A. Retinoids control normal cell growth, and cell differentiation. This medication is used to help halt the growth of cancer cells but comes with major side effects. These side effects include blood test abnormalities, rash, lowered white blood cell count, nausea, infection, and an increase of fat in the blood (cholesterol and triglycerides).

Background



7 11

In this study, we examined two analogue rexinoids that have a similar iNOS suppression to compound LG100268. The purpose in examining the percentage of iNOS and SREBP is to better identify rexinoids with potency that is more clinically acceptable and with a lower SREBP induction (fewer side effects) for patients of cancer. The analogues we examined have a very close iNOS suppression to LG100268 (an iNOS suppression of 15%), lower in scale than Bexarotene. On the other hand, Bexarotene has a lower percentage of SREBP then LG100268. The importance in targeting a molecule like LG100268 is to regulate the triglyceride levels and other alarming side effects in those who have weak immune systems. With the data down below, we examined the potency of our compounds that will later be introduced to mouse models. Synthesizing these rexinoids will help bring greater awareness and "design new rexinoids with appropriate interactions with coactivators and corepressors…"(12, Zhang) that will minimize side effects in cancer patients treated with these drugs.

Figure 1 [4]

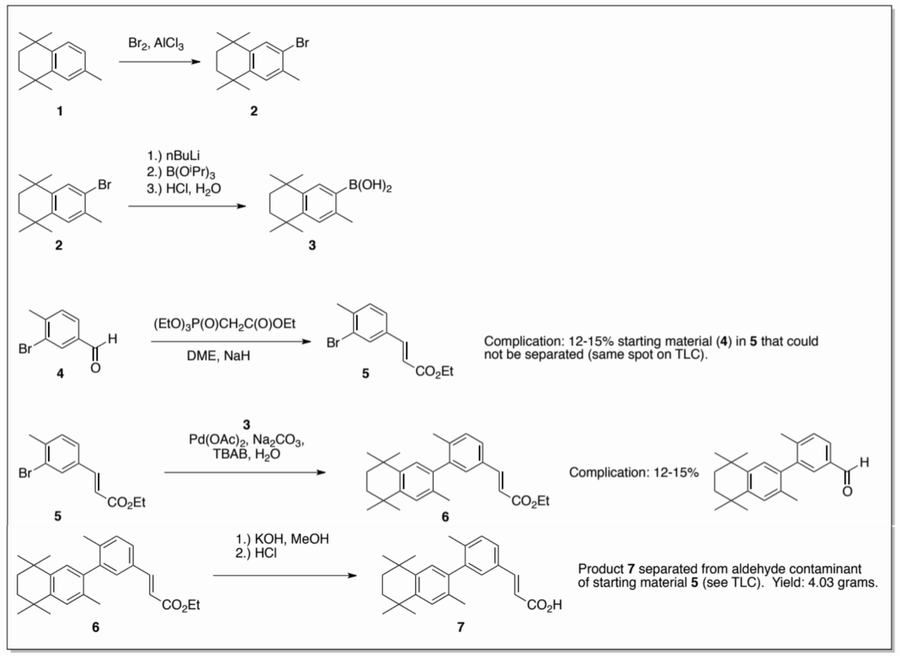
Compound structure	Name or number	iNOS suppression (% LPS-stimulated control) (±SD)	RXR activation (EC_{50}, nmol/L) (±SD)	SREBP activation (% of TO) (±SD)	Original Reference
	Bexarotene	24 (3)	55 (6)	71 (2)	48
	LG100268	15 (1)	15 (3)	87 (2)	20
	PyBex	20 (6)	44 (12)	88 (1)	22
	PyLG268	17 (6)	50 (10)	68 (3)	22
	**5**	23 (6)	34 (6)	65 (5)	49
	**6**	11 (2)	21 (2)	100 (7)	20
	**7**	17 (5)	14 (0.8)	62 (5)	50
	**8**	9 (5)	14 (1.5)	66 (5)	51
	**9**	12 (4)	41 (0.6)	67 (12)	51
	**10**	15 (1)	18 (0.4)	63 (6)	51
	**11**	19 (7)	8 (0.4)	57 (6)	52
	12	11 (0)	34 (0.3)	54 (5)	51
	**13**	12 (3)	42 (3)	72 (13)	22
	**14**	24 (9)	72 (11)	65 (15)	22

NOTE: To determine suppression of iNOS, RAW 264.7 cells were treated with 100 nmol/L rexinoid and then challenged with 1 ng/mL LPS for 24 hours. NO production was measured using the Griess assay, and results were normalized to the LPS-stimulated control. RXR and SREBP activation were evaluated as described in the Materials and Methods. TO = T0901317, a LXR ligand and known SREPB activator.

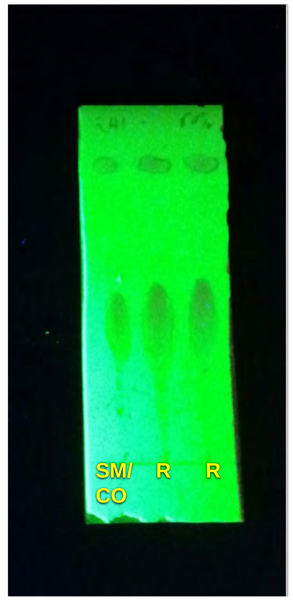
Hypothesis

We will be able to make between 4 and 5 grams of two different target molecules to have a collaborator be able to examine them in mouse models of human cancer (lung and breast).

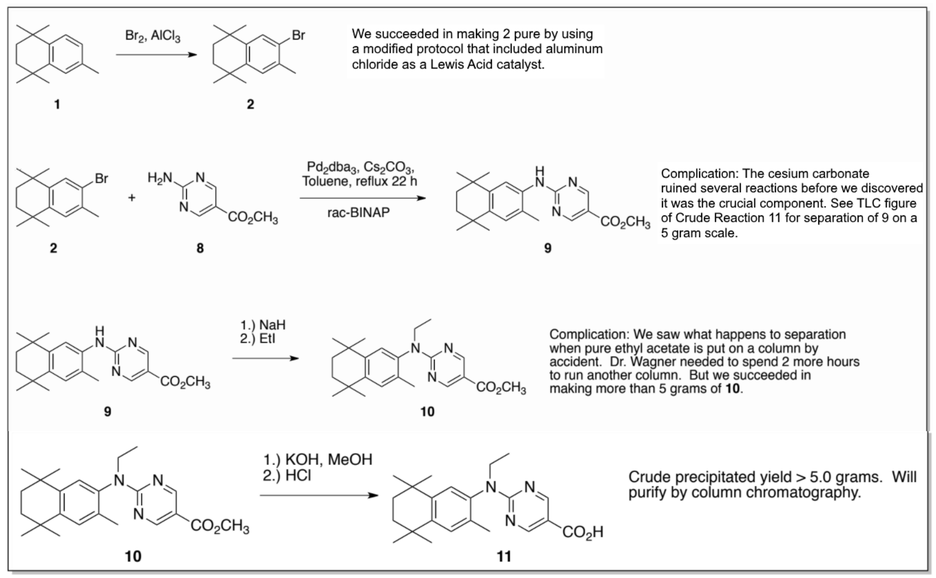
First Target Molecule Intermediate Reaction Scheme and Details:



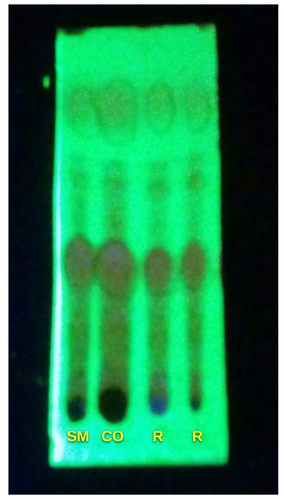
Crude Reaction TLC of 7



Second Target Molecule Intermediate Reaction Scheme and Details:



Crude Reaction TLC of 11



Results

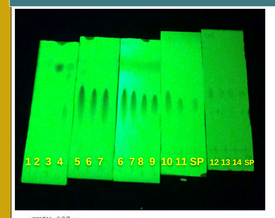


Figure 2) A TLC plate, proving purity by revealing fractions with a single spot of **7**.

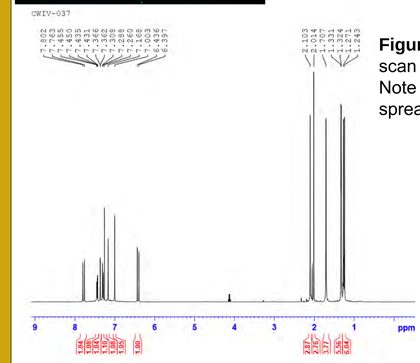


Figure 3) An HNMR scan of compound 7. Note the peaks and spread of protons.

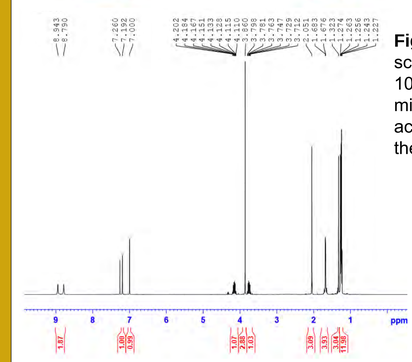


Figure 4) An HNMR scan of compound 10. Note the miniscule ethyl acetate peak just on the left of 4.

Conclusion

Yields were comparable to yields found in prior studies[2][3]. A proton nuclear magnetic resonance scan (figures 3 and 4) and a thin layer chromatography test (figure 2) proved purity. Future research includes testing compounds **7** and **11** in mouse models of human cancers, potentially lung and breast. These studies help with better understanding the mechanisms of rexinoids in cancer that will be clinically effective and accessible to those in need.

References

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Acknowledgements

Research reported in this poster was supported by the National Institute of Environmental Health Sciences of the National Institutes of Health under award number 1R25ES030238-01. We would also like to acknowledge Dominic Ivan for his assistance in the laboratory.

*Both investigators contributed equally to this project