Rationale: Phenytoin (Dilantin®; DPH) treats epilepsy but causes SERM-like side effects. We investigated interactions of DPH with estrogen receptors (ER). Experimental: (1) Computerized docking of DPH to the ER? ligand-binding domain (LBD) showed strong interactions and a contact at leucine (L540) in helix 12. Interaction with ERß is slightly less favorable without L540 interaction. E2, E1 and TMX do not contact L540. (2) Cellular actions: Luciferase-expressing ER? or ERß cells showed DPH to be a several orders weaker agonist than E2 on ER? and ineffective on ERß. DPH at clinical anticonvulsant blood concentrations (10-11M) powerfully antagonized E2 action on ER? cells while marginally inducing alkaline phosphatase (an estrogen action.) (3) ER competition - On Scatchard plots E2 is orders stronger in displacing labeled estradiol but DPH was approximately equimolar effective in blocking this action; DPH is a strong E2 antagonist. Conclusions: Phenytoin is an ER?-selective SERM. At anticonvulsant concentrations DPH is a strong E2 antagonist and interacts with the LBD of ER? at the hinge of helix 12. This raises interesting interactions with other ER ligands or with the mobility of helix 12 which could explain DPH's SERM actions. Korach's group has reported abnormal SERM action in on ER leucine-mutated mice. DPH interacts with the ERß LBD, but has negligible actions in cellular and binding studies. Our results explain DPH's SERM-like profile of actions and raise possibilities for the use of DPH or congeners in clinical management of ER?-dependent conditions.