# A general pattern for substrate recognition by P-glycoprotein


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P-glycoprotein actively transports a wide variety of chemically diverse compounds out of the cell. Based on a comparison of a hundred compounds previously tested as P-glycoprotein substrates, we suggest that a set of well-defined structural elements is required for an interaction with P-glycoprotein. The recognition elements are formed by two (type I unit) or three electron donor groups (type II unit) with a fixed spatial separation. Type I units consist of two electron donor groups with a spatial separation of 2.5 +/- 0.3 A. Type II units contain either two electron donor groups with a spatial separation of 4.6 +/- 0.6 A or three electron donor groups with a spatial separation of the outer two groups of 4.6 +/- 0.6 A. All molecules that contain at least one type I or one type II unit are predicted to be P-glycoprotein substrates. The binding to P-glycoprotein increases with the strength and the number of electron donor or hydrogen bonding acceptor groups forming the type I and type II units. Correspondingly, a high percentage of amino acids with hydrogen bonding donor side chains is found in the transmembrane sequences of P-glycoprotein relevant for substrate interaction. Molecules that minimally contain one type II unit are predicted to be inducers of P-glycoprotein over-expression.
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