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Abstract:

The DNA minor groove continues to be an important biological target in the development of anticancer, antiviral, and antimicrobial compounds. Among agents that target the minor groove, studies of well-established benzimidazole-based DNA binders such as Hoechst 33258 have made it clear that the benzimidazole-amidine portion of these molecules promotes an efficient, site-selective DNA association. Building on the beneficial attributes of existing benzimidazole-based DNA binding agents, a series of benzimidazole-amino acid conjugates was synthesized to investigate their DNA recognition and binding properties. In this series of compounds, the benzimidazole-amidine moiety was utilized as a core DNA “anchoring” element accompanied by different amino acids to provide structural diversity that may influence DNA binding affinity and site-selectivity. Single amino acid conjugates of benzimidazole-amidines were synthesized, as well as a series of conjugates containing 20 dipeptides with the general structure Xaa-Gly. These conjugates were synthesized through a solid-phase synthetic route building from a resin-bound amino acid (or dipeptide). The synthetic steps involved:

(1) the coupling of 4-formylbenzoic acid to the resin-bound amino acid (via diisopropylcarbodiimide and hydroxybenzotriazole); followed by (2) introduction of a 3,4-diaminobenzamidoxime in the presence of 1,4-benzoquinone to construct the benzimidazole ring; and, finally, (3) reduction of the resin-bound amidoxime functionality to an amidine via treatment with 1M $SnCl_2 \bullet 2H_2O$ in DMF before cleavage of final product from the resin. The synthetic route developed and employed was simple and straightforward except for the final reduction that proved to be very arduous. All target compounds were obtained in good yield (based upon weight), averaging 73% mono-amino acid and 78% di-amino acid final compound upon cleavage from resin. Ultimately, the DNA binding activities of the amino acid-benzimidazole-amidine conjugates were analyzed using a fluorescent intercalator displacement (FID) assay and calf thymus DNA as a substrate. The relative DNA binding affinities of both the mono- and di-amino acid-benzimidazole-amidine conjugates were generally weaker than that of netropsin and distamycin with the dipeptide conjugates showing stronger binding affinities than the mono-amino acid conjugates. The dipeptide conjugates containing amino acids with positively charged side chains, Lys-Gly-BI-(+) and Arg-Gly-BI-(+), showed the strongest DNA binding affinities amongst all our synthesized conjugates.

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