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Size dependence of docking scores in a retrospective evaluation of spiro[indoline-tetrazolo[1,5-*c*]quinazoline] derivatives against histone deacetylase 8

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Introduction. Histone deacetylase 8 (HDAC8) is a class I isoform implicated in Cornelia de Lange syndrome and in selected malignancies. Most established inhibitors coordinate the catalytic zinc ion, an interaction that limits discrimination among isoforms. Whether a scaffold devoid of such a group can engage the catalytic site through active-site contacts alone remains unresolved. An in-house series of spiro[indoline-tetrazolo[1,5-*c*]quinazoline] derivatives was therefore examined retrospectively – not to propose inhibitors, but to ask how far such a ranking may be trusted before synthesis.

Materials and methods. Ten compounds, nine spiro derivatives and the parent tetrazolo[1,5-*c*]quinazoline scaffold as control, were docked with CB-Dock2 [1] into the inhibitor-bound HDAC8 structure 2V5X [2], with five reference ligands as scale anchors; cavity detection used CurPocket and scoring AutoDock Vina. The template-based pose of the co-crystallised ligand reproduced its crystallographic placement to within 0.385 Å (centroid). Contacts were characterised in Discovery Studio Visualizer, distances to the catalytic zinc computed from the deposited coordinates and scores normalised to ligand efficiency [3].

Results and discussion. Under CB-Dock2 every ligand scored best in Pocket 1, the catalytic site, with *N*-(4-cyanophenyl)-2-oxo-6'*H*-spiro[indoline-3,5'-tetrazolo[1,5-*c*]quinazoline]-1-carboxamide and its 3-(trifluoromethyl)phenyl analogue heading the series (−12.3 and −11.0 kcal/mol, respectively). The reference set did not reproduce the reported potency order: PCI-34051 [4] (IC_{50} 10 nM) scored −8.8 kcal/mol, less favourably than the co-crystallised hydroxamate (−10.8). Two explanations cannot be separated: no metal-coordination term, penalising chelators, and a bias toward larger ligands. Score correlates with heavy-atom count ($r=-0.72$, $p=0.004$, $n=14$) and does not survive normalisation to ligand efficiency: the unsubstituted parent 6'*H*-spiro[indoline-3,5'-tetrazolo[1,5-*c*]quinazolin]-2-one attains the highest value, equal to PCI-34051, whereas the 4-cyanophenyl carboxamide falls to fifth and the hydroxamate to second from last. Much of the ordering thus reflects molecular size rather than pocket complementarity; no linker effect was detected (Kruskal–Wallis $p=0.58$).

The 4-cyanophenyl carboxamide complex engages the catalytic cavity: six of its eight assigned contacts belong to the active site of one monomer and two to the second, crystallographically independent copy. Stabilisation arises from π-stacking and π-anion contacts rather than metal coordination; His180 of the zinc-coordinating triad lines the cavity but carries no assigned contact. Cytotoxicity data for three synthesised members – one weakly cytotoxic, two inactive – neither support nor refute the ranking.

Conclusions. Under CB-Dock2 the series engages the HDAC8 catalytic cavity *in silico* without a zinc-binding group, approaching the metal centre through active-site contacts alone, yet the ranking is size-dependent and not, alone, a sufficient basis for selection. Until enzymatic assays and counter-screening against a further class I isoform exist, no claim of inhibition or selectivity is supported. Size-normalised reporting appears warranted whenever heterogeneous sets are ranked by docking.

References

1. Liu Y, Yang X, Gan J, et al. Nucleic Acids Res. 2022;50(W1):W159–W164.
2. Vannini A, Volpari C, Gallinari P, et al. EMBO Rep. 2007;8(9):879–884.
3. Hopkins AL, Groom CR, Alex A. Drug Discov Today. 2004;9(10):430–431.
4. Balasubramanian S, Ramos J, Luo W, et al. Leukemia. 2008;22(5):1026–1034.

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