Shape Description of the Minor Groove

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Since sequence-dependent shape is recognized more and more important in the binding of proteins to DNA [1], large molecule databases were screened for molecules potentially binding to the minor groove of DNA using a shape-based virtual screening protocol. The traditional view of DNA binding as realization of hydrogen bonding patterns was left towards a more general description of DNA by its characteristic three-dimensional shape. Since chemical properties and shape of DNA are closely related [2], this virtual screening approach was considered promising for the discovery of new minor groove binders, a group of molecules known to influence gene expression [3] and to prevent transcription factors from binding to DNA [4]. Several previously unknown minor groove binders were discovered with this method and confirmed experimentally by means of isothermal titration calorimetry (ITC), ^{1}H-NMR experiments, UV spectroscopy and DNA melting experiments [5].

ROCS [6] was used for virtual screening of the NCI database [7] using minor groove binders in bioactive conformation from X-ray structures as queries. ROCS represents heavy atoms by Gaussians with parametrized decay constants according to the van der Waals radii of the respective atoms. This depiction allows a fast comparison of molecules due to the straightforward calculation of volume overlaps being used as a measure for similarity of the molecules. Besides shape description ROCS includes “Color Force Fields” allowing basic inclusion of chemical information as additional “Color Gaussians”. Nevertheless the shape focus of this virtual screening application provides structurally diverse hits known as scaffold or lead hopping [8]. In our case four structurally uncommon minor groove binders were discovered, one of them completely lacking the traditional hydrogen bond donor functions in the central part of the molecule suggesting that this compound would not have been detected with conventional virtual screening approaches.

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