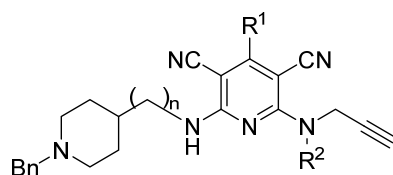


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**Table S1.** IC<sub>50</sub> values for the inhibition of AChE/BuChE, and MAO A/B by pyridines 1-12.



**1** R<sup>1</sup>, R<sup>2</sup> = H, n = 0

**8** R<sup>1</sup> = Ph, R<sup>2</sup> = H, n = 0

**11** R<sup>1</sup> = Ph, R<sup>2</sup> = Me, n = 1

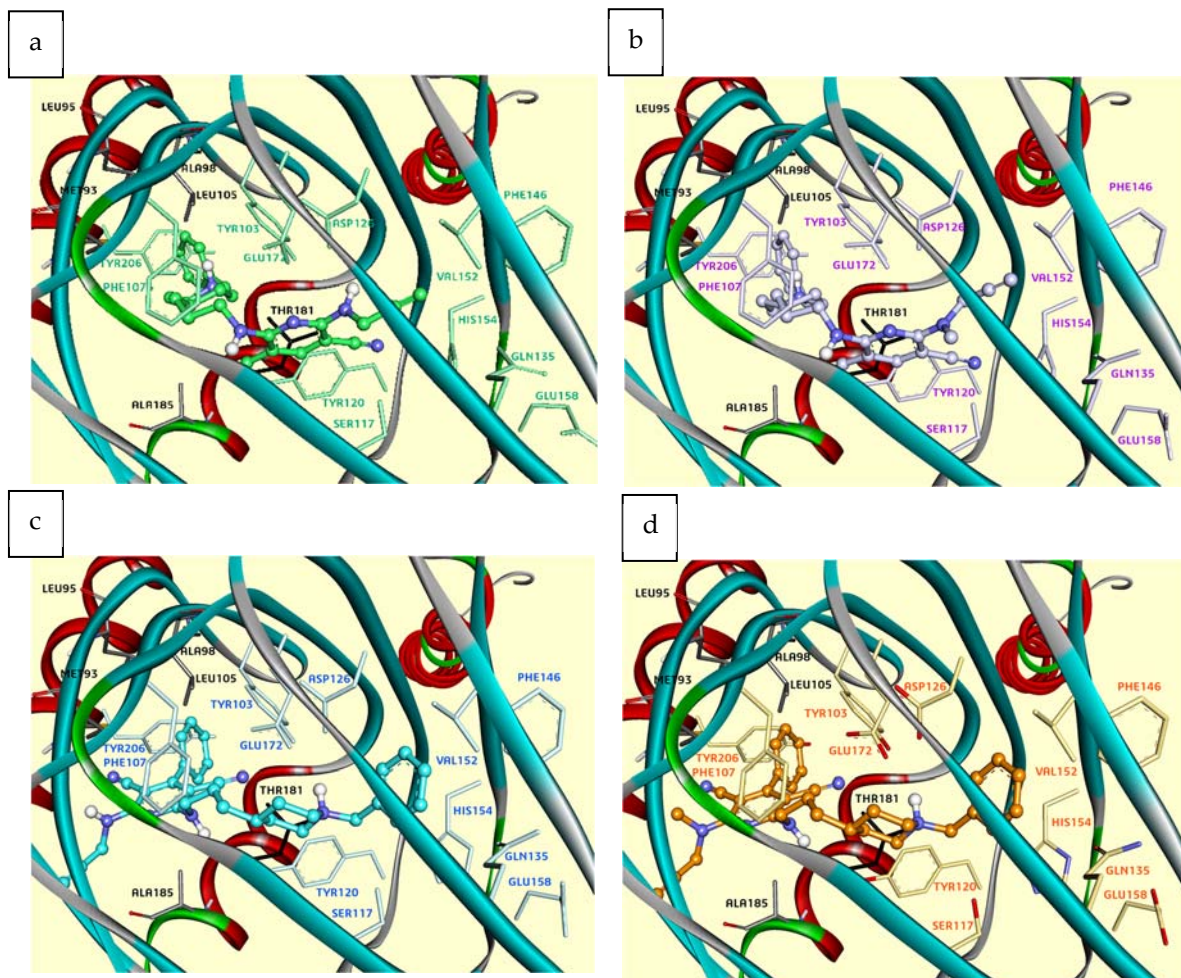
**2** R<sup>1</sup>, R<sup>2</sup> = H, n = 2    **5** R<sup>1</sup> = H, R<sup>2</sup> = Me, n = 2

**3** R<sup>1</sup>, R<sup>2</sup> = H, n = 3    **6** R<sup>1</sup> = H, R<sup>2</sup> = Me, n = 3    **9** R<sup>1</sup> = Ph, R<sup>2</sup> = H, n = 3    **12** R<sup>1</sup> = Ph, R<sup>2</sup> = Me, n = 3

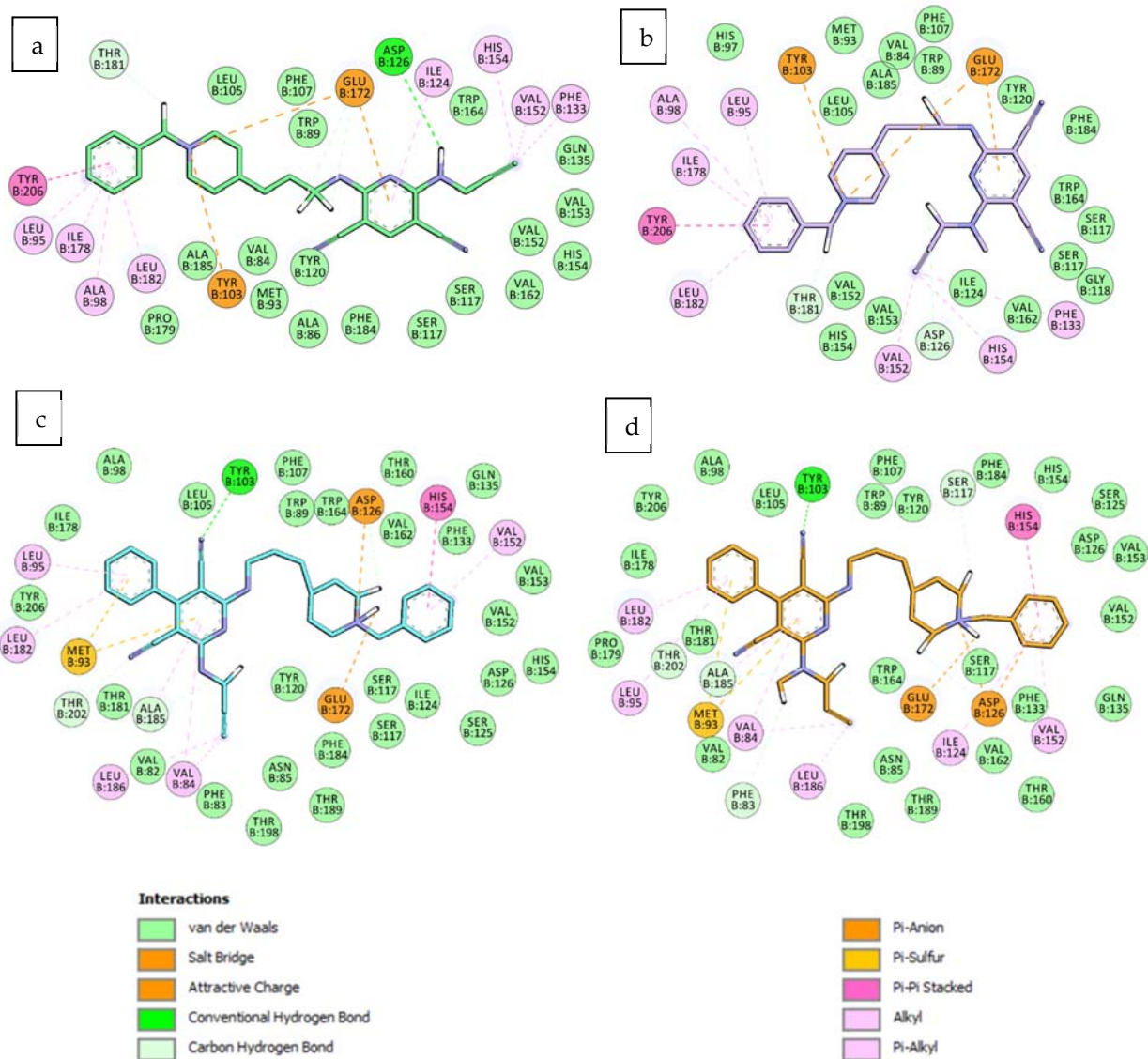
**4** R<sup>1</sup>, R<sup>2</sup> = H, n = 4    **7** R<sup>1</sup> = H, R<sup>2</sup> = Me, n = 4    **10** R<sup>1</sup> = Ph, R<sup>2</sup> = H, n = 4

Compounds	AChE <sup>a</sup> (nM)	BuChE <sup>b</sup> (nM)	MAO A <sup>c</sup> (nM)	MAOB <sup>d</sup> (nM)
<b>1</b>	530 ± 70	n.i.	n.i.	n.i.
<b>2</b>	16 ± 2	n.i.	n.i.	n.i.
<b>3</b>	4.7 ± 0.5	2030 ± 370	n.i.	n.i.
<b>4</b>	1.3 ± 0.3	530 ± 60	n.i.	n.i.
<b>5</b>	<b>13 ± 1</b>	<b>3100 ± 300</b>	<b>n.i.</b>	<b>n.i.</b>
<b>6</b>	6.2 ± 1.4	1120 ± 160	6110 ± 1400	n.i.
<b>7</b>	1.1 ± 0.3	600 ± 80	3950 ± 940	n.i.
<b>8</b>	4000 ± 100	n.i.	25 ± 1	n.i.
<b>9</b>	19 ± 5	n.i.	n.i.	n.i.
<b>10</b>	1.7 ± 0.3	840 ± 100	n.i.	n.i.
<b>11</b>	270 ± 52	5000 ± 700	n.i.	n.i.
<b>12</b>	14 ± 1	230 ± 30	n.i.	n.i.

<sup>a</sup> EeAChE; <sup>b</sup> eqBuChE; <sup>c</sup> human MAO A; <sup>d</sup> human MAO B; n.i.: no inhibition.

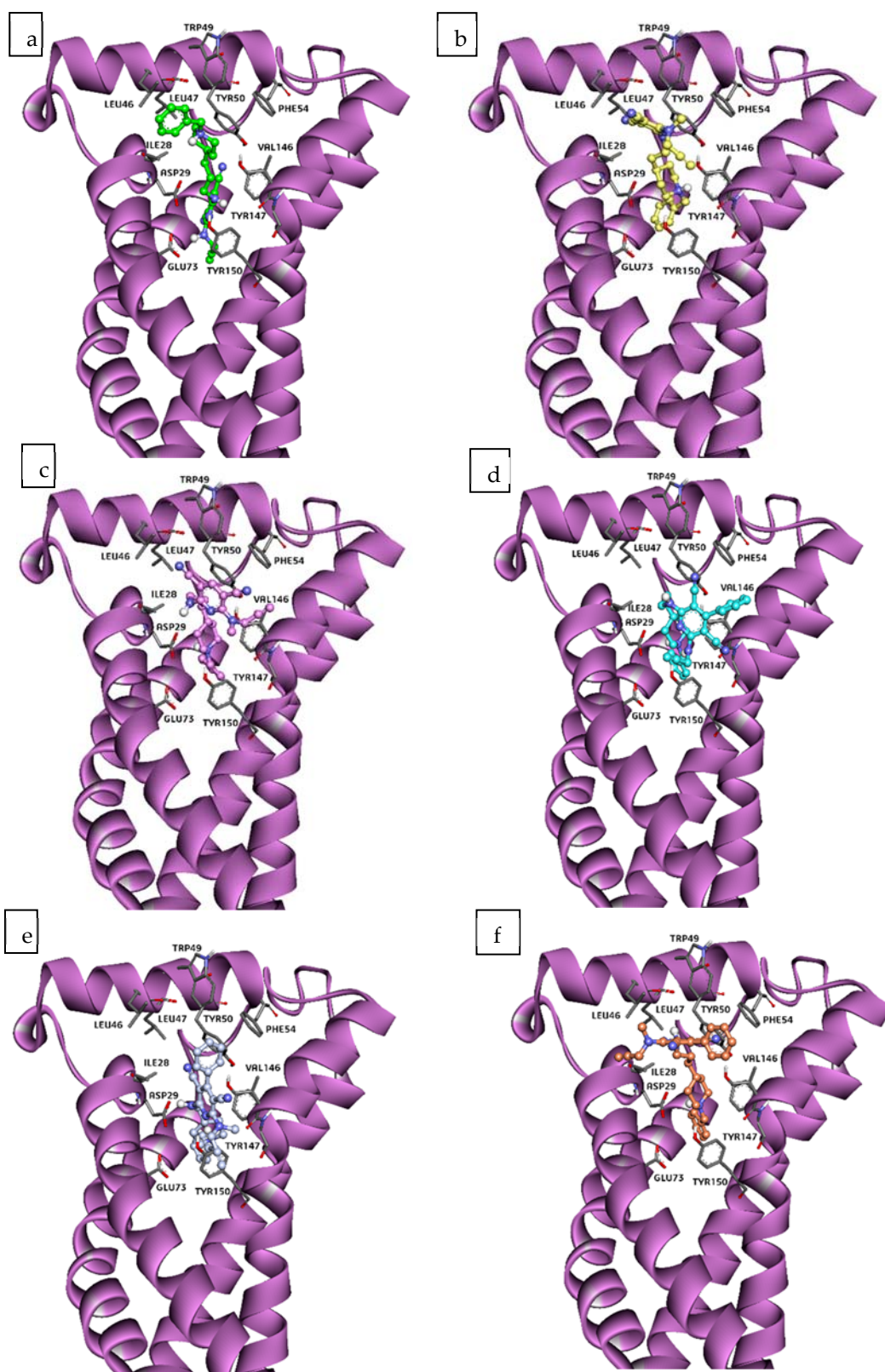


**Figure S1.** Docking poses of compounds 3 (green color balls and sticks), 6 (violet color balls and sticks), 9 (blue color balls and sticks), and 12 (orange color balls and sticks) in the active site  $\sigma 1R$ . Flexible residues are shown in the same color as the ligands.

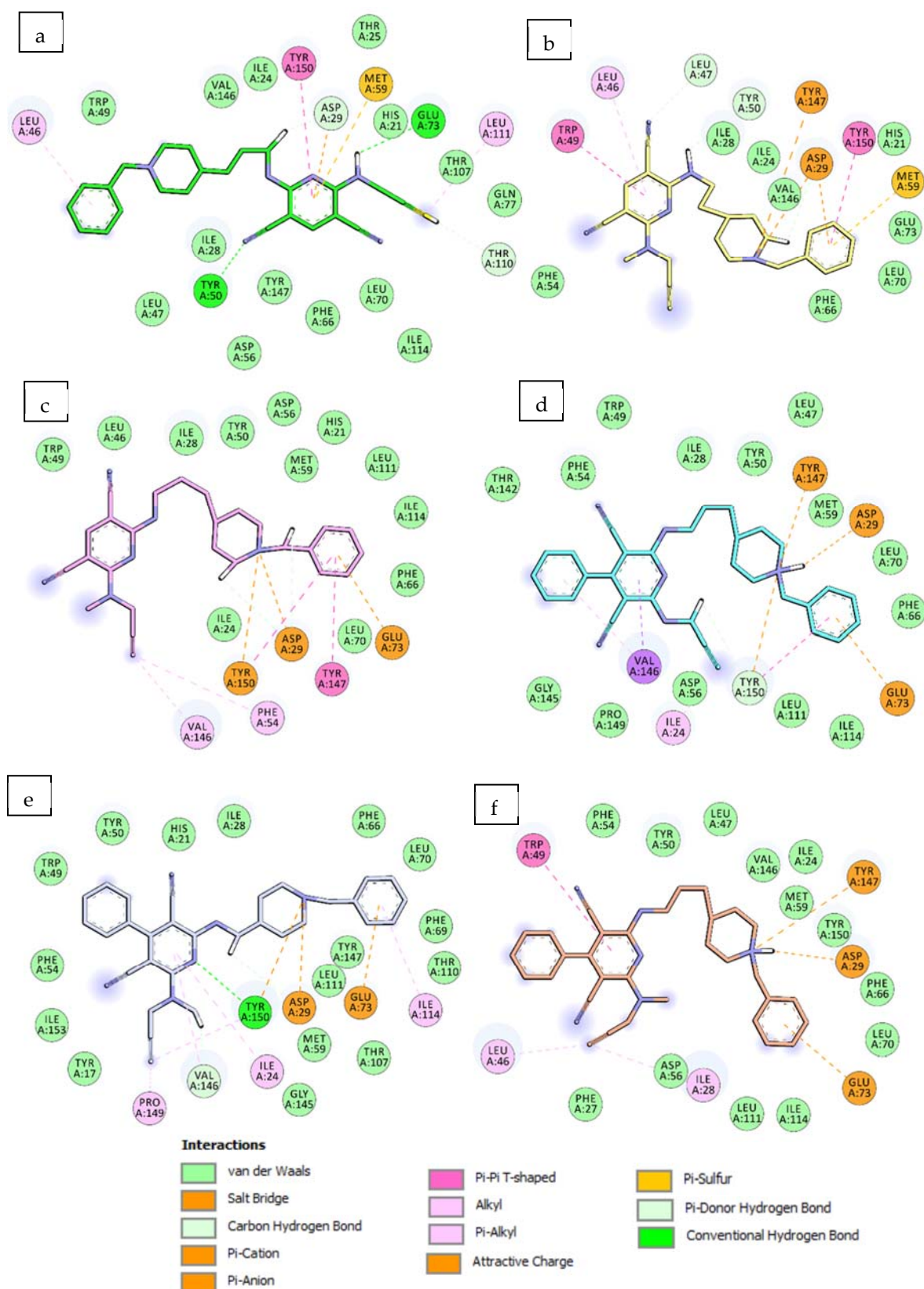


**Figure S2.** Ligand-receptor interactions of compounds 3 (green color stick), 6 (violet color stick), 9 (blue color stick) and 12 (orange color stick) in the active site of  $\sigma_1$ R.





**Figure S3.** Docking poses of compounds 3 (green color), 5 (yellow color), 6 (pink color), 9 (blue color), 11 (violet color) and 12 (orange color) in the active site of modeled rat  $\sigma 2R$ .



**Figure S4.** Ligand-receptor interactions of compounds **3** (green color stick), **5** (yellow color stick), **6** (pink color stick), **9** (blue color stick), **11** (violet color stick) and **12** (orange color stick) in the active site of modelled rat  $\sigma_2R$ .

**Table S2.** Physicochemical properties for compounds **3**, **6**, **9**, **11** and **12** calculated using QikProp.

Compound	MW	SASA	volume	donorHB	accptHB	QPlogPo/w	QPlogS	QPPCaco
<b>3</b>	412.536	798.400	1414.131	2.500	7.000	3.666	-5.437	70.446
<b>5</b>	412.536	799.155	1421.404	1.500	7.000	3.996	-6.156	102.577
<b>6</b>	426.563	831.835	1483.068	1.500	7.000	4.449	-5.776	126.528
<b>9</b>	488.634	904.336	1639.414	2.500	7.000	5.420	-7.310	127.331
<b>11</b>	474.607	781.632	1500.876	1.500	7.000	4.855	-7.106	191.733
<b>12</b>	502.661	929.952	1697.637	1.500	7.000	6.125	-7.677	221.120
Compound	PSA	QPlogBB	metab	QPlogKhsa	% HOA	ROF	ROT	
<b>3</b>	89.556	-1.626	3	0.480	81.485	0	1	
<b>5</b>	80.559	-1.361	3	0.593	86.336	0	1	
<b>6</b>	79.283	-1.348	3	0.711	90.618	0	1	
<b>9</b>	89.328	-1.459	3	1.022	83.395	1	1	
<b>11</b>	72.676	-0.887	3	0.834	96.226	0	1	
<b>12</b>	78.602	-1.167	3	1.244	78.857	2	1	

MW: Molecular weight of the molecule (130.0-725.0). SASA: Total Solvent Accessible Surface Area, in square angstroms, using a probe with a 1.4 Å radius (limits 300.0-1000.0). volume: Total solvent-accessible volume, in cubic angstroms, using a probe with a 1.4 Å radius (limits 500.0-2000.0). donorHB: Estimated number of hydrogen bonds that would be accepted by the solute (limits: 2.0-20.0). accptHB: Estimated number of hydrogen bonds that would be donated by the solute (limits: 0.0-6.0). QPlogPo/w: Predicted octanol/water partition coefficient (limits -2.0-6.5). QPlogS: Predicted aqueous solubility. S, in mol/dm<sup>3</sup>, is the concentration of the solute's saturated solution that is in equilibrium with crystalline solid (limits -6.5-0.5). QPPCaco: Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells is a model for the gut-blood barrier. QikProp predictions are for non-active transport. (< 25 poor, > 500 great). PSA: Van der Waals surface area of polar nitrogen and oxygen atoms (limits 7.0-200.0). QPlog BB: Predicted brain/blood partition coefficient (limits -3.0-1.2). metab: Number of likely metabolic reactions (limits 1-8). QPlogKhsa: Prediction of binding to human serum albumin (limits -1.5-1.5). HOA: Predicted qualitative Human Oral Absorption on 0 to 100% scale. ROF: Number of violations of Lipinski's Rule of Five (molecular weight < 500, QPlogPo/w < 5, number of hydrogen bond donor ≤ 5, number of hydrogen bond acceptors HB ≤ 10). ROT: Number of violations of Jorgensen's rule of three (QPlogS > -5.7, QPCaco > 22 nm/s, number of primary metabolites < 7).