New and Efficient Inibitors for Indoleamine 2,3-Dioxygenase

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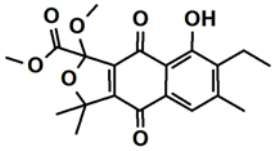
Human indoleamine 2,3-dioxygenase (IDO) (MW 47,000) has been implicated as a key participant in the development of senile cataracts (1) and in a variety of immunological roles (2), many of which have implications for treatment of cancer (3). To gain further insight into the mechanism by which IDO and inhibitors of IDO function, human IDO has been cloned and expressed primarily as the apo-enzyme in *E. coli*. The recombinant protein has been purified to homogeneity and reconstituted with heme to afford a product with the spectroscopic and kinetic properties reported for authentic IDO. A high-throughput *in vitro* assay has been used to screen a library of extracts prepared from marine invertebrates (*Coelenterates* and *Poriphera*) to identify new inhibitors of IDO. The structures of several new inhibitors obtained from two species (*Garveia annulata* and *Xestospongia*) have been determined at present. None of the new inhibitors is an indole derivative, none appears to be a competitive inhibitor with respect to Trp, and many are significantly more efficient than any IDO inhibitors previously reported. One new inhibitor discovered in this work (Annulin C, K_i = 144 nM) is shown in the Figure. (Supported by a CBS-CIHR Grant (RTAM), and NSERC Grant (RJA) and by CIHR Grant MOP-7182 (AGM)).



Annulin C, a representative new IDO inhibitor from *Garveia annulata*

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