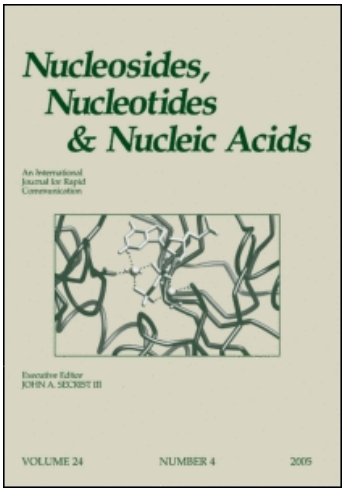

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Synthesis of Fluorescent Cationic Lipids for Evaluation of Cellular Pathways and Delivery Mechanisms of Antisense Oligonucleotides

Balkrishen Bhat[a]; Normand Heber't[a]; Eric G. Marcusson[a]; Nicholas M. Dean[a]; C. Frank Bennett[a]; Muthiah Manoharan[a]
[a] Isis Pharmaceuticals, Carlsbad, CA, USA

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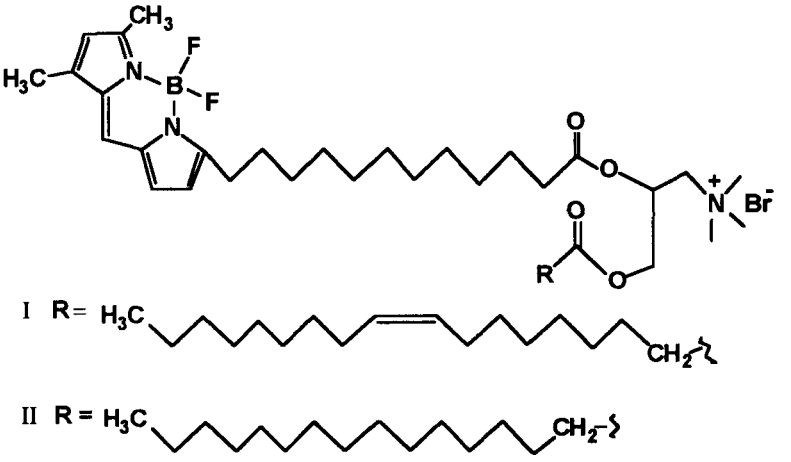
SYNTHESIS OF FLUORESCENT CATIONIC LIPIDS FOR EVALUATION OF CELLULAR PATHWAYS AND DELIVERY MECHANISMS OF ANTISENSE OLIGONUCLEOTIDES

Balkrishen Bhat*, Normand Heber't, Eric G. Marcusson, Nicholas M. Dean
C. Frank Bennett and Muthiah Manoharan

Isis Pharmaceuticals, 2292 Faraday Avenue, Carlsbad, CA 92008, USA

ABSTRACT: The synthesis of BODIPY conjugated cationic lipids was achieved in three steps from 3-bromopropane-1,2 diol as the starting material. These compounds were evaluated for their ability to enhance cellular uptake of the antisense oligonucleotides.

The use of antisense oligonucleotides to down regulate specific gene products requires oligonuleotides to enter cells and hybridize to target mRNA present in the cytoplasm and/or nucleus of cells [1-5]. Significant research efforts to increase the absorption of antisense oligonucleotides by cells is ongoing.. In this regard liposomal encapsulation [6], conjugation with other ligands such as cholesterol [7-8], cationic lipids [9-10] have been successfully used to deliver and increase the cellular uptake of oligonucleotides in cells.



To delineate the cellular trafficking mechanism and pathways several groups have attempted to use fluorescently labeled lipids or oligonucleotides [11-13]. In our efforts in understanding the role of cationic lipids as possible delivery agents, the synthesis of two different fluorescent labeled lipids was carried out by the reaction of 3-bromo 1,2 propanediol with the appropriate fatty acid (Fig) followed by reacting the corresponding esters with trimethylamine. The reaction of trimethylammonium esters with BODIPY labeled fatty acid in presence of EDC/DMAP gave labeled cationic lipids. The two lipids showed some differences in their ability to enhance the cellular uptake of rhodamine labeled antisense oligonucleotide in A549 cells .

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