Optimizing Dimer Linker Length of an Anti-Cancer Peptoid Drug-Lead

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ABSTRACT

Many recurrent tumors are caused by drug-resistant, self-renewing, and highly metastatic cancer stem cells (CSCs). H358 is a non-small cell lung cancer (NSCLC) cell line with CSCs containing the cell surface protein plectin that is targeted by peptoid dimer PCS2D1. We compared the effect of PCS2D1 to that of ten of its linker variations on the viability of H358 cells and found that PCS2D1's linker length allowed it to show optimal activity, while the modified compounds with shorter or longer linkers had less of an effect on the cells.

BACKGROUND

- Peptoid dimer PCS2D1 has been shown to be effective at reducing the viability of H358 NSCLC cells.
- Modifications have been made to the number of repeating units in the chain linking the two monomers in PCS2D1, with the shortest linker having 2 carbons and the longest 85 carbons.
- This gave rise to 10 more compounds, including PCS2D1.3, PCS2D1.5, PCS2D1.7, PCS2D1.9, and PCS2D1.11 (Figure 1), which have been renamed PCSD3, PCSD5, etc.
- PCS2D2.1, PCS2D2.2, PCS2D2.3, PCS2D2.4, and PCS2D2.5 (Figures 2-4) have also been synthesized.
- We now test the 10 new compounds for their effect on the viability of H358 cells to see if the cancer cells display reduced viability with these modifications when compared to the parent compound.

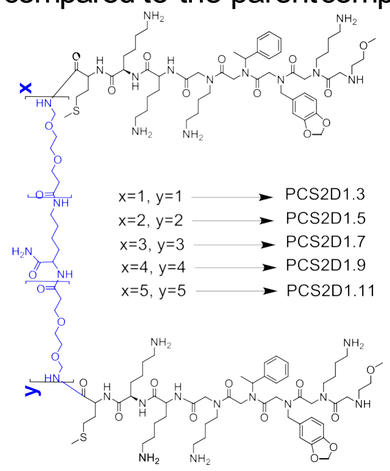


Figure 1: PCS2D1 series structures

METHODS

- Culture H358 cells in a T25 flask using proper passaging and aseptic technique.
- Seed 1500 cells per well in a 96-well plate and incubate for at least 12 hours to ensure cell adhesion.
- Serially dilute each compound using media to 80 µM, 50 µM, 30 µM, 10 µM, 3 µM, 1 µM, and 100 nM (80 µM replaced with 300 nM for compounds PCSD3 and PCSD5).
- In sets of 3 columns, remove media and replace with 100 µL of compound in each well. Pipette compounds in triplicates, making sure to always have PCS2D1 present as the control (Figure 5).

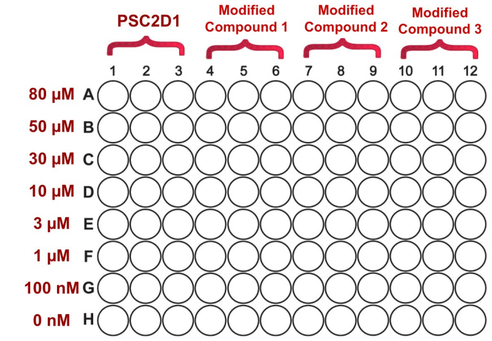
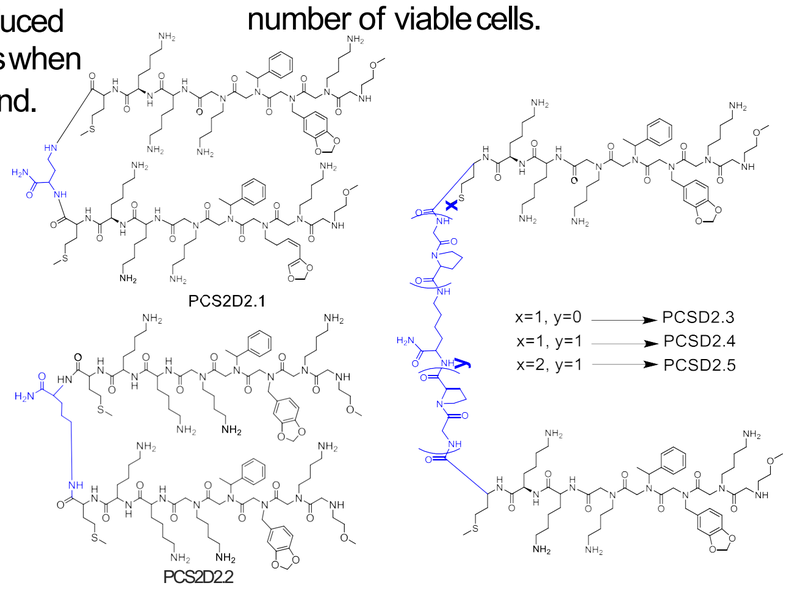


Figure 5: 96-well plate layout

- On the 5th day after treating cells with the compounds daily for 4 days, remove compounds and replace with 100 µL of 20% MTS (80% media) in each well.
- Incubate for 2 hours before using SoftMax Pro 6.4 software to read the number of viable cells.



Figures 2-4: PCS2D2 series structures

RESUL

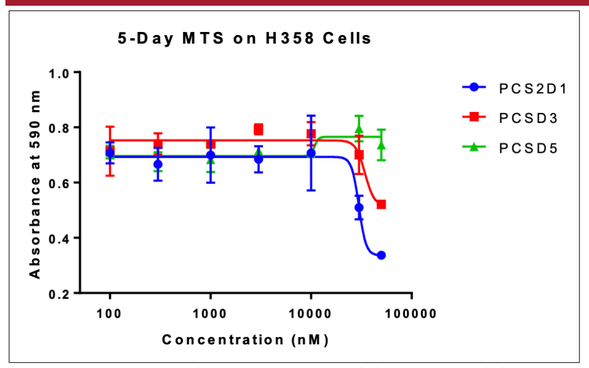


Figure 6: MTS results for PCSD3 and PCSD5

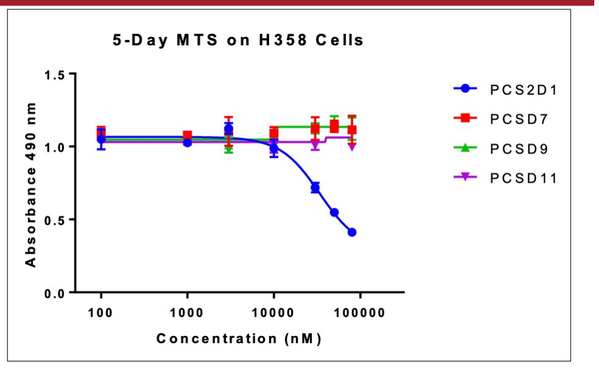


Figure 7: MTS results for PCSD7, PCSD9, and PCSD11

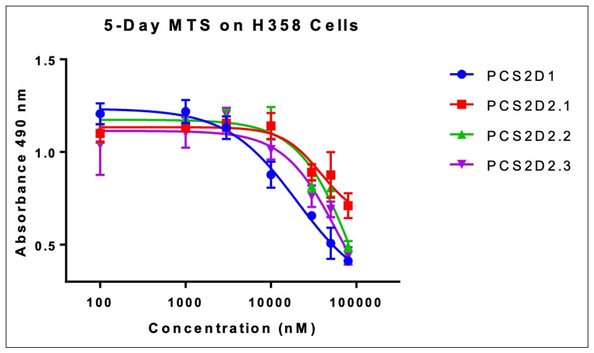


Figure 8: MTS results for PCSD2.1, PCSD2.2, and PCSD2.3

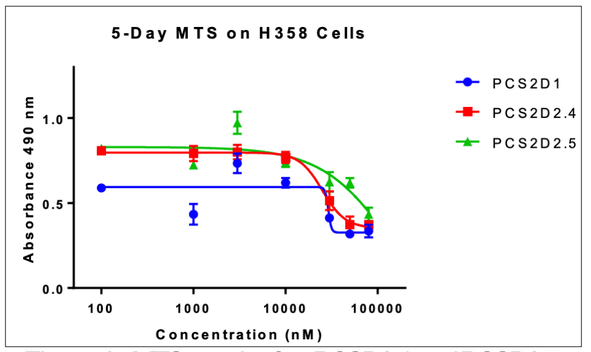


Figure 9: MTS results for PCSD2.4 and PCSD2.5

- Compounds PCSD5, PCSD7, PCSD9, and PCSD11 show no activity towards H358 cells and can be ruled out as candidates for a drug with potential to kill H358 CSCs.
- Compounds PCS2D2.1, PCS2D2.2, PCS2D2.3, PCS2D2.4, PCS2D2.5, and PCSD3 perform similarly to and/or slightly worse than the parent compound.

CONCLUSIONS

- The compounds with the shortest linker lengths, PCS2D2.1 with 2 carbons and PCS2D2.2 with 3 carbons, displayed some activity, although less than that of the parent compound, PCS2D1, which had a linker length of 4 carbons.
- Further lengthening the linker reduces the compound's activity, causing PCSD5 through PCSD11 to display no activity at all towards H358 cells.
- The parent peptoid, PCS2D1, is shown to have the optimal linker length.

ACKNOWLEDGEMENTS

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WORKS CITED

Raymond, A. C., Gao, B., Girard, L., Minna, J. D., & Udugamasooriya, D. G. (2019). Unbiased peptoid combinatorial cell screen identifies plectin protein as a potential biomarker for lung cancer stem cells. *Scientific reports*, 9(1), 1-15.