

Abstract & Introduction

Prostate cancer is the most frequently diagnosed form of cancer in American men.¹ In 2020, it is estimated that 191,930 men will be diagnosed with the disease and more than 33,330 men will die from prostate cancer making it the second leading cause of cancer related deaths in men.² The prostate gland is composed of numerous tubuloacinar glands that produce mixtures of exosomes, glycoproteins, and small molecules that nourish the sperm until ejaculation.³ Adenocarcinoma comprises about 95% of prostate cancer cases.¹ Prostate cancer can result in non-life threatening symptoms such as erectile dysfunction, incontinence, and infertility but can have deadly effects secondary to tumor metastasis.⁴ Common sites of metastasis include the bone, liver, brain, lungs, and adrenal glands. Approximately 25-35% of patients will have evidence of metastasis at diagnosis.¹ Current treatment for advanced prostate cancer includes androgen suppression therapy which is used to decrease levels of cancer-promoting hormones, with alternative options such as immunotherapy and chemotherapy.⁵ Since there are limited treatment options for advanced prostate cancer, there is a need for additional therapies that can target prostate carcinoma cells effectively. Chalcone compounds have both anti-inflammatory and anticancer properties through the formation of a Michael Acceptor. The Michael Acceptor, an α,β -unsaturated ketone, suppresses inflammatory protein, NF- κ B, formation via the covalent modification of IK β kinases (IKKs) providing a promising treatment for inflammatory related cancers.⁶ The Claisen-Schmidt Condensation reaction was performed to synthesize the chalcone compounds for this experiment. The compounds were isolated and verified by thin layer chromatography, mass spectrometry, and NMR.

Objectives

1. Design chalcones specialized in targeting and wiping out prostate cancer.
2. Use of appropriate lab techniques to synthesize, isolate and purify the target molecules.
3. Confirm the presence and purity of the desired chalcone with the help of Mass spectrometry and NMR techniques.

Reaction Schemes

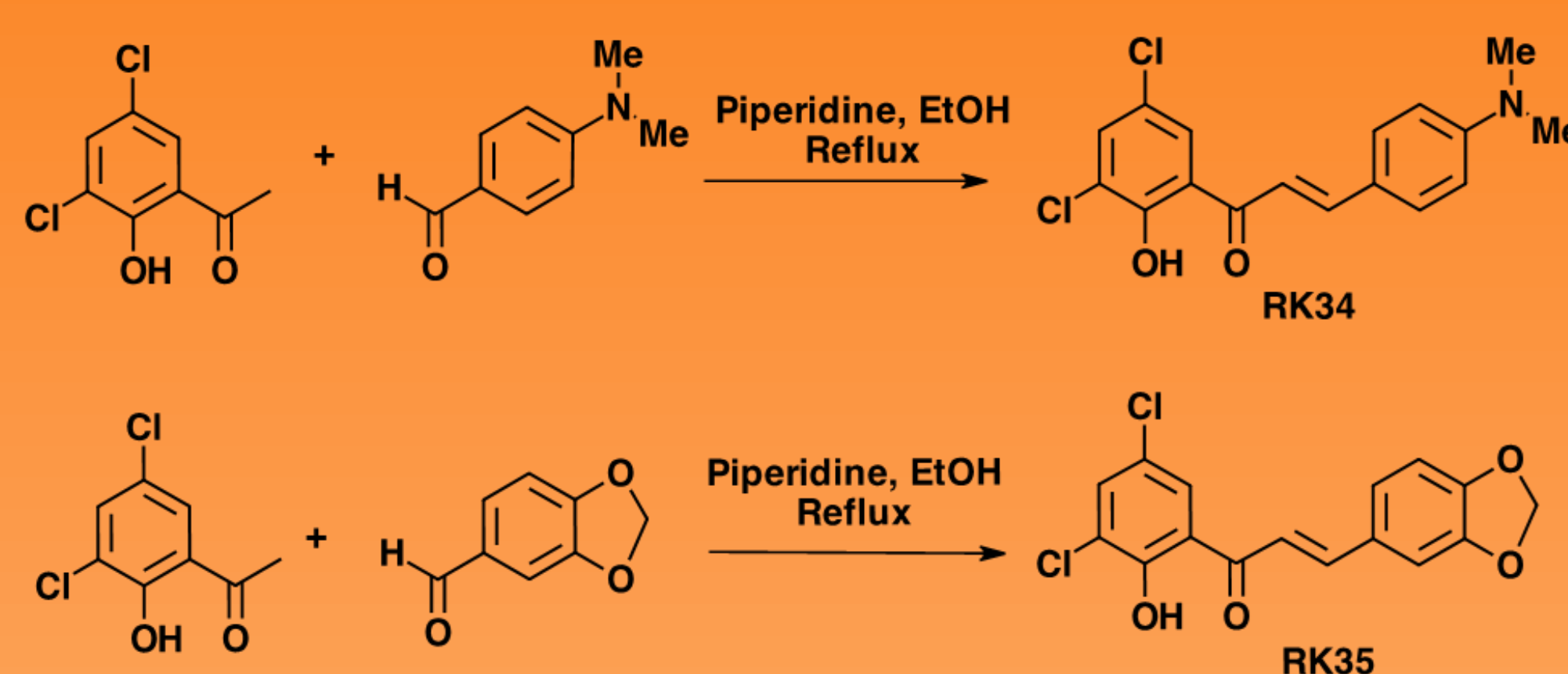


Figure 1. Chemical reaction scheme used to synthesize RK34 and RK35. Piperidine and EtOH were used to help catalyze the reactions.

Methods

Aldehyde and ketone molecules with the appropriate side chains were measured to be reacted via the Claisen Condensation reaction. Ethanol (EtOH) was added to the measured components to catalyze the reaction and refluxed in the presence of piperidine, an organic base, to provide us with the desired compounds. The reaction time varied from 8-12 hours. Final products were isolated through use of a fritted funnel and evaporation of the organic base. The compounds were cleansed using methanol and dried prior to conducting any testing. Thin layer chromatography, mass spectrometry, and NMR were completed to confirm the compounds produced in the reactions and verify structural integrity.

Discussion

The synthesized molecules, RK34 and RK35, are chalcones which were created by reacting ketone and aldehyde components together. Current treatments for prostate cancer include androgen suppression therapy, immunotherapy and chemotherapy. Additional treatment options are desired. The key pharmacophore in chalcones is the α,β -unsaturated ketone which acts as a Michael Acceptor. This Michael Acceptor allows RK34 and RK35 to possess anti-inflammatory properties and essentially an anti-cancer element through the suppression of key inflammatory mediators. The molecules were successfully synthesized and isolated. Further testing is needed to determine the impact RK34 and RK35 have on prostate cancer and normal cells.

Results and Spectroscopy

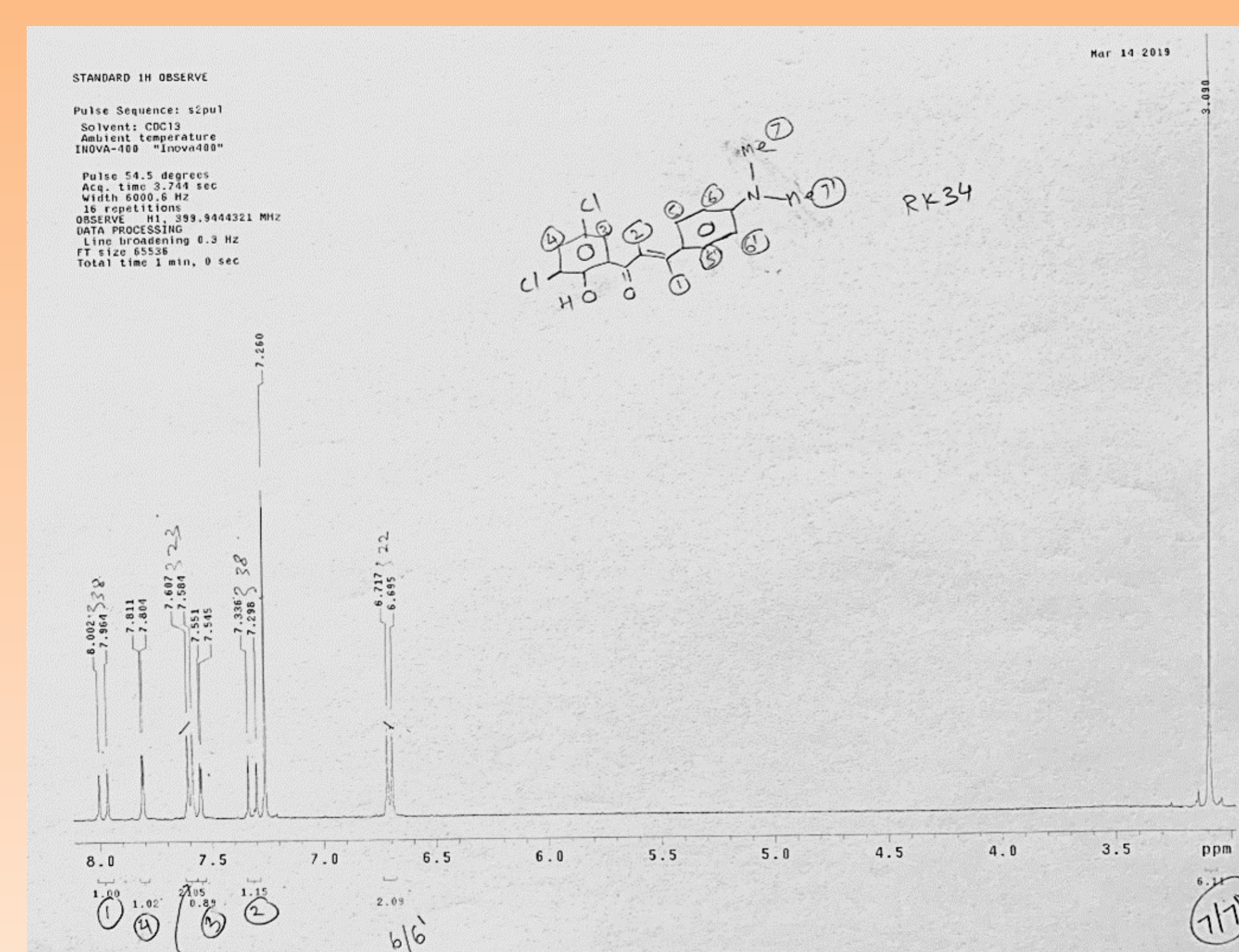


Figure 2. NMR Spectra of RK34

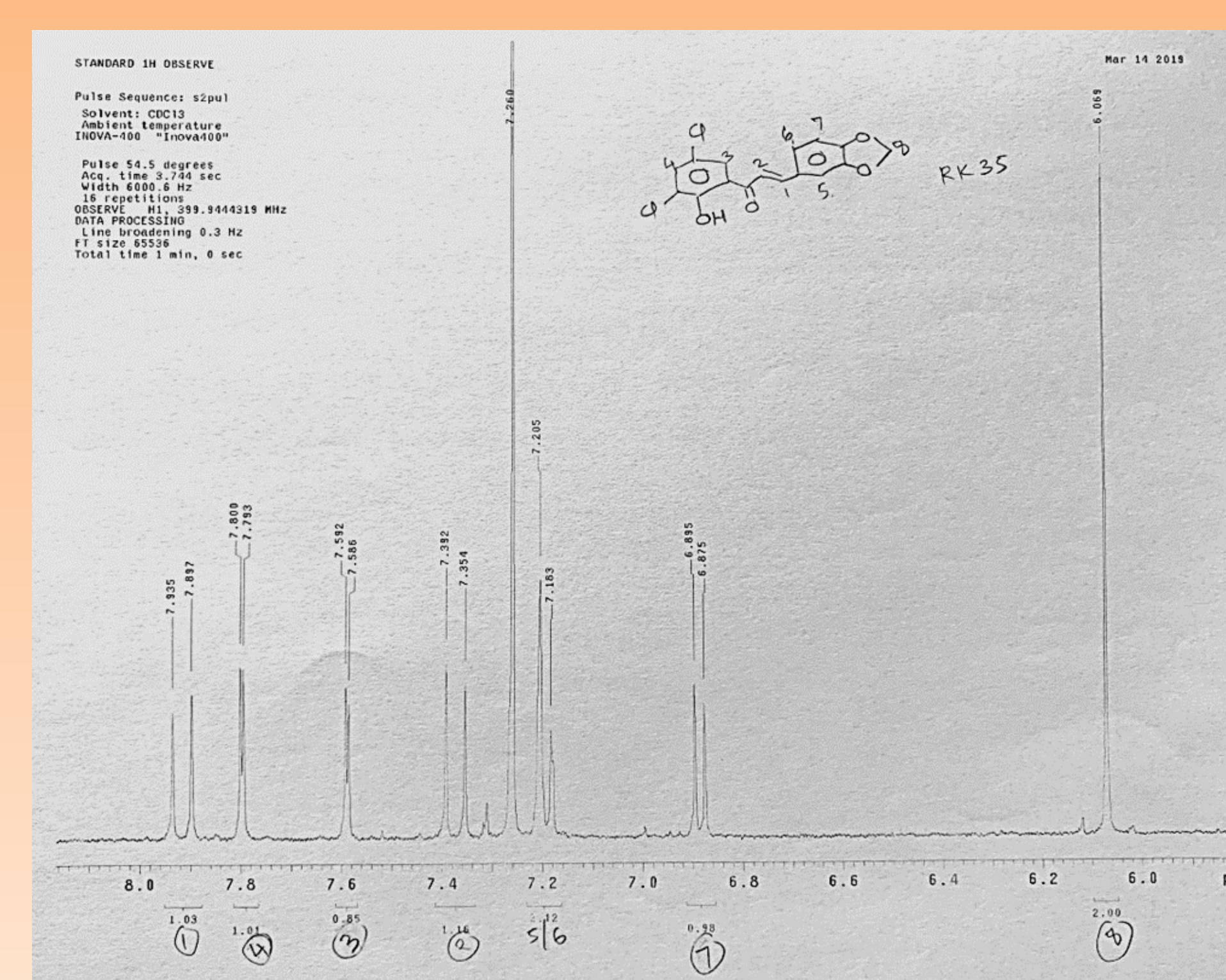


Figure 3. NMR Spectra of RK35

NMR (Nuclear Magnetic Resonance) was used to confirm the structures of the target compounds. The x-axis is composed of units that represent the chemical shift in reference to the standard tetramethylsilane (TMS) at 0 parts per million (ppm). The NMR solvent used was deuterated chloroform (CDCl₃). Regions of interest include the aromatic region that falls within 6-8 ppm and the aliphatic region that falls within 2-3 ppm. The NMR spectra shown in figures 2 and 3 for RK34 and RK35 are consistent with the assigned structures.

Future Directions

Additional testing should be completed with these molecules through bioassays to evaluate their impact on both prostate cancer cells and surrounding healthy cells. With additional testing, the structure-activity relationship (SAR) of the compound will be studied and used to determine structural adjustments, identify receptor targets and increase both the biological activity and effectiveness of the compound in the desired action site. In addition, the bioassays can be used to help synthesize future molecules. Further testing and purification techniques need to be completed prior to animal testing, which is the desired outcome in the future.

REFERENCES

1. Norris LB, Kolesar JM, DiPiro JP, et al. Pharmacotherapy: a pathophysiologic approach. 10th Edition. New York (NY): McGraw Hill; 2017
2. Cancer.Net Doctor Approved Patient Information from ASCO [Internet]. Alexandria (VA): ASCO; c2005-2020. Prostate Cancer: Statistics; [updated 2020 Jan; cited 2020 Mar 8];[1 screen]. Available from: <https://www.cancer.net/cancer-types/prostate-cancer/statistics>
3. Mescher AL. Junqueira's basic histology: text and atlas. 15th Edition. New York (NY): McGraw Hill; 2018
4. Prostate Cancer [Internet]. Phoenix (AZ): Mayo Foundation for Medical Education and Research; c1998-2020. Complications; [updated 2019 Apr 17; cited 2020 Mar 8];[1 screen]. Available from: <https://www.mayoclinic.org/diseases-conditions/prostate-cancer/symptoms-causes/syc-20353087>
5. Treating Prostate Cancer [Internet]. Atlanta (GA): American Cancer Society; c2020. Hormone Therapy for Prostate Cancer; [updated 2019 Aug 1; cited 2020 Mar 8];[about 8 screens]. Available from: <https://www.cancer.org/cancer/prostate-cancer/treating/hormone-therapy.html>
6. Zhuang C, Zhang W, Cheng C, et al. Chalcone: a privileged structure in medicinal chemistry. American Chemical Society. 2017 May 10; 117(12): 7762-96