climacteric maladies by non-feminizing estrogens will also be unlikely.

Table 1. Physicochemical properties, drug-likeness, estrogen receptor (ER) binding affinities and antioxidant properties of human estrogens and their 2-adamantyl-subtituted derivatives.

Compound	Molecular Mass	logP	logS	Drug-likeness Score[a]	ER-binding Affinity[b] (IC_{50}, nM)		Antioxidant Potency (IC_{50}, μM)[c]
					ERα	ERβ	
E2	272.1	3.88	-4.02	0.09	1.3	0.7	11.8 ± 1.6
E1	270.0	4.02	-4.07	-0.41	6.1	3.5	17.7 ± 2.3
Ada-E2	406.2	6.01	-6.73	-1.23	>10,000	>10,000	1.5 ± 0.1
Ada-E1	404.2	6.15	-6.78	-1.72	>10,000	>10,000	5.3 ± 1.2

[a] *Drug-likeness scores, along with logP and logS values, were calculated through the Osiris Property Explorer [26]. Negative values indicate unfavorable drug-likeness.*
[b] *Measured by competitive radioligand-binding assay [21]*
[c] *Determined experimentally by the FTC method [12,22]*

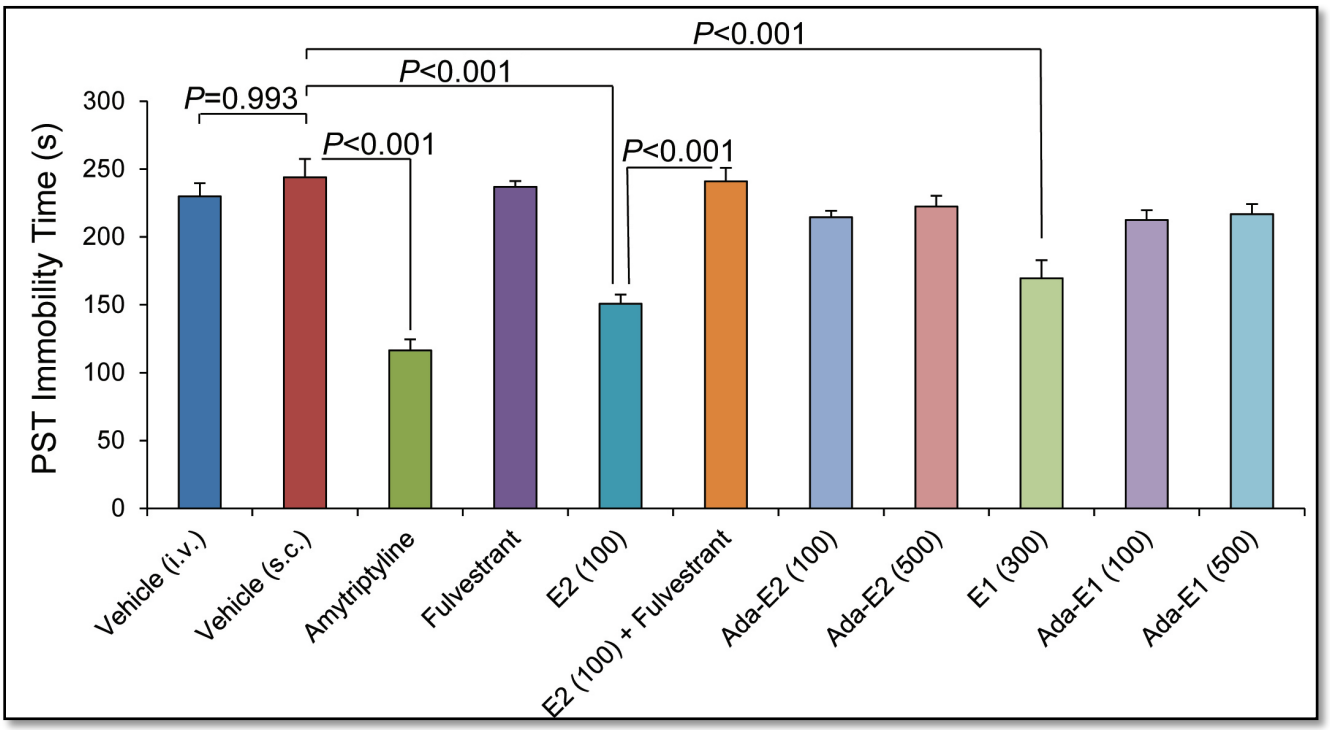

Figure 2. Evaluation of E2, E1, Ada-E2 and Ada-E1 (doses given in parentheses as μg/kg body weight) for antidepressant-like activity in the PST using OVX young adult CD1 mice. Displayed data are means ± SEM (N/group=6 except for s.c. vehicle, where N/group was 12). One-way ANOVA: $F_{(10,61)}$=15.0, P<0.001.

CONCLUSION

In conclusion, our lead evaluation has confirmed both genomic and non-genomic mechanisms are required for broad-spectrum estrogen neuro-protection and treatment of menopausal symptoms. Therefore, non-feminizing estrogens are not suitable to fulfill their overall premise. In addition, our analyses have revealed serious shortcomings regarding pharmaceutically important properties and drug-likeness of prototypical lead compounds. On the other hand, our

recently published brain-selective estrogen therapy promises to provide full benefits of the hormone's activity through both genomic and non-genomic mechanisms with a concomitant improvement in drug-like properties and, also, fully avoiding peripheral impacts that leads to feminizing effects [25]. Consequently, the creation of novel non-feminizing estrogens as lead compounds has lost it impetus in the context of drug discovery and development.

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