The Properties of Hydroxyl Groups in Marketed Drugs

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Hydroxyl groups are frequently involved in biomolecular recognition events and, thus, a common feature of drug molecules. The high directionality and strongly polar nature of the interactions of this functional group holds the potential for highly favorable interactions. However, dramatic penalties in binding enthalpy due to high desolvation costs can reduce binding affinity by several orders of magnitude, if interaction vectors of hydroxyl groups are inappropriately saturated. As a result, great care has to be exercised when the inclusion of hydroxyl groups is considered during the design of a drug molecule. An analysis of the ChEMBL database shows that more than a third of all marketed drugs contain alcohols. However, when the compound entries are examined with regard to the origin of the respective pharmacophore structure, it becomes evident that drugs derived from natural products are far more likely to contain one or multiple OH groups than purely synthetic molecules. A dataset of hydroxyl groups in marketed drugs reveals privileged structural features that contribute to OH interactions by complementing directional hydrogen bond interactions and preorganization of productive binding poses.

Because of their unique physico-chemical properties, the introduction of hydroxyl groups can have a dramatic effect on the properties of a drug molecule. A set of guidelines derived from the analysis of prevalent structural features in marketed drugs can help medicinal chemists to make more informed decisions during lead optimization.