Figure legends

Figure 1. Density $Q_{cano}(\lambda^{(\alpha)}, \lambda^{(\beta)}, \lambda^{(\gamma)})$ of (a) the sertraline-mSin3B, (b) YN3-mSin3B, and (c) acitretin-mSin3B systems in the 3D-RC space. In GA-guided mD-VcMD, the distribution is defined originally by $Q_{cano}(L^{(\alpha)}, L^{(\beta)}, L^{(\gamma)})$, where $L^{(\alpha)}, L^{(\beta)}$, and $L^{(\gamma)}$ are respectively indices to specify the positions $\lambda^{(\alpha)}$, $\lambda^{(\beta)}$, and $\lambda^{(\gamma)}$ in the 3D-RC space. Then, we convert $[L_i^{(\alpha)}, L_j^{(\beta)}, L_k^{(\gamma)}]$ to: $\lambda_l^{(\alpha)} = 0.5\{\left[\lambda_i^{(\alpha)}\right]_{min} + \left[\lambda_i^{(\alpha)}\right]_{mas}\}$, where $i = 1, \dots, n_{vs}(\alpha)$, $\lambda_j^{(\beta)} = 0.5\{\left[\lambda_j^{(\beta)}\right]_{min} + \left[\lambda_j^{(\beta)}\right]_{mas}\}$, where $j = 1, \dots, n_{vs}(\beta)$, and $\lambda_j^{(\beta)} = 0.5\{\left[\lambda_j^{(\gamma)}\right]_{min} + \left[\lambda_j^{(\gamma)}\right]_{mas}\}$, $k = 1, \dots, n_{vs}(\gamma)$. See Supplementary Table S3 for values of $\left[\lambda_i^{(h)}\right]_{min}$, $\left[\lambda_i^{(h)}\right]_{max}$, and $n_{vs}(h)$ $(h = \alpha, \beta, \gamma)$. Then, $Q_{cano}(\lambda^{(\alpha)}, \lambda^{(\beta)}, \lambda^{(\gamma)})$ is normalized so that the highest density is set to 1. Contour levels are presented by colors in inset.

Figure 2. Spatial density $\rho_{CG}^{(s)}(\boldsymbol{r})$ of the geometric center (GC) at position $\boldsymbol{r}$ for (a) the sertraline-mSin3B, (b) YN3-mSin3B, and (c) acitretin-mSin3B systems in the 3D real space. See Supplementary Section 4 for procedure to calculate $\rho_{CG}^{(s)}(\boldsymbol{r})$. Contour levels are shown in inset where $\rho_0 = 0.001$. Displayed structure of mSin3B is that after NPT simulation for each system, where labels H2 and H3 represent helix 2 and helix 3, respectively. The high-density cluster ($\rho_{CG}^{(s)}(\boldsymbol{r}) > 0.5\rho_0$) in the cleft of mSin3B (PAH1) is named as Cluster A, and one near the N-terminal of mSin3B as Cluster B. (d) NMR structure of REST/NRSF–mSin3B complex (PDB ID: 2CZY), where cyan-colored model is REST/NRSF, and the magenta-colored segment is the LIML sequence of REST/NRSF. Label C indicates the position of the C-terminal tail of mSin3B. Two magenta-colored side-chains are Leu 46 and Leu 49 of the LIML sequence. Black broken-line circle indicates the position of the two sidechains. Those circles in panels (a), (b), and (c) are presented to indicate the sidechain position of Leu 46 and Leu 49. Green-colored sidechains are Val 75, Phe 93, and Phe 96 of mSin3B (see also green-colored sidechains of Supplementary Figure S12a), which form a hydrophobic core with Leu 46 and Leu 49 of the LIML sequence.

Figure 3. Radial distribution functions (RDFs) $p(r_R^{(s)})$ for (a) the sertraline–mSin3B, (b) YN3–mSin3B, and (c) acitretin–mSin3B systems. Three RDFs $p(r_{Val75}^{(s)})$, $p(r_{Phe93}^{(s)})$, and $p(r_{Phe96}^{(s)})$ are shown by different colors as indicated in inset of panel (a). See Supplementary Section 6 for procedure to calculate RDF.

Figure 4. Spatial density $\rho_{CGA}^{(s)}(\boldsymbol{r})$ (blue-colored contours) for the geometric center of Ring A of sertraline in the sertraline-mSin3B system, where the contour level is $\rho_{CGA}^{(s)}(\boldsymbol{r}) = 0.5\rho_0$ $(\rho_0 = 0.001)$. Chemical structure of sertraline is also shown. Red-colored contours are $\rho_{CG}^{(s)}(\boldsymbol{r})$ for the geometric center of the entire sertraline. Labels H2 and H3 represent helices 2 and 3, respectively. Green-colored residues are Val 75, Phe 93, and Phe 96 of mSin3B. See Supplementary Section 4 for procedure to calculate $\rho_{CGA}^{(s)}(\boldsymbol{r})$.

Figure 5. (a)–(d) Sertraline-mSin3B complexes picked randomly from regions of $\rho_{CGA}^{(s)}(\boldsymbol{r}) > 0.5\rho_0$ $(\rho_0 = 0.001)$, which are shown by blue-colored contours. Magenta-colored portion is Ring A of Sertraline. Red-colored vectors are those pointing from Ring-BC geometrical center to that of Ring A (see Supplementary Figure S1b for positions of Ring A and BC). Green-colored residues are Val 75, Phe 93, and Phe 96 of mSin3B. Labels H1,…, H4 are helices 1–4 of mSin3B (PAH1 domain).

Figure 6. Spatial pattern of $< \boldsymbol{e}^{(s)}(\boldsymbol{r}) >$ for sertraline in the cleft of mSin3B viewed from two different directions. Red and black vectors are those with $| < \boldsymbol{e}^{(s)}(\boldsymbol{r}) > | \geq 0.5$ and $| < \boldsymbol{e}^{(s)}(\boldsymbol{r}) > | < 0.5$, respectively. Gray contours represent the high-density regions of $\rho_{CG}^{(s)}(\boldsymbol{r}) > 0.5\rho_0$ $(\rho_0 = 0.001)$. The vectors $< \boldsymbol{e}^{(s)}(\boldsymbol{r}) >$ are shown in regions with $\rho_{CG}^{(s)}(\boldsymbol{r}) > 0.5\rho_0$. This figure also displays REST/NRSF bound to mSin3B, and the magenta-colored segment is the LIML sequence of REST/NRSF. Note that REST/NRSF is not involved in the current simulation. The shown structure is the REST/NRSF–mSin3B complex structure (PDB ID: 2CZY). Labels H1,…, H4 are helices 1,…, 4 of mSin3B (PAH1 domain).

Figure 7. Spatial pattern of $< \boldsymbol{e}^{(s)}(\boldsymbol{r}) >$ for YN3 in the cleft of mSin3B viewed from two different directions. Gray contours represent the high-density regions of $\rho_{CG}^{(s)}(\boldsymbol{r}) > 0.5\rho_0$ $(\rho_0 = 0.001)$. See caption of Figure 6 for more information.

Figure 8. Spatial pattern of $< \boldsymbol{e}^{(s)}(\boldsymbol{r}) >$ for acitretin in the cleft of mSin3B viewed from two different directions. Gray contours represent the high-density regions of $\rho_{CG}^{(s)}(\boldsymbol{r}) > 0.1\rho_0$ ($\rho_0 = 0.001$). See caption of Figure 6 for more information.

Figure 9. (a) Structures of the three compounds sertraline, YN3, and acitretin. For each compound, inter-atomic distance $r_{atom-pair}^{(s)}$ ($s =$ sertraline, YN3, or acitretin) is defined between cyan- to orange-colored atoms. A cyan-colored atom, which is involved in a ring for each ligand, is not set on the ring rotation axis to detect the ring-rotational motions. (b) Distance distribution functions (DDFs) $P(r_{atom-pair}^{(s)})$ for the three distances. See Supplementary Section 6 for procedure to calculate DDF.

Figure 10. (a) Chemical structures of mSin3B binders, and their orientation aligned from head to tail sides. Rings A, B and C of sertraline are depicted in magenta, black, and orange, respectively. Blue circles represent aromatic rings that are expected to interact with the hydrophobic cleft of mSin3B from conventional structure-activity relationship (SAR). Green circles represent π-electron rich regions. (b) Presence/absence of Medulloblastoma cell-growth inhibition activities for the compounds. (c) The actual orientations of the compounds with respect to the cleft of mSin3B, predicted by the present MD simulation study.

Figure 11. Scheme of a compound that binds to the cleft of mSin3B.