Halogen-substituted Drugs and their Intermolecular Interactions

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Halogen substitution is an important tool in drug design. Halogenation alters physicochemical properties and enhances the potency of membrane-soluble anesthetics. The presence and identity of halogen (X) substituents pendant on an aromatic nucleus in anticonvulsant and anxiolytic drugs have significant consequences for activity. Explanations of the Structure-activity effects of halogens have been limited to considerations of membrane solubility and the steric effects of X substituents on aromatic rings even though much is know about the effect of halogens on crystal packing. Crystal engineering originated with a study of the packing of Cl substituents [1]. Subsequent investigations using the CSD [2] and theoretical calculations have established the intermolecular interactions important in crystals of halogen compounds: (a) X atoms are potential H-bond acceptors able to interact with strong and weak H-bond donors [3], although the evidence is equivocal for C-F as a H-bond acceptor [4]; (b) C-H•••X interactions are weakly attractive yet highly dependant on the molecular environment of the halogen [5, 6] and (c) X•••aromatic ring and X•••H are stronger interactions than X•••X [7]. Structure activity relationships in CNS drugs will be interpreted in light of these intermolecular interactions to explain identify key factors for binding.

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