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Title : Design of high affinity inhibitors of DNA polymerase beta by virtual screening and NMR.

Abstract : DNA polymerase beta is a pharmacological target involved in tumor progression, cisplatin resistance and neuro-degenerative diseases. Even if molecules leading to pol beta inhibition have already been discovered, there is a great interest in identifying inhibitors with higher affinity. SAR (Structure Activity Relationship) by NMR is a strategy that allows the design of high affinity molecules, by tethering together two micromolar affinity small molecules for pol beta that bind to proximal subsites of the target. The final molecule affinity is about the product of bound fragments affinities. The first fragment, pamoic acid (PA), was already known and the structural characterization of the complex pol beta-PA was helpful in identifying two adjacent sites to PA binding site. A virtual screening of 28714 fragments, combining to NMR screening, leads to selecting 4 fragments, whose binding site was close enough to PA binding site. Four hybrid molecules, like PA-linker-fragment, have been synthesized and tested for their ability to inhibit in vitro replication by pol beta. Two of them showed increased inhibition by a factor of 5 compared to PA. So, PA affinity has been improved confirming that the SAr by NMR strategy works. The designed molecules are good hits that have to be optimized to become lead molecules in the pharmaceutical pipeline.

Keywords : DNA polymerase beta, fragment-based drug design, NMR, screening