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## **Nucleosides, Nucleotides and Nucleic Acids**

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## **The Synthesis and Interaction of Novel GTP Derivatives with Ras Oncogene Proteins**

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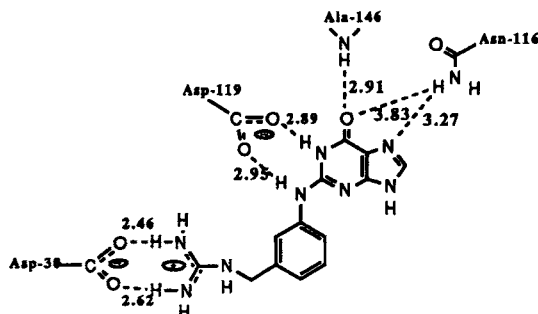
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## THE SYNTHESIS AND INTERACTION OF NOVEL GTP DERIVATIVES WITH RAS ONCOGENE PROTEINS.

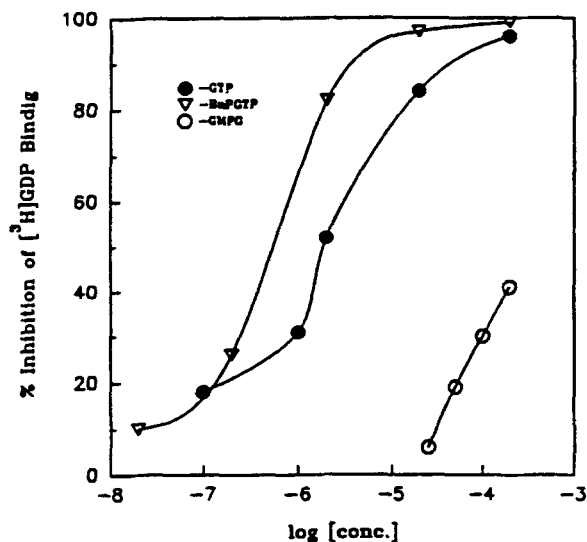
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**Abstract:** A series of novel GTP derivatives were synthesized and screened as probes and possible inhibitors of the *ras* encoded G protein p21. Based on these results and the x-ray crystallographic data on p21 we synthesized a non-nucleotide guanine analog designed to interact with specific amino acid sidechains of p21.

Several sugar- and base-modified analogs of GTP were tested for their ability to bind to cellular and oncogenic forms of the *ras* encoded protein, termed p21<sup>1</sup>. Substituents in the N<sup>2</sup>-position of GTP were non-obtrusive to binding to p21, and in some cases enhanced binding of the analog to the proteins. These results, and the recent elucidation of the x-ray crystallographic structure of p21<sup>2</sup>, allowed us to predict a N<sup>2</sup>-substituted guanine analog which may interact with specific amino acid sidechains of p21. By placing a *m*-(guanidinomethyl)phenyl substituent in the N<sup>2</sup>-position this should place the guanidinium moiety in close proximity to an aspartate at position 30 in p21, mimicking the hydrogen bonding scheme observed between aspartate 119 of p21 and N1 and N<sup>2</sup> of GTP (see below).

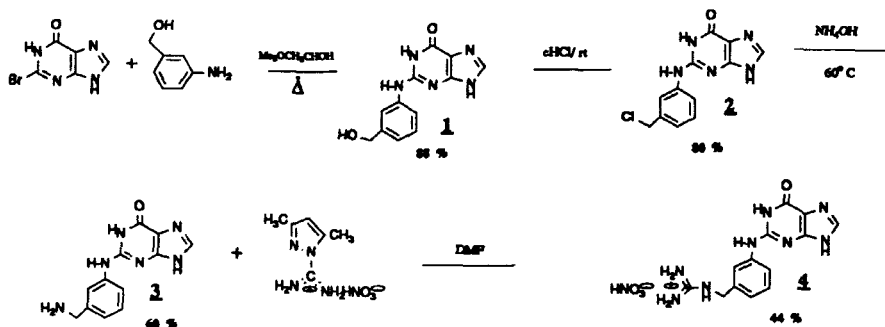


2-Bromohypoxanthine was reacted with *m*-aminobenzyl alcohol in refluxing methoxyethanol to yield N<sup>2</sup>-(*m*-hydroxymethylphenyl)guanine, (**1**), which was converted to N<sup>2</sup>-(*m*-chloromethylphenyl)guanine (**2**), by stirring in concentrated hydrochloric acid at ambient temperature for 48 h. Compound **2** was



Preliminary binding studies of GMPG on Leu-61 p21 show binding, however at much higher concentrations than BuPGTP. Earlier studies involving  $N^2$ -substituted guanine bases (data not shown) have shown no demonstrable binding at similar concentrations, suggesting that the binding is due to the *m*-(guanidinomethyl-phenyl) substituent. Further studies will include higher concentrations of GMPG in order to obtain a  $K_{\text{rel}}$  of GMPG on both normal EC and Leu-61 p21. And, in an effort to establish that GMPG is actually binding in the GTP/GDP site of p21, we plan to synthesize and test the corresponding nucleoside of GMPG. Benzylguanidine will be included in these future binding studies to eliminate the possibility of non-specific binding of GMPG which could impede GDP exchange.

placed in a pressure bomb at 60°C with ammonium hydroxide for 24 h to yield  $N^2$ -(*m*-aminomethyl-phenyl)guanine, (**3**).  $N^2$ -(*m*-Guanidinomethylphenyl)guanine, (**4**, GMPG), was derived from reacting **3** with 3,5-dimethylpyrazole-1-carboxamide in DMF at room temperature for 48 h<sup>3</sup>.



## REFERENCES

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