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The design and discovery of CXCR4 chemokine receptor antagonists through incorporation of GPCR-medchem based fragments

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In the world of G-protein coupled receptor drug research, there have been many profitable developments leading to historical and recent therapeutic breakthroughs. The chemokine receptors are a newer addition to the list of the growing number considered as GPCR "druggable" targets with two drugs now approved in this area. Our interest in the chemokine receptor CXCR4 comes from the involvement of this GPCR in immune system complex functions. Designing antagonists of this receptor would result in potential drugs for treatments varying from stem cell mobilization to prevention of HIV virus entry and infection. The recent drug approval of the cyclam AMD3100 illustrates the potential. Our effortts involve the design of new ligands of the CXCR4 receptor based on fragments and chemotypes in a de novo hit-to-lead effort. These fragments were selected based on their frequency of appearance in medicinal chemistry and GPCR small molecule research. This has resulted in the discovery of CXCR4 antagonists containing the tetrahydro-isoquinoline (TIC) and piperazine fragments, which possess nanomolar potencies against the receptor in various bioassays of ligand (SDF-1/HIV) and receptor (CXCR4) involvement. The strategy and design along with the synthesis and biological results will be presented. Also, some computational modeling showing proposed binding modes of these molecules and the CXCR4 receptor will be shown.

Biography

Larry Wilson completed his Ph.D. from Emory University and postdoctoral studies from Stanford University. He has served various roles in research and development groups at several large pharmaceutical and small biotech companies. He has over 50 publications, patents, and review articles. He is currently principal scientist at Emory University, where he serves as project leader of the discovery of CXCR4 antagonists for potential treatments in stem cell mobilization, cancer, and HIV infection.

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