Benchtop nuclear magnetic resonance spectroscopy enables the discovery and optimization of novel trifluorinated 2,4-dihydropyrimidine compounds as antiproliferative agents

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Introduction

Benchtop nuclear magnetic resonance (NMR) spectroscopy:

- Real-time reaction monitoring with quantitative precision
- Provides structural insight into reaction mechanism
- Proton lock capabilities permit the use of non-deuterated solvents

Fluorinated bioactive compounds:

- Fluorine is comparable in size to hydrogen, yet 160% as electronegative[1]
- Fluorine confers conformational and inductive effects that remarkably alter chemical reactivity and neighboring group pK_a values[1]
- ➜ Fluorinated drugs exhibit improved cell permeability, biological activity, metabolic stability, and bioavailability[1]

Biginelli cyclocondensation:

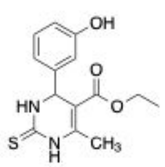
- Multicomponent reaction used to synthesize dihydropyrimidine privileged scaffolds[2]
- Acid-catalyzed reaction between an aldehyde, ß-ketoester, and urea[2]
- Dihydropyrimidines with biological activity:
  - Monastrol: Inhibits kinesin Eg5, arresting cells in mitosis[3]
  - LaSOM 63: Inhibits ecto-5'nucleotidase/CD73 activity, inducing apoptosis[4]

This study:

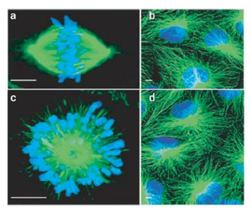
- Applying benchtop ^{19}F NMR spectroscopy toward monitoring the synthesis of trifluorinated dihydropyrimdines with biological activity

Significance & Background

Bioactive privileged scaffolds: small-molecule anticancer therapeutics

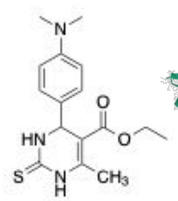


Monastrol

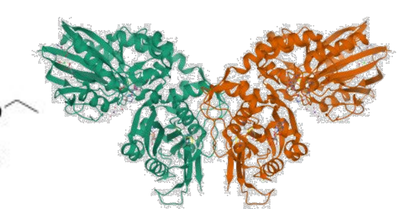


← normal mitotic function

← abnormal mitotic function (with 30 µL monastrol)

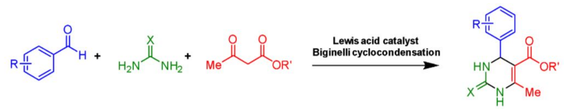


LaSOM-63



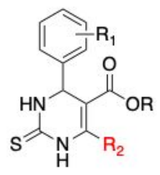
Will synthesizing fluorinated analogs of current anti-cancer small molecules enable the discovery of biological therapeutics with greater potency?

Biginelli Cyclocondensation

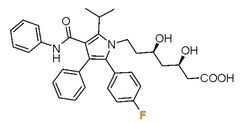


Previously, ester and aromatic substitutions have been widely explored....

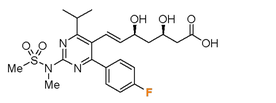
...but not much research has been put into R_2 substitutions.



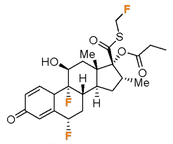
Fluorinated Small Molecules



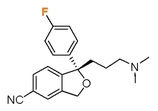
Lipitor (atorvastatin)
Cholesterol lowering drug



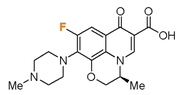
Crestor (rosuvastatin)
Cardiovascular disease



Fluticasone
Anti-inflammatory

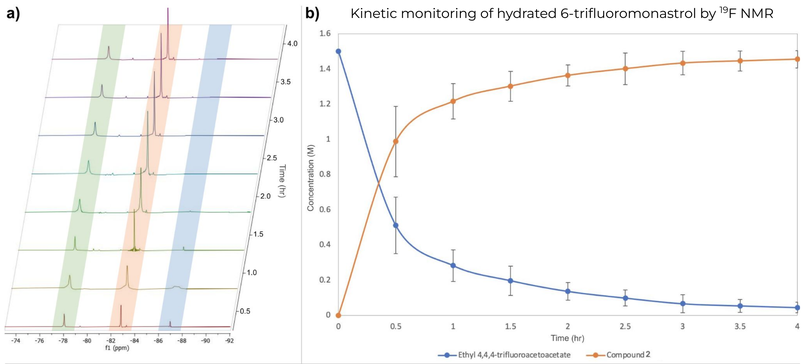


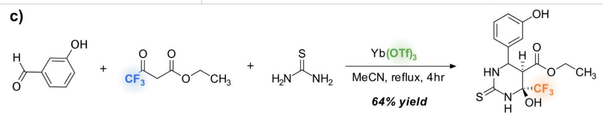
Escitalopram
Antidepressant

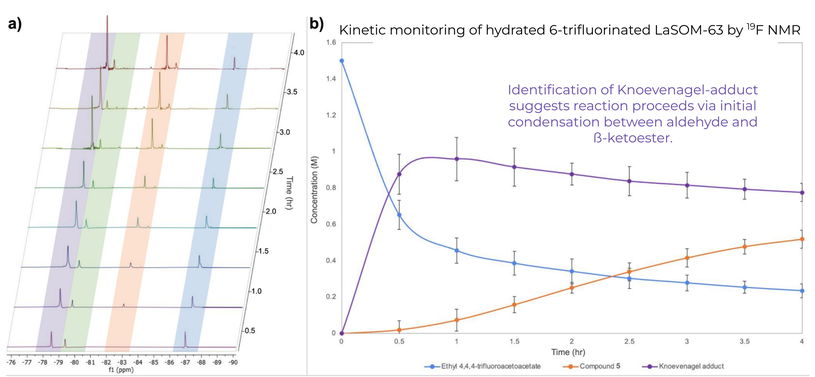


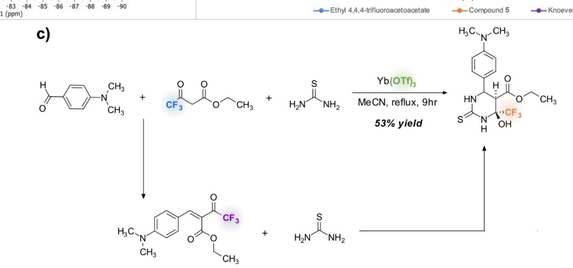
Levofloxacin
Antibiotic

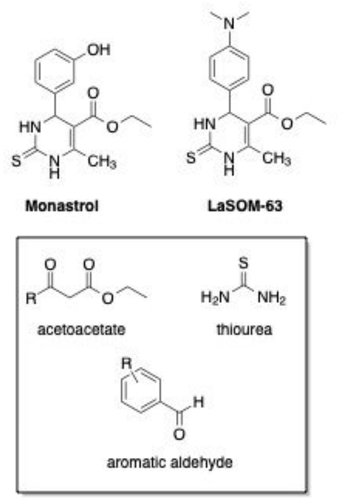
^{19}F NMR Reaction Monitoring



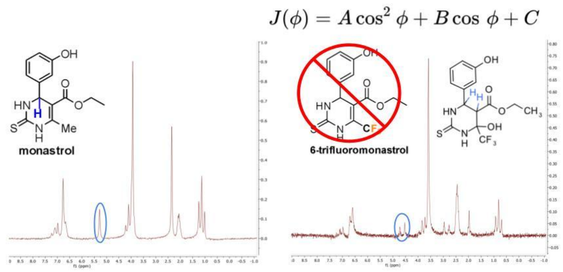


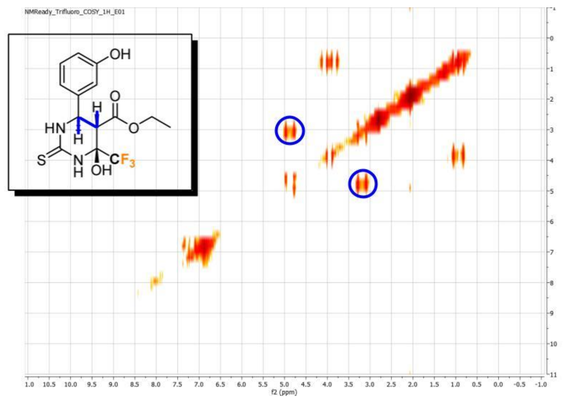






NMR Characterization





Future Directions & Conclusions

- Results present an efficient workflow for the synthesis of fluorinated antiproliferative agents using heteronuclear benchtop NMR spectroscopy
- Mechanistic insight has been gained into formation of trifluorinated dihydropyrimidines, revealing that the trifluoromethyl functionality prevents the final dehydration and suggesting alternate reaction mechanisms through the identification of reactive intermediates

Current efforts:

- Biological assaying of compounds to evaluate cytotoxic properties on human colorectal carcinoma and T lymphocyte cell lines

References

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