Supplemental material

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Estimating the AD partition coefficient into lipid bilayers

Solute binding to lipid bilayers can be described using different frameworks (Peitzsch and McLaughlin, 1993; Heerklotz and Blume, 2012): as partitioning between two immiscible phases (e.g., White et al., 1998), where the solute (drug) concentration in the lipid phase ($[\mathrm{Drug}]_\mathrm{L}$, in moles/volume) is related to the aqueous drug concentration ($[\mathrm{Drug}]_\mathrm{W}$, in moles/volume) by a dimensionless partition coefficient (K_1):

$$[\mathrm{Drug}]_\mathrm{L} = K_1 \cdot [\mathrm{Drug}]_\mathrm{W}; \quad \text{(S1)}$$

or as adsorption to the bilayer/electrolyte interface (e.g., Ketterer et al., 1971), where the surface drug concentration in the lipid phase ($\{\mathrm{Drug}\}_\mathrm{L}$, in moles/area) is related to the aqueous drug concentration by an adsorption coefficient with units of length (K_2):

$$\{\mathrm{Drug}\}_\mathrm{L} = K_2 \cdot [\mathrm{Drug}]_\mathrm{W}. \quad \text{(S2)}$$

Binding to the bilayer also can be described using a molar partition coefficient (e.g., Tamm, 1991), where the molar ratio of the drug in the membrane ($x_\mathrm{Drug} = [\mathrm{Drug}]_\mathrm{L}/[\mathrm{Lipid}]_\mathrm{L}$, where $[\mathrm{L}]_\mathrm{L}$ is the concentration of lipid in the membrane phase) is related to the aqueous drug concentration by a partition coefficient with units of M^{-1} (K_3):

$$x_\mathrm{Drug} = K_3 \cdot [\mathrm{Drug}]_\mathrm{W}. \quad \text{(S3)}$$

Antidepressants, being hydrophobic primary, secondary, or tertiary amines, will be membrane permeant (e.g., Bean et al., 1968; Yu et al., 2016) and partition into both the extravesicular and intravesicular leaflets, and K_1, K_2, *and* K_3 will be related as

$$K_1 = K_2 \cdot 2/d_0 = K_3/\nu_\mathrm{L}, \quad \text{(S4)}$$

where ν_L denotes the molar volume of the lipid.

Basic distribution relations

The total amount of drug in the system ($\langle\mathrm{Drug}\rangle_\mathrm{T}$) is given by (e.g., Bruno et al., 2007; Heerklotz and Keller, 2013):

$$\langle\mathrm{Drug}\rangle_\mathrm{T} = [\mathrm{Drug}]_\mathrm{nom} \cdot V_\mathrm{W} = [\mathrm{Drug}]_\mathrm{W} \cdot V_\mathrm{W} + [\mathrm{Drug}]_\mathrm{L} \cdot V_\mathrm{L} = [\mathrm{Drug}]_\mathrm{W} \cdot (V_\mathrm{W} + K_1 \cdot V_\mathrm{L}) \quad \text{(S5a)}$$

or

$$\langle\mathrm{Drug}\rangle_\mathrm{T} = [\mathrm{Drug}]_\mathrm{nom} \cdot V_\mathrm{W} = [\mathrm{Drug}]_\mathrm{W} \cdot V_\mathrm{W} + \{\mathrm{Drug}\}_\mathrm{L} \cdot A_\mathrm{L} = [\mathrm{Drug}]_\mathrm{W} \cdot (V_\mathrm{W} + K_2 \cdot A_\mathrm{L}), \quad \text{(S5b)}$$

where $[\mathrm{Drug}]_\mathrm{nom}$ is the nominal drug concentration in the system, and V_W, V_L, and A_L denote the volumes of the aqueous and lipid phases and the surface area of the lipid phase (the sum of the areas of the two leaflets). When $V_\mathrm{L}/V_\mathrm{W} \ll 1$ (or $d_0 \cdot A_\mathrm{L}/2 \cdot V_\mathrm{W} \ll 1$), the system volume can be approximated as V_W, in which case:

$$[\mathrm{Drug}]_\mathrm{W} = [\mathrm{Drug}]_\mathrm{nom} \cdot \frac{V_\mathrm{W}}{(V_\mathrm{W} + K_1 \cdot V_\mathrm{L})} = \langle\mathrm{Drug}\rangle_\mathrm{T} \cdot \frac{1}{(V_\mathrm{W} + K_1 \cdot V_\mathrm{L})} \quad \text{(S6a)}$$

or

$$[\mathrm{Drug}]_\mathrm{W} = [\mathrm{Drug}]_\mathrm{nom} \cdot \frac{V_\mathrm{W}}{(V_\mathrm{W} + K_2 \cdot A_\mathrm{L})} = \langle\mathrm{Drug}\rangle_\mathrm{T} \cdot \frac{1}{(V_\mathrm{W} + K_2 \cdot A_\mathrm{L})} \quad \text{(S6b)}$$

and

$$[\mathrm{Drug}]_\mathrm{L} = K_1 \cdot [\mathrm{Drug}]_\mathrm{W} = [\mathrm{Drug}]_\mathrm{nom} \cdot \frac{K_1 \cdot V_\mathrm{W}}{(V_\mathrm{W} + K_1 \cdot V_\mathrm{L})} = \langle\mathrm{Drug}\rangle_\mathrm{T} \cdot \frac{K_1}{(V_\mathrm{W} + K_1 \cdot V_\mathrm{L})} \quad \text{(S7a)}$$

or

$$\{\mathrm{Drug}\}_\mathrm{L} = K_2 \cdot [\mathrm{Drug}]_\mathrm{W} = [\mathrm{Drug}]_\mathrm{nom} \cdot \frac{K_2 \cdot V_\mathrm{W}}{(V_\mathrm{W} + K_2 \cdot A_\mathrm{L})} = \langle\mathrm{Drug}\rangle_\mathrm{T} \cdot \frac{K_2}{(V_\mathrm{W} + K_2 \cdot A_\mathrm{L})}, \quad \text{(S7b)}$$

and the total amount of drug in the lipid phase ($\langle\mathrm{Drug}\rangle_\mathrm{L} = [\mathrm{Drug}]_\mathrm{L} \cdot V_\mathrm{L} = \{\mathrm{Drug}\}_\mathrm{L} \cdot A_\mathrm{L}$) is given by

$$\langle \text{Drug} \rangle_L = \langle \text{Drug} \rangle_T \cdot \frac{K_1 \cdot V_L}{(V_W + K_1 \cdot V_L)} = \langle \text{Drug} \rangle_T \cdot \frac{K_2 \cdot A_L}{(V_W + K_2 \cdot A_L)}. \quad \text{(S8)}$$

In the case of charged drugs, it becomes convenient to quantify drug binding using K_2 as the measure of the solute's affinity for the bilayer–solution interface. For comparison with cLogP estimates of hydrophobicity, we will convert to K_1 using Eq. S4.

Determining K_2

To determine K_2, the amount of lipid in the system is increased by adding n aliquots (volume δV) of a suspension of lipid vesicles to the system, which produces a shift of drug from the aqueous phase to the lipid phase. K_2, then, can be determined by monitoring how the shift from the aqueous to the lipid phase varies as function of the amount of added lipid.

The surface area of added lipid in each aliquot (δA_L) is given by:

$$\delta A_L = \delta V \cdot C_L \cdot a_L, \quad \text{(S9)}$$

where C_L denotes the lipid concentration in the aliquot and a_L is the molar area of the lipid. After the ith injection, the drug concentration in the aqueous phase ($[\text{Drug}]_W(i)$), and the amount of drug in the lipid and aqueous phase ($\langle \text{Drug} \rangle_L(i)$) are:

$$[\text{Drug}]_W(i) = \langle \text{Drug} \rangle_T \cdot \frac{1}{V_W + i \cdot \delta V \cdot (1 + K_2 \cdot C_L \cdot a_L)}, \quad \text{(S10)}$$

$$\langle \text{Drug} \rangle_L(i) = K_2 \cdot i \cdot \delta V \cdot C_L \cdot a_L \cdot [\text{Drug}]_W = \langle \text{Drug} \rangle_T \cdot \frac{K_2 \cdot i \cdot \delta V \cdot C_L \cdot a_L}{V_W + i \cdot \delta V \cdot (1 + K_2 \cdot C_L \cdot a_L)}, \quad \text{(S11)}$$

where V_W denotes the initial volume of the system.

Partitioning of charged drugs

In the case of charged drugs, drug partitioning into the membrane will give rise to a surface charge (σ), which in turn will establish a surface potential (ϕ_0), and the aqueous drug concentration at the interface ($[\text{Drug}]_0$) will differ from the bulk $[\text{Drug}]_W$ (McLaughlin and Harary, 1976):

$$[\text{Drug}]_0 = \exp\left\{ -\frac{z_{\text{Drug}} \cdot F \cdot \phi_0}{RT} \right\} [\text{Drug}]_W, \quad \text{(S12)}$$

where z_{Drug} denotes the drug valence, F is Faraday's constant, R the gas constant, and T the temperature in degrees kelvin. This impacts drug partitioning, because

$$\{\text{Drug}\}_L = K_2 \cdot [\text{Drug}]_0 = K_2 \cdot \exp\left\{ -\frac{z_{\text{Drug}} \cdot F \cdot \phi_0}{RT} \right\} \cdot [\text{Drug}]_W. \quad \text{(S13)}$$

The effective adsorption coefficient after i injections ($K_2^{\text{eff}}(i)$) thus becomes

$$K_2^{\text{eff}}(i) = K_2 \cdot \exp\left\{ -\frac{z_{\text{Drug}} \cdot F \cdot \phi_0(i)}{RT} \right\} = K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\}, \quad \text{(S14)}$$

where $\beta = z_{\text{Drug}} \cdot F/RT$ and $\phi_0(i)$ is the surface potential after the ith injection.

Combining Eqs. S11 and S14,

$$\langle \text{Drug} \rangle_L(i) = \langle \text{Drug} \rangle_T \cdot \frac{K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\} \cdot i \cdot \delta V \cdot C_L \cdot a_L}{V_W + i \cdot \delta V \cdot (1 + K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\} \cdot C_L \cdot a_L)}. \quad \text{(S15)}$$

The total surface area of the system (A_T) will be the sum of the area due to the lipid (A_L)

$$A_L = \langle \text{Lipid} \rangle_L \cdot a_L = i \cdot \delta V \cdot C_L \cdot a_L \quad \text{(S16)}$$

and the area due to the drug (A_D)

$$A_D = \langle \text{Drug} \rangle_L \cdot a_D. \quad \text{(S17)}$$

After the ith injection, the total membrane area ($A(i)_T$) becomes

$$A_T(i) = i \cdot \delta V \cdot C_L \cdot a_L \cdot \left(1 + \frac{\langle \text{Drug} \rangle_L(i) \cdot a_D}{i \cdot \delta V \cdot C_L \cdot a_L}\right). \quad \text{(S18)}$$

ϕ_0 can be estimated using the Gouy–Chapman theory (Aveyard and Haydon, 1973). For univalent electrolytes:

$$\sigma = F \cdot z_{Drug} \cdot \{Drug\}_L = \kappa \cdot \sqrt{C_S} \cdot \sinh\left\{\frac{\beta \cdot \phi_0}{2}\right\}, \quad \text{(S19)}$$

where $\kappa = \sqrt{8 \cdot RT \cdot \varepsilon \cdot \varepsilon_0 \cdot 1,000}$, ε is the dielectric constant, ε_0 the permittivity of free space, and C_S the total concentration of univalent salt (the factor 1,000 converts concentrations in moles/liter to moles/m^3). Combining Eqs. S10 and S13–S19:

$$\sigma(i) = F \cdot z_{Drug} \cdot \langle Drug \rangle_T \cdot \frac{K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\}}{V_W + i \cdot \delta V \cdot (1 + K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\} \cdot C_L \cdot a_L)} \cdot f(i), \quad \text{(S20)}$$

where $\sigma(i)$ is the surface charge density after the ith injection and $f(i)$ is given by

$$f(i) = \frac{1}{1 + \frac{\langle Drug \rangle_L \cdot a_D}{i \cdot \delta V \cdot C_L \cdot a_L}} = \frac{V_W + i \cdot \delta V \cdot (1 + K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\} \cdot C_L \cdot a_L)}{V_W + i \cdot \delta V \cdot (1 + K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\} \cdot C_L \cdot a_L) + \langle Drug \rangle_T \cdot K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\} \cdot a_D} \quad \text{(S21)}$$

and, cf. Eq. S19,

$$\phi_0(i) = \frac{2}{\beta} \cdot \sinh^{-1}\left\{\frac{\sigma(i)}{\kappa \cdot \sqrt{C_S}}\right\}. \quad \text{(S22)}$$

Enthalpy of partitioning and determining K_2

The amount of drug that has transferred from the aqueous phase to the lipid phase can be determined using ITC (Seelig et al., 1993; Wenk et al., 1997; Heerklotz and Seelig, 2000; Tan et al., 2002). The integrated enthalpy of partitioning in injections 1 through i ($\Sigma h_{Drug}(i)$) is given by cf. Eq. S15:

$$\Sigma h_{Drug}^{W \to L}(i) = H_{Drug}^{W \to L} \cdot \langle Drug \rangle_L(i) = H_{Drug}^{W \to L} \cdot \langle Drug \rangle_T \cdot \frac{K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\} \cdot i \cdot \delta V \cdot C_L \cdot a_L}{V_W + i \cdot \delta V \cdot (1 + K_2 \cdot \exp\{-\beta \cdot \phi_0(i)\} \cdot C_L \cdot a_L)}, \quad \text{(S23)}$$

where $H_{Drug}^{W \to L}$is the molar enthalpy of drug partitioning into the lipid phase. Combining Eqs. S20 and S23:

$$\sigma(i) = \frac{z_{Drug} \cdot F \cdot \langle Drug \rangle_L(i)}{i \cdot \delta V \cdot C_L \cdot a_L} = \frac{z_{Drug} \cdot F \cdot \Sigma h_{Drug}^{W \to L}(i)}{i \cdot \delta V \cdot C_L \cdot a_L \cdot H_{Drug}^{W \to L}} \cdot f(i), \quad \text{(S24)}$$

where $f(i)$, cf. Eq. S21, can be expressed in terms of $\Sigma h_{Drug}^{W \to L}(i)$ and $H_{Drug}^{W \to L}$:

$$f(i) = \frac{i \cdot \delta V \cdot C_L \cdot a_L}{i \cdot \delta V \cdot C_L \cdot a_L + \frac{\Sigma h_{Drug}^{W \to L}(i)}{H_{Drug}^{W \to L}} \cdot a_D}, \quad \text{(S25)}$$

and

$$\sigma(i) = \frac{z_{Drug} \cdot F \cdot \Sigma h_{Drug}^{W \to L}(i)}{i \cdot \delta V \cdot C_L \cdot a_L \cdot H_{Drug}^{W \to L} + \Sigma h_{Drug}^{W \to L}(i) \cdot a_D}. \quad \text{(S26)}$$

Combining Eqs. S19 and S26,

$$\frac{z_{Drug} \cdot F \cdot \Sigma h_{Drug}^{W \to L}(i)}{i \cdot \delta V \cdot C_L \cdot a_L \cdot H_{Drug}^{W \to L} + \Sigma h_{Drug}^{W \to L}(i) \cdot a_D} = \kappa \cdot \sqrt{C_S} \cdot \sinh\left\{\frac{\beta \cdot \phi_0(i)}{2}\right\}, \quad \text{(S27)}$$

or

$$\phi_0(i) = \frac{2}{\beta} \cdot \arcsin\left\{\frac{z_{Drug} \cdot F}{\kappa \cdot \sqrt{C_S}} \cdot \frac{\Sigma h_{Drug}^{W \to L}(i)}{i \cdot \delta V \cdot C_L \cdot a_L \cdot H_{Drug}^{W \to L} + \Sigma h_{Drug}^{W \to L}(i) \cdot a_D}\right\}. \quad \text{(S28)}$$

Eqs. S23 and S28 allow for estimating K_2 and $H_{Drug}^{W \to L}$ from the experimental $\Sigma h_{Drug}(i)$ versus i relation. Initial estimates for K_2 and $H_{Drug}^{W \to L}$ were obtained from the experimental $\Sigma h_{Drug}^{W \to L}(i)$ – i relations setting $z_{drug} = 0$. Using these estimates as initial guesses, one can construct a 1 by n array (n being the total number of injections) of surface charge densities after each injection: $\{\sigma(1), \ldots \sigma(i), \ldots \sigma(n)\}$, where $\sigma(i)$ is calculated using Eq. S24 and a 1 by n array of surface potentials after each injection $\{\phi_0(1), \ldots \phi_0(i), \ldots \phi_0(n)\}$, where

$\phi_0(i)$ is calculated using Eq. S28. Using the new estimates for $\phi_0(i)$ in Eq. S23, we obtain new estimates for $\Sigma h_{\mathrm{Drug}}^{\mathrm{W}\to\mathrm{L}}(i)$, denoted $\Sigma h_{\mathrm{Drug}}^{\mathrm{W}\to\mathrm{L}^*}(i)$, and $\sigma(i)$, cf. Eq. S24, and K_2 and $H_{\mathrm{Drug}}^{\mathrm{W}\to\mathrm{L}}$ can be estimated using non-linear least squares fitting that minimizes $\sum_1^n \left(\Sigma h_{\mathrm{Drug}}^{\mathrm{W}\to\mathrm{L}}(i) - \Sigma h_{\mathrm{Drug}}^{\mathrm{W}\to\mathrm{L}^*}(i)\right)^2$.

Drug surface density and mole fraction in the bilayer

Knowing K_2, the surface density and mole fraction (m_{Drug}) of the drug in the bilayer, as well as $[\mathrm{Drug}]_{\mathrm{W}}$, can be estimated for any $[\mathrm{Drug}]_{\mathrm{nom}}$ as (cf. Eqs. S20 and S21):

$$\{\mathrm{Drug}\}_{\mathrm{L}} = \frac{\langle\mathrm{Drug}\rangle_{\mathrm{T}} \cdot K_2 \cdot \exp\{-\beta\cdot\phi_0\}}{V_{\mathrm{W}} + K_2 \cdot \exp\{-\beta\cdot\phi_0\} \cdot (\langle\mathrm{Lipid}\rangle_{\mathrm{T}} \cdot a_{\mathrm{L}} + \langle\mathrm{Drug}\rangle_{\mathrm{T}} \cdot a_{\mathrm{D}})}, \quad \text{(S29)}$$

$$m_{\mathrm{Drug}} = \frac{\{\mathrm{Drug}\}_{\mathrm{L}}}{\{\mathrm{Drug}\}_{\mathrm{L}} + \{\mathrm{Lipid}\}_{\mathrm{L}}} = \frac{\{\mathrm{Drug}\}_{\mathrm{L}}}{\{\mathrm{Drug}\}_{\mathrm{L}} + \{\mathrm{Lipid}\}_{\mathrm{L}}} \cdot \left(1 - \{\mathrm{Drug}\}_{\mathrm{L}} \cdot a_{\mathrm{D}} \big/ a_{\mathrm{L}}\right) \quad \text{(S30)}$$

and

$$[\mathrm{Drug}]_{\mathrm{W}} = \frac{\langle\mathrm{Drug}\rangle_{\mathrm{T}} - \{\mathrm{Drug}\}_{\mathrm{L}} \cdot (\langle\mathrm{Lipid}\rangle_{\mathrm{T}} \cdot a_{\mathrm{L}} + \langle\mathrm{Drug}\rangle_{\mathrm{T}} \cdot a_{\mathrm{D}})}{V_{\mathrm{W}}} = \frac{\langle\mathrm{Drug}\rangle_{\mathrm{T}}}{V_{\mathrm{W}} + K_2 \cdot \exp\{-\beta\cdot\phi_0\} \cdot (\langle\mathrm{Lipid}\rangle_{\mathrm{T}} \cdot a_{\mathrm{L}} + \langle\mathrm{Drug}\rangle_{\mathrm{T}} \cdot a_{\mathrm{D}})}, \quad (45)$$

where $\{\mathrm{Lipid}\}_{\mathrm{L}}'$ denotes the lipid surface density in the absence of drug binding, $\{\mathrm{Lipid}\}_{\mathrm{L}}' = 1/a_{\mathrm{L}}$.

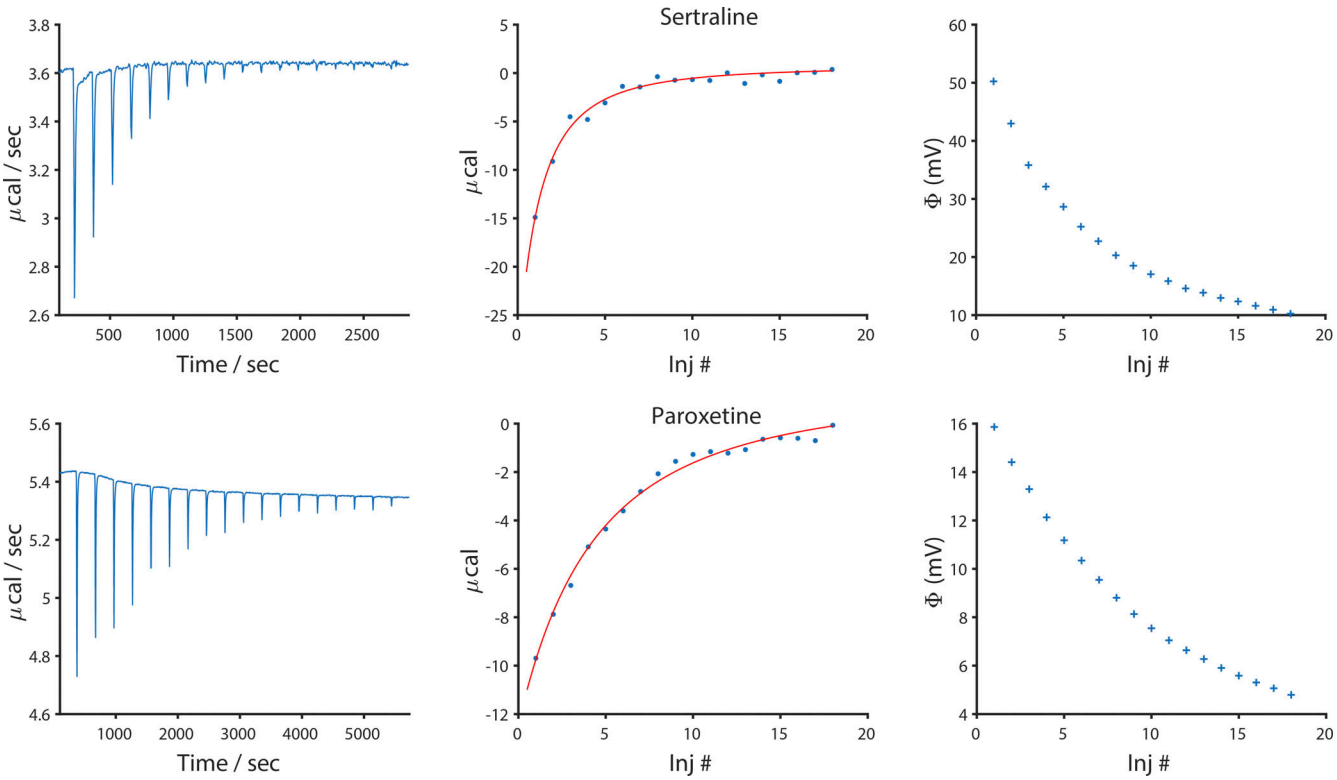


Figure S1. **Determining partition coefficients from ITC experiments.** Results for sertraline, which has the highest partition coefficient and paroxetine, which has a low partition coefficient. Left: ITC traces. Middle: Integrated heats, $\Sigma h_{\mathrm{Drug}}^{\mathrm{W}\to\mathrm{L}}(i)$, versus injection number. Right: The estimated surface potential (from Eqs. S26 and S28), which decreases as more lipid is added to the system.

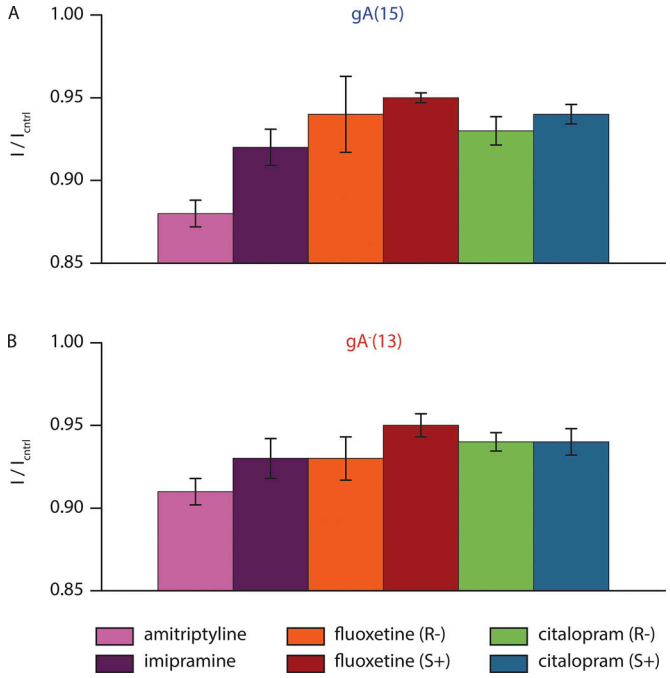


Figure S2. **Effect of antidepressants on the conductances of gA⁻(13) and AgA(15) channels**. **(A)** AD-induced decreases in AgA(15) single-channel conductances. **(B)** AD-induced decreases in A⁻(13) single-channel conductances. Results are shown only for the highest drug concentrations tested (250 µM for the citalopram enantiomers and 100 µM for the other four compounds). Values represent mean ± SE; $n \geq 3$.

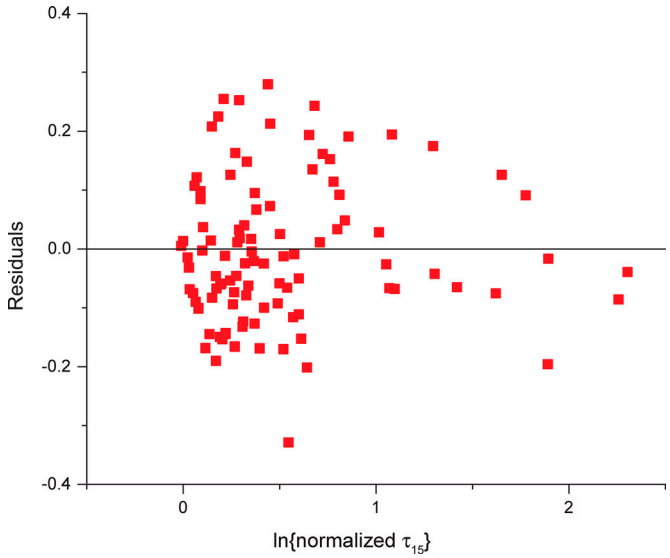


Figure S3. **The residuals from the straight line fit to the results in Fig. 8 A.** Plot of the residuals ($Y_{fit} - Y$) from the least-squares fit to the ln{normalized τ_{13}} as a linear function of ln{normalized τ_{15}}.

Table S1: TCAs and SSRIs inhibit many membrane proteins: A survey of IC50s

The color codes for the entries below are:

< 1 μM | 1-10 μM | 10-100 μM | > 100 μM | Inhibition; no dose-response | No effect

	Membrane Protein	TCAs							SSRIs						
		Clomipramine	Lofepramine	Amitriptyline	Nortriptyline	Imipramine	Desipramine	Doxepin	Fluoxetine	Norfluoxetine	Sertraline	Paroxetine	Fluvoxamine	Citalopram	Zimelidine
Voltage-gated channels	Kv1.1[1]			22					55						
	Kv1.3[2]								6	1.4					
	Kv1.4[3]								33						
	Kv1.5[4]										0.7		2	3	
	Kv3.1[5]								13	0.8					
	Kv7.2/7.3[6]			10											
	hERG (Kv 11.1)[7]			5-23			12-50		1	2			4		
	L/T-type Ca^{2+} [8]	12		4-70		4-30	12		3-30	1-5	2			60-65	
	Proton channel[9]			5.8		5.7			2.1						
	Nav (inactivated)[10]			0.2-56	0.3-63	1-68	1		1.3			1.5			12
	Nav (resting)[11]			90	30	40	20		49-70			9-20		100-174	
Inward Rectifier K^+ channels	GIRK (Kir 3)[12]	40		110	130	50	40		20			14	NE	NE	NE
	Kir 4.1 [13]			62	16	98	55		15		7		196		

Table S1 (continued)

Membrane Protein		TCAs							SSRIs						
		Clomipramine	Lofepramine	Amitriptyline	Nortriptyline	Imipramine	Desipramine	Doxepin	Fluoxetine	Norfluoxetine	Sertraline	Paroxetine	Fluvoxamine	Citalopram	Zimelidine
Ligand-gated channels	$GABA_A$ receptors [14]								130	1					
	NMDA receptors [15]		NDR	14-57		NDR	1-7		10->100					180	
	AMPA receptors [16]			>300			>100		36-43					>300	
	nACh receptors [17]	<10		0.9-<10	0.1-<10	<10	~0.3	7-16	<10	<10	0.8-21	1.5-23		0.9-3	>10
	TRPV1 [18]			60											
	α adrenoceptors [19]			6-8	6-7.5	6-7									
	SK [20]				20	40	30		7-20						
Other channels	TREK1 [21]								14	9					
	VRAC [22]								6		2	3	12	28	
	CFTR [23]								27						
Transporters	Na^+,K^+-ATPase [24]			70	50	130	80	150	>100						
	Ca^{2+}-ATPase [25]	~200				~750	~500								
	ATP Synthase [26]					~150									
	TH transporters [27]						>250								
	OCT2 transporter [28]				0.4-0.8	0.2-0.3	0.3-1.3		1-4		5-7	2.5-4			
	OCT3 transporter [29]				19	11	5		22		7	12			
	GLUT1 [30]			1430	980	560	720								

	P-glycoprotein [31]								116		32	30				
Other proteins	σ_1 [32]					0.3	2		0.2	2.4	.06	1.9	.04	0.3		
	σ_2 [33]					2	11		16	35	5	23	8	5		

[1] (Yeung et al., 1999; Punke and Friederich, 2007)
[2] (Choi et al., 1999)
[3] (Choi et al., 2003)
[4] (Lee et al., 2016; 2010a; b)
[5] (Choi et al., 2001; Sung et al., 2008)
[6] (Punke and Friederich, 2007)
[7] (Jo et al., 2000; Milnes et al., 2003; Rajamani et al., 2006; Hong et al., 2010; Friemel and Zünkler, 2010; Staudacher et al., 2011)
[8] (Choi et al., 1992; Park et al., 1999; Deák et al., 2000; Hamplová-Peichlová et al., 2002; Magyar et al., 2004; Traboulsie et al., 2006; Zahradník et al., 2008)
[9] (Song et al., 2012)
[10] (Lenkey et al., 2006; Dick et al., 2007; Horishita et al., 2017)
[11] (Lenkey et al., 2006; Thériault et al., 2015; Nakatani and Amano, 2018)
[12] (Kobayashi et al., 2003; 2004a; 2006; 2004b; Takahashi et al., 2006)
[13] (Ohno et al., 2007; Su et al., 2007; Furutani et al., 2009)
[14] (Robinson et al., 2003)
[15] (Watanabe et al., 1993; Tohda et al., 1995; Szasz et al., 2007; Kiss et al., 2012; Barygin et al., 2017)
[16] (Barygin et al., 2017)
[17] (Schofield et al., 1981; Rana et al., 1993; García-Colunga et al., 1997; Fryer and Lukas, 1999; Hennings et al., 1999; López-Valdés and García-Colunga, 2001; Gumilar et al., 2003; Freysoldt et al., 2009; Arias et al., 2010c; b; 2010a; Weber et al., 2013)
[18] (Oláh et al., 2007)
[19] (Nojimoto et al., 2010)
[20] (Terstappen et al., 2001; 2003)
[21] (Kennard et al., 2005)
[22] (Maertens et al., 1999; 2002)
[23] (Maertens et al., 1999)
[24] (Carfagna and Muhoberac, 1993; Zanatta et al., 2001)
[25] (Plenge-Tellechea et al., 1999; Soler et al., 2000)
[26] (Weinbach et al., 1986)
[27] (Roth et al., 2010)
[28] (Wang et al., 2014)
[29] (Zhu et al., 2012)
[30] (Pinkofsky et al., 2000)
[31] (Weiss et al., 2003)

[32] (Narita et al., 1996)
[33] (Narita et al., 1996)

Table S2: TCA and SSRI structures and physicochemical properties[34]

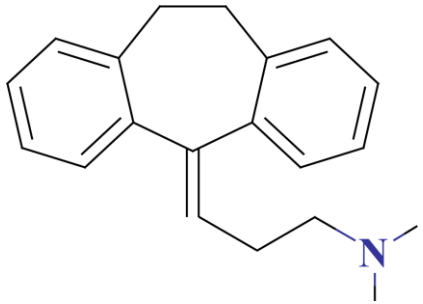
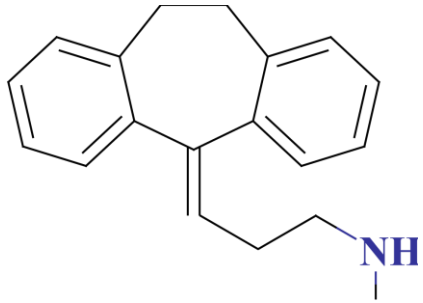
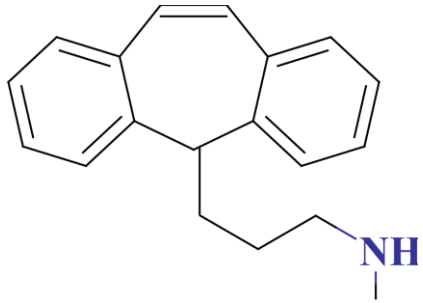
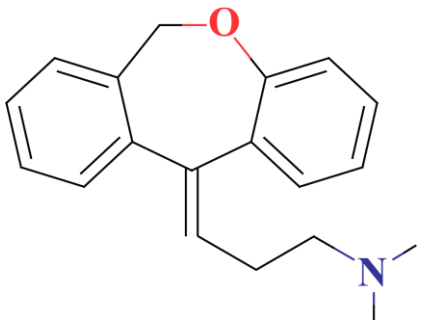
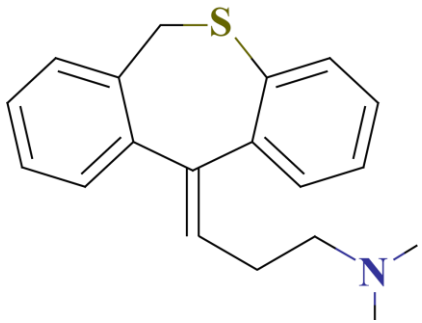
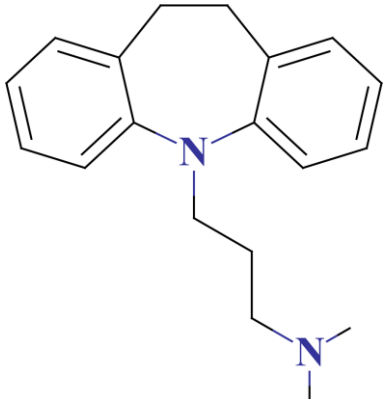
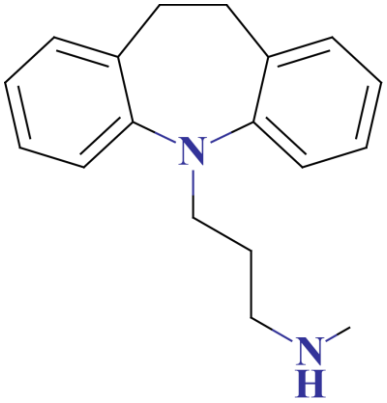
TCAs – Amitriptyline and derivatives (pKa / clog$P_{o:w}$):		
Amitriptyline (9.2 / 4.7) 	Nortriptyline (10 / 4.8) 	Protriptyline (10.6 / 4.7) 
Doxepin (9.2 / 4.3) 	Dothiepin (9.1 / 4.7) 	

Table S2 continued: TCAs – Imipramine and derivatives (pKa / clog$P_{o:w}$):

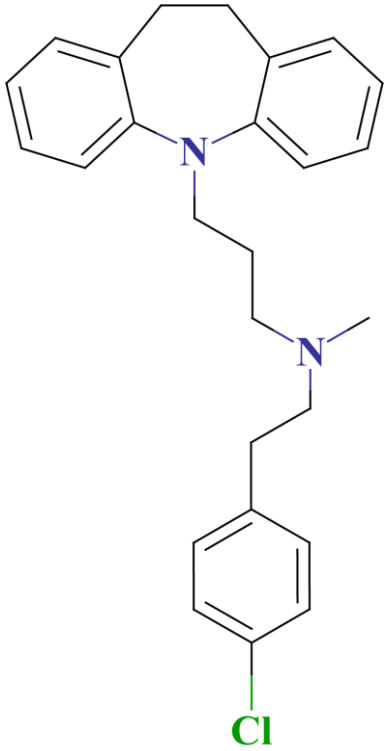
Imipramine (9.5 / 3.7)



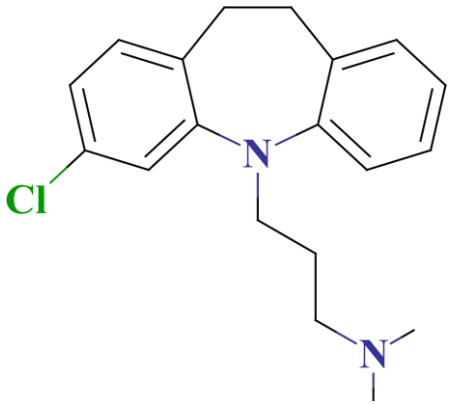
Desipramine (10.4 / 4.3)



Lofepramine (6.5 / 6.3)



Clomipramine (9.5 / 5.3)



Trimipramine (9.4 / 5.0)

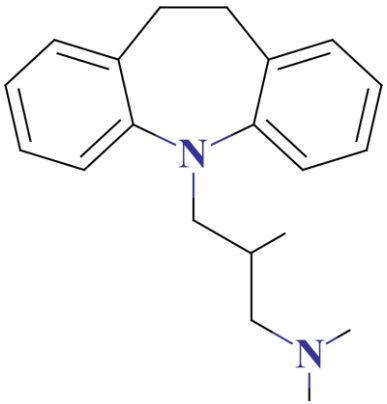


Table S2 continued: SSRIs (pKa / clog$P_{o:w}$):

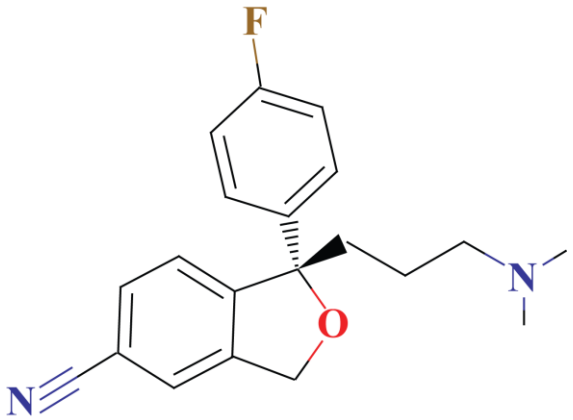
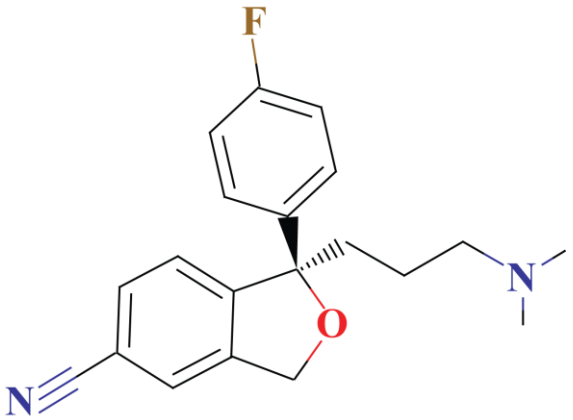
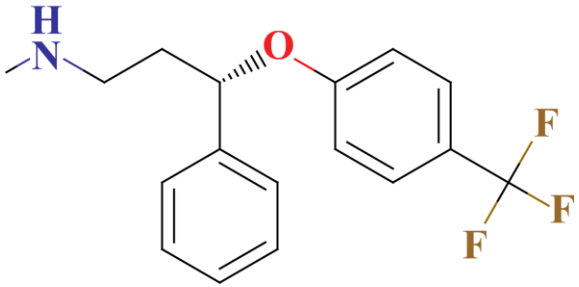
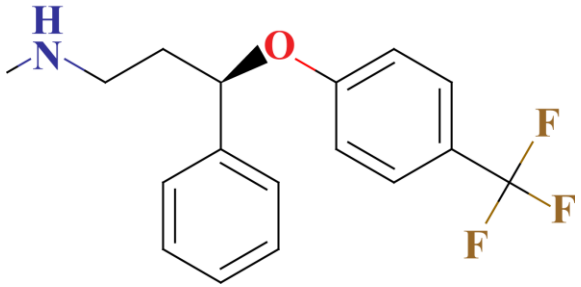
Citalopram (S+)	(9.6 / 3.4)	Citalopram (R-)
		
Fluoxetine (S+)	(10.1 / 4.3)	Fluoxetine (R-)
		

Table S2 continued: SSRIs (pKa / clog$P_{o:w}$):

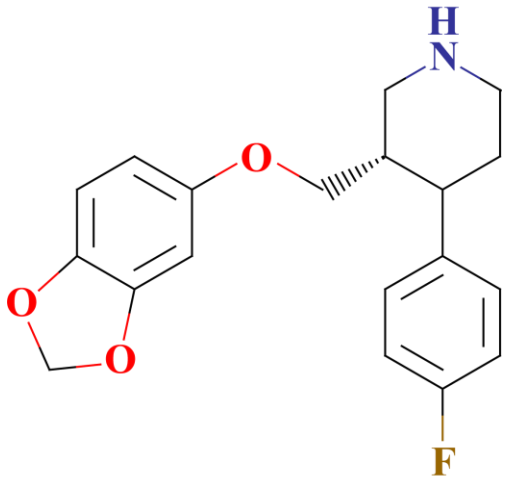
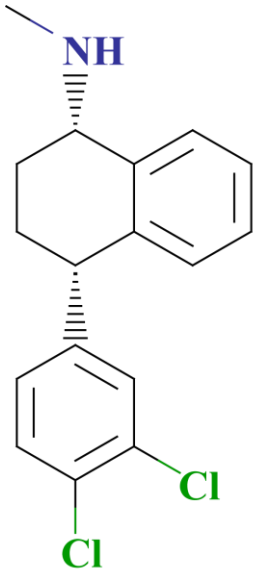
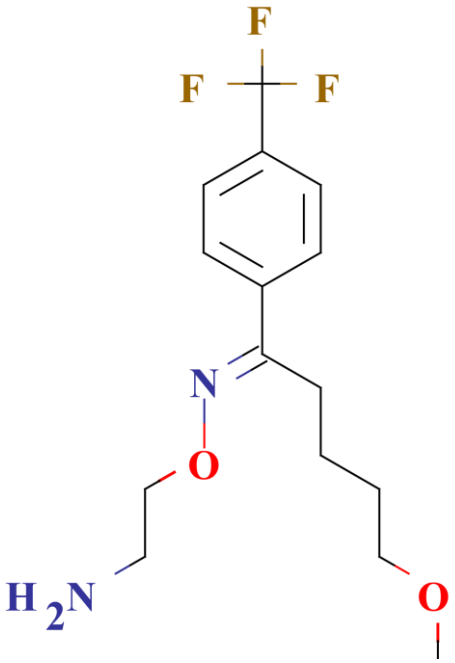
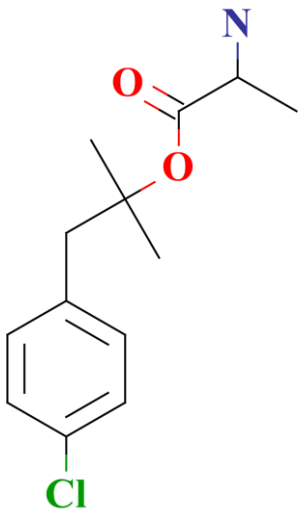
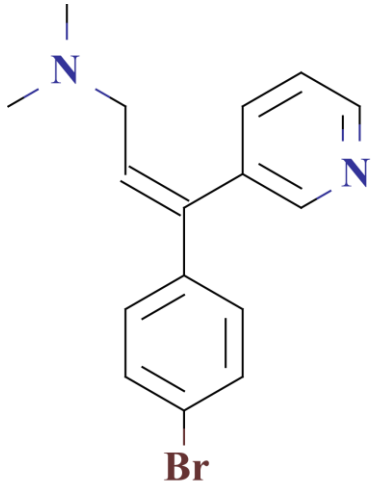
Paroxetine (9.7 / 3.7)	Sertraline (9.5 / 5.2)	Fluvoxamine (9.4 / 3.0)
		

Table S2 continued: SSRIs (pKa / clogP):	
Alaproclate (7.8 / 2.9)	Zimelidine (7.9 / 3.7)
	

[34] clogP determined using the ACD/Percepta PhysChem Suite (https://www.acdlabs.com/products/percepta/, (ACD/Percepta PhysChem Suite, 2012) accessed December 20, 2018)

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