

# Diversity Oriented Virtual Compound Selection Strategy for High Throughput Screening of Potential Anticancer Agents

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The CancerGrid consortium was formed by ten life sciences companies and academic centers in 2007 to carry out a three-year multidisciplinary research program funded by the European Commission ([www.cancergrid.eu](http://www.cancergrid.eu)). The consortium members work together to develop novel methods to increase the chance of finding potential anticancer agents. Grid-based computing technology is applied to the virtual screening of huge discovery libraries in order to identify promising lead compounds. According to the project plan 30,000 small molecules are selected by various state-of-the-art computational methods, and are then screened in cell-based and target-based assays. This stage will be followed by model development and validation based on the large number of screening data.

In order to discover novel chemotypes for anticancer agents, a multi-step virtual screening procedure was developed and carried out on the initial compound set which includes merged collections from repositories of University of Bari (1,500) and AMRI (199,100) leading to a diverse library (30,000) for biological screening. Forty percent of the compounds were selected against specific cancer targets (HSP90, RET, HDAC and MMP), or their known, biologically active ligands by using *in silico* similarity and 2D/3D target-based methods [1-4]. Another 50% of the compounds were selected using *Drug Like Index* (DLI) [5] and strict ADME filters [6]. In order to support future works of HTS as well as QSAR model building, a reference set was selected randomly (5%) and a "Trojan horse"-type of counter set (5%) having poor *Drug Like Index* and ADME properties was also included. We present here the generation of the discovery screening library carried out by the various research groups.

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1. Nicolotti, O.; Miscioscia, T. F.; Leonetti, F.; Muncipinto, G.; Carotti, A. *J. Chem. Inf. Mod.*, **2007**, 47, 2439-48;
2. Langer, T.; Hoffmann, R. D., *Expert Opinion on Drug Discovery* **2006**, 1(3), 261-267;
3. Tovar, A.; Eckert, H.; Bajorath, J. *ChemMedChem*. **2007**, 2, 208-217;
4. Mestres, J.; Martín-Couce, L.; Gregori-Puigjané, E.; Cases, M.; Boyer S. *J. Chem. Inf. Model* **2006**, 46: 2725-2736;
5. Rayan, A.; Marcus, D.; Givaty, O.; Barasch, D.; Goldblum, A.; *Abstracts of Papers of the American Chemical Society* **2005**, 230, U1013 .
6. Fontaine, F., Pastor M., Zamora I., Sanz F. *J Med Chem*. **2005**, 48(7):2687-94.