Novel human indoleamine 2,3-dioxygenase inhibitors form a long-lived complex with the enzyme

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Human indoleamine 2,3-dioxygenase 1 (IDO) catalyzes the conversion of L-tryptophan (L-Trp) to N-formylkynurenine through a heme and O_2-dependent oxidation process. IDO is recognized as a central regulator of immune responses in a broad variety of physiological and pathological settings and is thus considered an attractive therapeutic target. In search of novel IDO inhibitors, we identified 4-amino-1,2,3-triazoles. Using crystallographic, biochemical and spectroscopic techniques we have fully characterized a representative molecule of this molecular series (VIDOi1) and shown that: VIDOi1 is non-competitive for D-Trp; VIDOi1 interacts with the IDO heme iron VIDOi1 binds to both the ferric and the ferrous form of the enzyme; VIDOi1establishes a slow complex with the ferrous form of IDO; and the VIDOi1-IDO complex is long-lived. The generation of this tight binding complex between IDO and the 4-amino -1,2,3-triazoles leads to exceptional potencies of this molecule series in a cellular context.

Biography

Julie Alexandre is specialized in Kinetics at the Vertex Pharmaceuticals Europe Ltd., (Abingdon, UK). She holds a PhD in Biochemistry from the University of Edinburgh (Scotland, UK) and undertook Post-doctoral Research in Enzymology at the Pierre-and-Marie-Curie University (Paris, France). She has been working at Vertex since 9 years and has contributed in many internal drug discovery efforts in oncology, targeting kinases, proteases and redox enzymes, through characterization of enzymes substrates and inhibitors kinetics and mode of action.

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