Probing the Treatment of Bipolar Disorder

Microwave Syntheses and Spectral Characterization of Coumarin-Based Li⁺ Fluoroionophores

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Introduction

Lithium salts are currently the best treatment for bipolar disorder. The harsh side effects, which include nausea, kidney damage and possibly death, have inspired investigations into the cellular activity of Li⁺. In order to explore where and how lithium acts in the brain, fluorescent probes could be used to track ions. Fluoroionophores are a type of fluorescent probe. Fluoroionophores are molecules that consist of a fluorophore component, which exhibits fluorescence characteristics and an ionophore component, which exhibits ion-binding capabilities. Fluoroionophores can act as detectors of ions due to their ability to bind ions and exhibit a change of fluorescent intensity or wavelength. A potential lithium-ion fluoroionophore could consist of coumarin and a 12-crown-4 as the fluorophore and ionophore respectively. Coumarin is a fluorophore that is known to cross cell membranes and has been used as the fluorophore of fluoroionophores for other ions. A 12-crown-4 is a highly selective ionophore for Li⁺. A fluoroionophore composed of a coumarin derivative linked by a methylene bridge to a nitrogen substituted 12-crown-4 is the focus of this study. The desired properties of this fluoroionophore are that it would selectively bind Li⁺, change fluorescent emission significantly when bound to Li⁺ and possess in vivo capabilities.

Goals

A fluoroionophore designed to bind Li⁺ will be
1. Synthesized by microwave synthesis
2. Characterized spectrally to determine if it selectively binds Li⁺

Microwave Synthesis Easily Yields Pure Product

Scheme 1: Synthesis of mono-substituted aza-12-crown-4 Li⁺ fluoroionophore.

Scheme 2: Synthesis of bis-substituted diaza-12-crown-4 Li⁺ fluoroionophore.

The microwave syntheses were adapted from a 24 hour reaction at room temperature. The use of the microwave yields a product with no detected by-products or remaining starting material. The protonated base, Et₃NHBr, was removed by filtering the crude product with EtOH. 1 and 2 were isolated as a yellow caked powders.

Future Steps

• Conduction ion-binding studies in a solvent system that does not change fluorescence or absorbance in the region of interest.
• Synthesize and characterize fluoroionophores with different substituents to increase solubility in water.

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Number of Coumarins Determines Spectral Characteristics of Fluoroionophore

Solvent Reaction to Light Confounded Results of Li⁺ Binding Studies

1 was titrated with LiCl (0.37mM in 1:1 MeOH:CHCl₃). 0.12 eq in 10 μL up to 1 eq to determine its ability to sense Li⁺. Results from this titration were inclusive because similar increases in emission of 1 were observed upon addition of equal volumes of solvent. Spectra of the solvent exposed to light increased in fluorescence and absorbance at peaks that were too close to the peaks of the fluoroionophore.