RANGE AND SENSITIVITIES OF 2-[(CARBOXYMETHYL)SULFANYL]-4-OXO-4-ARYLBUTANOIC ACIDS PROPERTY SPACES. PART 2. MULTIDIMENSIONAL FREE ENERGY LANDSCAPES

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The 2-[(carboxymethyl)sulfanyl]-4-oxo-4-arylbutanoic acids (CSAB, Figure 1) exert antiproliferative potency toward all NCI sixty human tumor cell lines^[1 a)] in submicromolar to low micromolar concentrations.^[1 b)] In this communication we are focused on the observed selectivity of compounds, comparing potency toward human cervix carcinoma cells (HeLa) vs. healthy human cells.^[2] Previously, selectivity of selected compounds was correlated with properties derived from their conformational assemblies. Using the concept of ranges and sensitivities of property spaces^[3] we demonstrated that the range of apolar surface areas, obtained by conformational search in vacuum (OPLS2005 FF), was well correlated with the selectivity giving bilinear correlation.^[4] Here, we have extended our findings on the whole prepared set. In this way, along with statistical significance of correlation obtained, compounds can be classified from highly potent/highly selective via highly potent/moderately selective to those that exert less significant potency (IC₅₀ in low μ M concentrations) and relatively low selectivity. To put results on a solid theoretical background, 20 ns molecular dynamics (MD) simulations (CHARMM FF) were performed for all compounds in the explicit

n-octanol/water (4: 1) and in the explicit water. During simulations, a biasing force was applied over three collective variables (geometric parameter that measure progression of conformational change) to obtain free energy landscape of compounds.^[5 a)] The enhanced sampling of MD trajectories was obtained, as well as the estimate of free energy gradient for the whole conformational space of the each compound in a given medium. The good correlation obtained between selectivity of compounds and the time needed for



Figure 1. Structure of the title compounds.

conformational change from the 'bent' to the 'extended' in n-octanol/water should be considered as significant; because the time of the whole simulation enables uniform sampling along each applied reaction coordinate. Next, few local minima appear on 3D maps of the free energy landscape of the compounds having both high potency and high selectivity, opposite to those exerting lower potency and selectivity. This sheds light on, at the first sight somewhat paradoxical, observation that the more flexible compounds exerts both higher selectivity and better potency. It should be noted that differences in

8th ≝0 SA



flexibilities are due only to different substitution patterns on the phenyl ring.

To the best of our knowledge, this is the first, and the first successful application of the concept of the ranges and sensitivities of the property spaces on the selectivity data; as well as their first corroboration by physically well-grounded concept of the adaptive biasing force calculations, [5a, b] that give good distinction between the metastable and stable conformational states. On the other hand, derived results are very applicable for the further design of the title class of compounds.

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