Identification of spirocyclic inhibitors of the transcription factor HIF2α: soluble ligands targeting a lipophilic binding site

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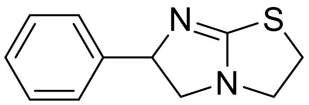
Hypoxia-inducible factors (HIFs) are members of the basic helix-loop-helix superfamily of transcription factors that play a central role in regulating oxygen homeostasis. Aberrant signaling through HIF2α has been implicated as a driver of certain cancers, most notably in clear cell renal cell carcinoma due to the loss of function of the von Hippel-Lindau tumor suppressor.

This paper will describe our experiences from applying multiple hit-finding approaches towards the fully-enclosed lipophilic cavity within the PAS-B domain of HIF2α which identified a number of relatively lipophilic and apolar starting points. Of these starting points levamisole, originally developed as an antiparasitic agent, was prioritised for further evaluation due to the presence of the ionisable 5,5-ring system that offered the possibility for improved physical properties. Further evolution of the levamisole hit led to the discovery of novel spirocyclic analogues with improved HIF2α inhibitory activity and which retained the desired physical property profile.



levamisole