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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 (IC_{50} in low μM 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 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

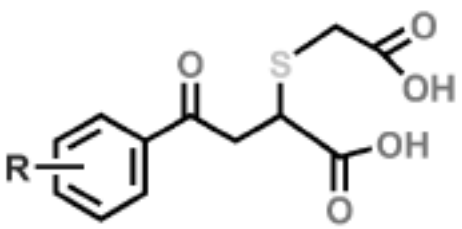

Figure 1. Structure of the title compounds.

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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References:

[1] a) R. H. Shoemaker, *Nat. Rev. Cancer* **6** (2006) 813, b) Unpublished results; [2] B. J. Drakulić, Z. D. Juranić, T. P. Stanojković, I. O. Juranić, *J. Med. Chem.* **48** (2005) 5600; [3] a) G. Vistoli, A. Pedretti, L. Villa, B. Testa, J. *Am. Chem. Soc.* **124** (2002) 7472, b) G. Vistoli, A. Pedretti, B. Testa, *Drug Discov. Today* **13** (2008) 285; [4] B. J. Drakulić, Z. D. Juranić, T. P. Stanojković, M. F. Zloh, I. O. Juranić, The XVI European Symposium on Quantitative Structure-Activity Relationships and Molecular Modelling, *Book of Abstracts* (2006) pp. 274-275; [5] a) J. Hénin, G. Fiorin, C. Chipot, M. L. Klein, *J. Chem. Theory Comput.* **6** (2010) 35, and references cited therein, b) NAMD 2.7b2 User guide, http://www.ks.uiuc.edu/Research/namd/2.7b2/ug/.

4-ARYL-4-OXO-N-PHENYL-2-AMINYLBUTYRAMIDES AS NOVEL CLASS OF ACETYLCHOLINESTERASE INHIBITORS*

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The twenty 4-aryl-4-oxo-N-phenyl-2-aminylbutyramides (Fig. 1) were designed and synthesized. Their inhibition of acetylcholinesterase activity (AChE, EC 3.1.1.7) was tested using Ellman's spetrophotometric assay. Eight derivatives showed inhibition activity in low-micromolar range. The presence of voluminous alkyl substituents (4-*i*-Pr, 2,4-di-*i*-Pr and *β-tetralinoyl*) on the aroyl moiety of piperidino- and imidazolo-derivatives changes anti-AChE activity for two orders of magnitude in respect to unsubstituted congeners. Replacement of piperidino methylene group with oxygen in morpholino derivatives results with complete loss of anti-AChE activity. The most potent piperidino- and imidazolo- derivative showed mixed inhibition type, indicating their binding to free enzyme and enzyme-substrate complex. Alignment-independent 3D QSAR study, based on molecular interaction fields (MIF's) was performed on the set containing reported compounds and the ones taken from the literature. Totally 38 compounds were collected, including secolycorines [1], 1-[bis(4-fluorophenyl)-methyl]piperazines [2], litebamine derivatives [3], imidazolyl-isoxazolines [4], 3-aryl-N-methyl-tetrahydropyridine derivatives [5], spanning range of potencies 0.8 - 240 μM ($\sim$ 2.5 log(1/(IC_{50})) units). All compounds were submitted to Pentacle, and for the model building HBD (N1), HBA (O) and hydrophobic (DRY) probe were used. Obtained model has good statistics and predictivity (R_{acc}^2 = 0.91, Q_{acc}^2 (RG) = 0.54). The analysis confirmed that alkyl substitution on the aroyl moiety of molecules is requisite for inhibition activity. The presence of hydrophobic moiety at a close distance from hydrogen bond acceptor has favorable influence on inhibition potency. The presence of hydrogen bond acceptor and hydrogen bond donor on spatial distance of $\sim$ 12.5 Å yields less potent compounds. To investigate possible ligand-AChE interactions, docking studies were performed on electric eel AChE to generate binding model for the most active 2,4-di-*i*-Pr imidazolo derivative, using AutoDock 4.0.1. Docking studies showed that both enantiomers of the compound bind probably in the middle of the active site gorge of AChE, interacting with anionic site of the AChE (Trp 86), acyl pocket (Phe 295 and Phe 297) and peripheral anionic site (Tyr 72, Tyr 124).

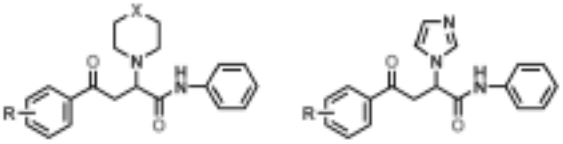

Figure1. 4-Aryl-4-oxo-N-phenyl-2-aminylbutyramides, X = -CH2- or -O-;. R=H, 2,5-di-Me, 4-Cl, 4-MeO, 4-i-Pr, 2,4-di-i-Pr and β-tetralinoyl.

References:

[1] Lee, S-S.; Venkatesham, U.; Prasad Rao, C.P.; Lam, S-H.; Lin, J-H. *Bioorg. Med. Chem*. **2007**, 15, 1034; [2] Sadashiva, C. T.; Chandra, J. N. N. S.; Ponnappa, K. C.; Gowda, T. V.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2006**, 16, 3932; [3] Chiou, C-M.; Kang, J-J.; Lee, S-S. *J. Nat. Prod.* **1998**, 61, 46; [4] Rangappa, K. S. B. *J. Phys. Org. Chem.* **2005**, 18, 773; [5] Benaka Prasad, S. B.; Sunil Kumar, Y. C.; Ananda Kumar, C. S.; Sadashiva, C. T.; Vinaya, K.; Rangappa, K. S. *The Open Med. Chem.* J., **2007**, 1, 4.

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