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Potential New Inhibitors of Growth Factors Via the Coupling Between an Hydroxybisphosphonic Acid and an Oligonucleotide

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POTENTIAL NEW INHIBITORS OF GROWTH FACTORS VIA THE COUPLING BETWEEN AN HYDROXYBISPHOSPHONIC ACID AND AN OLIGONUCLEOTIDE

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Recent studies have shown that antisens phosphorothioate oligodeoxynucleotide did not allow the VEGF/VPF (vascular endothelial growth factor, vascular permeability factor) expression in normal epidermal keratinocytes. We suggest to compare the biological activity of an oligonucleotide bound to a hydroxybisphosphonic acid via an aminolink to the phosphorothioate oligonucleotide. We report here the synthesis of this compound. After obtaining the carboxylic function, methyl esters of 2 were transesterified by 4,2 eq of bromotrimethylsilane. Compound 3 which is very sensitive to hydrolysis was reacted with

$$C_{8}H_{5} - CH_{2}O - C - (CH_{2})_{3} - C - CI \xrightarrow{i} (CH_{3})_{3}C - Si - O - C - (CH_{2})_{3} - C - OH \xrightarrow{ii}$$

$$CH_{3} - CH_{2}O - C - (CH_{2})_{3} - C - OH \xrightarrow{ii}$$

$$CH_{3} - CH_{3} - COH_{3}C - COH \xrightarrow{iii}$$

$$CH_{3} - CH_{3}C - COH_{3}C - COH \xrightarrow{iii}$$

$$CH_{3} - CH_{3}C - COH_{3}C - CO$$

i; a°) P(OCH₃)₂/ CH₃Cl, b°) tBu-Si(CH₃)₂-O-P(OCH₃)₂, c°) H₂, Pd/C,, ii: Me₃SiBt/CH₃CN,, iii: a°) BOP/ tertiary amine/RNH₂/CH₃CN, b°) (CH₃(CH₂)₃)₄NF/H₂O/THF

SCHEME 1

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1 eq of R– NH_2 , 1 eq of distillated tertiary amine and 1 eq of BOP in acetonitrile solution to give the compound **4.** The coupling reaction was performed with success on an amine model like benzylamine. In the same way and with the same success, this method was transposed to the following sequence 5' CGCCGTAGC 3' before applying it on the sequence of the prior study.