Douglas S. Auld, Noel T. Southall, Ajit Jadhav, Ronald L. Johnson, David J. Diller, Anton Simeonov, Christopher P. Austin and James Inglese
J. Med. Chem., 2008, 51 (8), pp 2372–2386
DOI: 10.1021/jm701302v
Publication Date (Web): March 26, 2008

Abstract

To aid in the interpretation of high-throughput screening (HTS) results derived from luciferase-based assays, we used quantitative HTS, an approach that defines the concentration−response behavior of each library sample, to profile the ATP-dependent luciferase from Photinus pyralis against more than 70000 samples. We found that approximately 3% of the library was active, containing only compounds with inhibitory concentration−responses, of which 681 (0.9%) exhibited IC50 < 10 μM. Representative compounds were shown to inhibit purified P. pyralis as well as several commercial luciferase-based detection reagents but were found to be largely inactive against Renilla reniformis luciferase. Light attenuation by the samples was also examined and found to be more prominent in the blue-shifted bioluminescence produced by R. reniformis luciferase than in the bioluminescence produced by P. pyralis luciferase. We describe the structure−activity relationship of the luciferase inhibitors and discuss the use of this data in the interpretation of HTS results and configuration of luciferase-based assays.