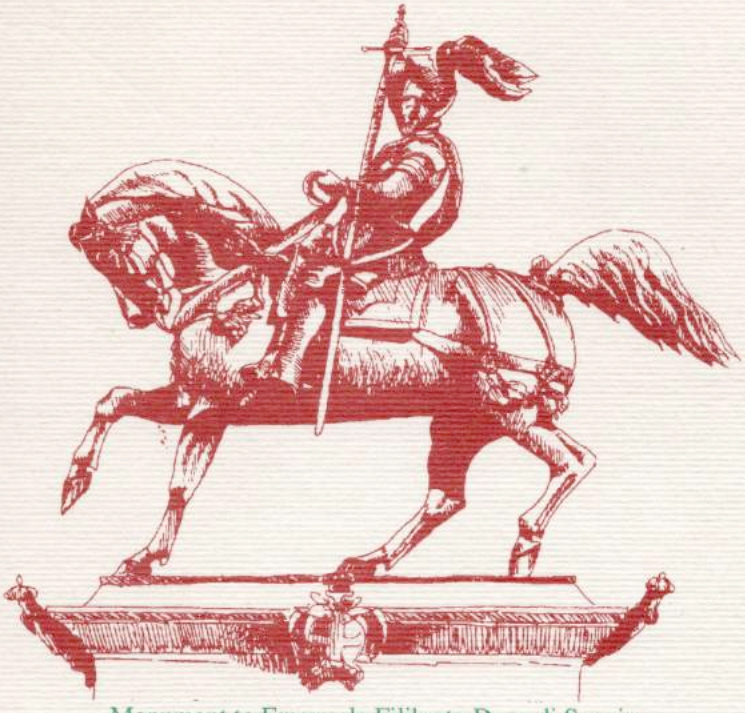
Italian Chemical Society
Division of Medicinal Chemistry

University of Turin

New Swiss Chemical Society
Section of Medicinal Chemistry

FIRST ITALIAN-SWISS MEETING ON MEDICINAL CHEMISTRY

Torino Incontra Congress Center
September 23-26, 1997 - Torino, ITALY



Monument to Emanuele Filiberto Duca di Savoia
1528 - 1580

Abstract

edizioni MAF Servizi - Torino

"Structure-Based Discovery & in Parallel Optimization of Novel Inhibitors of Thymidylate Synthase"

Tondi, D.,§ Slomczynska, U.§, Ghelli, S.⌘, Watterson, D.M.§, Costi, M.P.⌘, Shoichet, B.K.§*

§Department of Molecular Pharmacology and Biological Chemistry, Northwestern University Medical School, Chicago,IL. ⌘Dipartimento di Scienze farmaceutiche, Universita' degli Studi di Modena, Italy.

*Corresponding author.

Protein structures have facilitated the discovery of new lead compounds for a large number of enzymes and receptors [1-3]. The subsequent optimization of these leads has typically involved the one-by-one synthesis of variants, which is often slow. To speed up the "rational drug design cycle" [4, 5] we have combined structure-based methods with combinatorial technologies [6].

We began with the structure of Thymidylate Synthase (TS) a well known target for the design of antiproliferative drugs [7]. Using the computer program DOCK [8], we investigated the active site of TS with a database of 180.000 commercially available compounds. The program generated a list of potential ligands for the enzyme from which we identified a new non-substrate analog TS inhibitor. This inhibitor had a Ki of 160 μM. Using solid phase in parallel techniques, we synthesized a small library of compounds, analogs of the original lead, and tested them against *Lactobacillus casei* TS. A first round analog had a Ki of 1.5 μM. A second round library is now being constructed to further optimize this series of compounds.

Structure-based inhibitor discovery has proven to be a useful technique for the discovery of novel lead compounds for drug design. Combinatorial chemistry is able to introduce focused diversity into a series of compounds efficiently. Our preliminary efforts to combine these techniques have allowed us to discover a novel lead, predict a binding site and rapidly optimize the affinity of the series of compounds.

1) Bohacek, R.S., Mc Martin, C., Guida, W.C. (1996). ***Med. Res. Rev.*** 16 (1) 3-50
2) Blundell, T.L. (1996). ***Nature*** 384, 23-26 (Supp.)
3) Shoichet, B.K, Stroud, R.M., Santi, D.V., Kuntz, I.D., Perry, K. (1993). ***Science*** 259, 1445-1450
4) Verlinde, C.L.M.J., et al. (1994). ***Protein Science*** 3: 1670-1686
5) Colman, P.M. (1994). ***Current Opinion in Structural Biology*** 4: 868-874
6) Hogan, J.C. (1996). ***Nature*** 384, 17-19 (Supp.)
7) Carreras, C.W. and Santi, D.V. (1995). ***Annu. Rev. Biochem.*** 64: 721-62
8) Kuntz, I.D. (1992). ***Science*** 257; 1078