As the substitute of polybrominated diphenyl ethers (PBDEs), further assessments about the potential ecological safety and health risks of phosphorus-containing flame retardants (PFRs) are required because the worldwide demand for PFRs has been increasing every year. In this study, we examined the agonistic/antagonistic activity of a group of PFRs by three in vitro models (luciferase reporter gene assay, yeast two-hybrid assay, and E-screen assay). Molecule docking was used to further explain the interactions between ERα and PFRs. Data from luciferase reporter gene analysis showed three members of the nine tested PFRs significantly induced estrogenic effects, with the order of TPP > TCP > TDCPP, while TCEP and TEHP have remarkable antiestrogenic properties with calculated REC20 and RIC20 values of 10(-6) M or lower. Results from the luciferase reporter gene method are generally consistent with results obtained from the yeast two-hybrid assay and E-screen, except for the positive estrogenic activity of TBP in E-screen testing. Docking results showed that binding between ligands and ERα was stabilized by hydrophobic interactions. As a proposed alternative for brominated flame retardant, PFRs may have anti/estrogenic activity via ERα at the low dose typical of residue in environmental matrix or animals. PFRs with a short chain, halogen, and benzene ring in the substituent group tend to be estrogenic. Our research suggests that comprehensive evaluations, including health and ecological assessments, are required in determining whether PFRs are preferable as an emerging industrial substitute.