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Specificity score and fragment-based virtual screening

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Fragment-based method has been emerging as a promising strategy for lead identification recently, whereas it is still a challenge to distinguish active fragments from inactive ones by molecular docking. Here, we propose a novel approach to improve validity of docking score to identify active fragments, by means of normalizing scores by molecular size and optimizing scoring parameters. This approach has several outstanding points. (1)It can identify the active fragments and lead-like compounds which have room to add new chemical groups for lead optimization. (2)It can decrease the number of false-positives by optimizing parameters in consideration of separation of known active and inactive compounds. (3) It can prevent over-fitting to noise-rich activity data. We will report the results of parameter optimization, cross-validation and an example of fragment screening and lead design.