TITLE: Synthesis of thiophene analogs as potential antagonists of Chemokine Receptor Type 4 (CXCR4)

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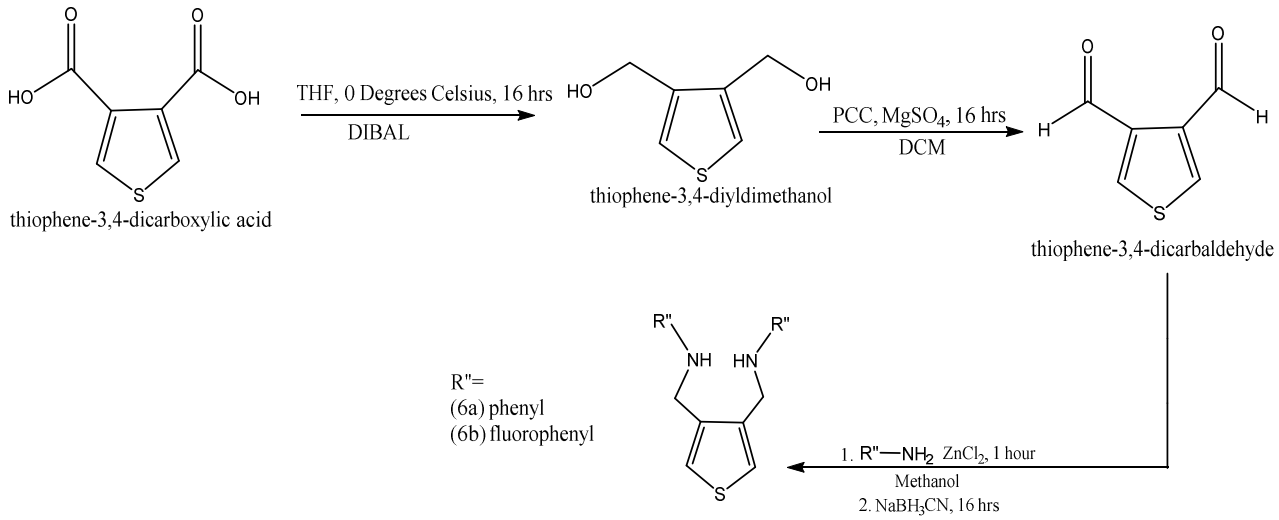
Introduction: CXCR4 is a chemokine receptor involved in the progression of several disease pathways. Inhibition of CXCR4 with small molecules and peptides has been shown to: 1) reduce the inflammatory response in people suffering from autoimmune disorders such as Rheumatoid Arthritis, 2) in slowing the spread of cancer, and 3) in HIV-1 infection. We have designed a new series of thiophene compounds that have the potential to inhibit CXCR4.

Purpose: The purpose of this study is to synthesize a new class of CXCR4 antagonists that can be applied clinically to treat cancer metastasis and inflammatory conditions.

Method: Thiophene-3,4-carboxylic acid was used to synthesize thiophene-3,4-dicarbaldehyde in using in two steps; a reduction of the carboxylic groups to alcohols, and then an oxidation of the resulting alcohols to aldehydes. From the aldehyde multiple CXCR4 antagonists were synthesized. The various antagonists were synthesized by reductive amination of the resulting aldehyde with various amines. The synthesized compounds were subjected to biological assays to determine how well they would bind to CXCR4 in vitro.



Results: Two thiophene analogs were synthesized, and tested in two preliminary assays – a phenyl derivative and a 3-fluorophenyl derivative. The phenyl analog derivative shows the most potential as a CXCR4 antagonist. It has an effective concentration in the binding affinity assay of 10 nM and was able to inhibit invasion by 72% compared to the control (0%).

Conclusions: The results of the two assays indicate that these thiophene derivatives are potential CXCR4 inhibitors. Currently, we are synthesizing a larger series of compounds for analysis. We will also conduct structure-activity relationship studies to determine which functional groups lead to the best activity.