Evaluation of novel Akt1 inhibitors as anticancer agents using virtual co-crystallized pharmacophore generation.

Al-Sha'er MA¹, Mansi I², Almazari I³, Hakooz N³.

Author information

- ¹Faculty of Pharmacy, Zarqa University, P.O.Box 132222, Zarqa, 13132, Jordan. Electronic address: a.mahmoud@zu.edu.jo.
- ²Faculty of Pharmaceutical Sciences, The Hashemite University, P.O. Box 330127 Zarqa, 13115 Jordan.
- ³Faculty of Pharmacy, Zarqa University, P.O.Box 132222, Zarqa, 13132, Jordan.

Abstract

The pharmacophoric features of the virtual co-crystallized protein of 17 Akt1 proteins were downloaded from the protein data bank, and explored to end up with 132 generated pharmacophores that had been evaluated using the decoy list composed of 1724 compounds. The areas under the curve of the Receiver-Operating Characteristic (ROC-AUC) were sorted, and the highest ranked pharmacophore 3MV5_2_01 was selected to be used as a searching tool in the National Cancer Institute (NCI) database. The captured hits were mapped based on successful hypotheses and the best fitted compounds were selected. The inhibition of Akt1 was measured and expressed as a percentage of inhibition. 24 out of the 40 compounds showed inhibition of Akt1, out of which 13 compounds showed more than 50% inhibition. Compound 1 showed 93.3% inhibition at 100 μM concentration. To confirm the inhibition of Akt1 phosphorylation, MCF10A cell line was co-treated with 12-O-tetradecanoylphorbol-13-acetate (TPA) and 100 μM of each of the most potent 13 Akt inhibitors (1-13). It was found that compounds 1 exert 91.6% inhibition of Akt1 phosphorylation in MCF10A cell line.

Copyright © 2015 Elsevier Inc. All rights reserved.

KEYWORDS:

Akt1; Cancer; Co-crystallized structure; Cox-2; Docking; MCF10A; Pharmacophore; Roc analysis