

## EXPLORATORY CHEMISTRY TOWARD THE IDENTIFICATION OF NEW CLASSES OF MDR REVERTERS

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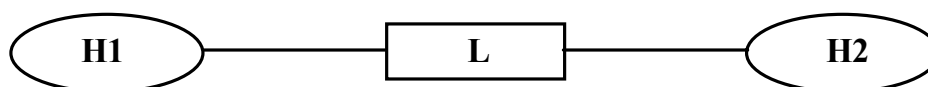
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Multidrug resistance (MDR) is a kind of acquired drug resistance of cancer cells and microorganisms to a variety of chemotherapeutic drugs that usually are structurally and mechanistically unrelated [1]. This kind of resistance is often referred to as classical MDR and is due to a lower cell concentration of cytotoxic drugs associated with accelerated efflux of the chemotherapeutic, as a consequence of the over expression of proteins such as Pgp and MRP1 [2] that act as extrusion pumps by using ATP as energy source. Based on the structure of MsbA protein, obtained from two different bacteria, several Pgp homology models have been developed [3-5]. From these and many other reports on the structure of extruding pumps, it appears that the recognition sites are large, flexible, rich of aminoacids able to establish a variety of interactions with substrates, in particular aromatic hydrophobic interactions. Information gathered on the structure of Pgp and sister proteins point to the existence of a large, polymorphous drug binding domain, where a variety of substrates and inhibitors can be accommodated in a plurality of binding modes [6].

Taking into account the emerging picture of Pgp recognition site, it can be predicted that flexible molecules, carrying a basic nitrogen flanked, at properly modulated distance, by two aromatic moieties, as is the case of verapamil [7-10] and pervilleines [11], will easily adapt to the recognition site and bind with high affinity.

To verify our hypothesis, we designed a new series of molecules having the general structure shown below, where H1 and H2 represent a variety of aromatic moieties found present in previously studied MDR reverters, while L is a linker of variable length carrying one or two basic nitrogen atoms.



The good results obtained, that will be presented together with the synthesis of the new molecules, can be considered the proof of concept of our approach.

[1] Mitscher, L.A. et al., *Med. Res. Reviews.* **1999**, *19*, 477-96. [2] Arzalos, A. et al. *Anticancer Res.* **1998**, *18*, 2937. [3] Stenham, D. R. et al., *FASEB J.*, **2003**, *17*, 2287-2289. [4] Seigneuret, M. et al. *J. Biol. Chem.*, **2003**, *278*, 30115-30124. [5] Pleban, K. et al., *Mol. Pharmacol.*, **2005**, *67*, 365-374. [6] Yu, E.W. et al. *Science*, **2003**, *300*, 976-980. [7] Teodori, E. et al. *J. Med. Chem.*, 1999, *42*, 1687-1697. [8] Dei, S. et al. *Bioorg. & Med. Chem.*, 2001, *9*, 2673-2682. [9] Teodori, E., et al., *Med. Chem. Res.*, 2001, *10*, 563-576. [10] Dei, S. et al. *Bioorg. & Med. Chem.* **2005**, *13*, 985-998. [11] Mi, Q. et al., *Cancer Research*, **2001**, *61*, 4030-4037.