Synthesis of a Charged Receptor With a Bis-Phenolic Ether Scaffold and Its Binding Studies With Phosphatidylglycerol, a Bacterial Membrane Lipid

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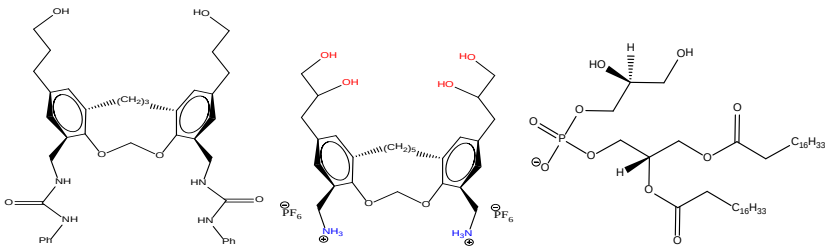
Abstract. An ongoing project in our research group is the development of synthetic receptors for the head group of Phosphatidylglycerol, an anionic phospholipid found in bacterial membranes, as a component part of new antimicrobials. Previous studies with these types if bis-phenolic oxygen linked scaffoldings having neutral binding sites showed relatively weak binding to the Phosphatidylglycerol (PG) anion. Here we discuss the synthesis leading to: 1. the expansion of the binding pocket, 2. the incorporation of positively charged binding sites and 3. determination of the lipid binding ability of the receptor.

1. Introduction

The emergence of various strains of multidrug resistant bacteria has energized researches to discover new antibiotics to use against them. As a result the use of antimicrobial peptides or their mimics as potential antibiotics has gained attention of the scientists. Antimicrobial peptides (AMPs) are part of the innate immune system of multicellular organisms. These host defense peptides exhibit a wide range of activity against Gram-positive & Gram-negative bacteria. The cationic antimicrobial peptides (CAMPs) are believed to disrupt bacterial membrane by binding to their inner membrane anionic lipid head groups, followed by insertion into the membrane, which leads to bacterial cell death. However CAMP's do possess substantial host effects such as toxicity [1].
At present, we are engaged in a project whose goal is the preparation of synthetic anion receptors with high affinity towards the bacterial membrane component anionic Phosphatidylglycerol (PG), without binding to zwitterionic phospholipids which comprises the outer leaflets of eukaryotic cell membranes [2]. Linking these receptors to proven membrane disruptors would pave the way to synthetic antibiotics that could mimic CAMPs action with lessened host toxicity.

2. Experiment, Results, Discussion, and Significance

Receptor 1 with neutral binding sites synthesized & characterized by our colleagues, exhibited a moderate binding with Tetrabutyl ammonium phosphatidylglycerol (TBAPG) [3].



Receptor 1 Receptor 2 PG anion

Therefore to impart more selectivity, we decided to strengthen the binding sites affinity towards PG by introducing positive charges. Also, to accommodate the PG head group, binding pocket was expanded by increasing the number of methylene bridging units in the scaffolding (receptor 2). The synthesis of receptor 2 started from 2-bromoanisole and had fourteen synthetic steps [4, 5]. The receptor is multifunctional with ammonia binding units for the phosphate anion portion of PG and two bis hydroxyl groups to bind to the glycerol hydroxyls of PG head group. The receptor's initial characterization by means of ^{1}H NMR binding studies with Phosphatidylglycerol anion has also been carried out [6].

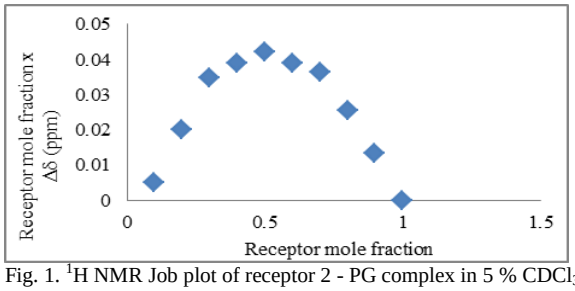


Fig. 1. ^{1}H NMR Job plot of receptor 2 - PG complex in 5 % $CDCl_3$ in DMF-d_7 at 30 ^{0}C

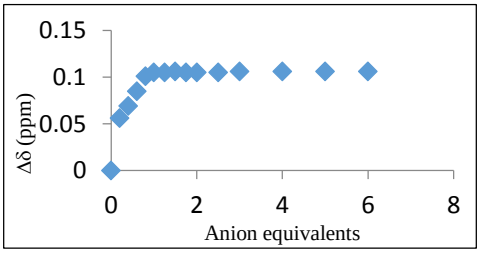


Fig. 2. ^{1}H NMR titration curve of receptor 2 with TBAPG in 5 % $CDCl_3$ in DMF-d_7 at 30 ^{0}C

Table: 1
Binding constants of receptors 1 and 2

Receptor	Binding ratio	K (M^{-1})	Anion salt
1	1:1	3.4×10^{2}	TBA PG
2	1:1	1.7×10^{4}	TBA PG

3. Conclusions

A multifunctional receptor for PG was synthesized. Initial characterization with ^{1}H NMR binding studies indicated 1:1 binding ratio and 1.7×10^{4} M^{-1} binding constant for PG anion.

4. References

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