Parabens have been widely used in packaged foods, pharmaceuticals, and personal-care products. Considering their potential hydrolysis, we herein investigated structural features leading to the disruption of human androgen receptor (AR) and whether hydrolysis could alleviate such effects using the recombinant yeast two-hybrid assay. Parabens with an aryloxy side chain such as benzyl paraben and phenyl paraben have the strongest antiandrogenic activity. The antiandrogenic activity of parabens with alkyloxyl side chains decreases as the side chain length increases from 1 to 4, and no antiandrogenic effect occurred for heptyl, octyl, and dodecyl parabens with the number of alkoxyl carbon atoms longer than 7. The antiandrogenic activity of parabens correlates significantly with their binding energies ($R2 = 0.84$, $p = 0.01$) and were completely diminished after the hydrolysis, particularly for parabens with aryloxy side chains. The Km for the hydrolysis of parabens with aromatic moiety side chain is 1 order of magnitude higher than that of the parabens with alkyl side chains. Both in vitro and in silico data, for the first time, suggest parabens with aromatic side chains are less prone to hydrolysis. Our results provide an insight into risk of various paraben and considerations for design of new paraben-related substitutes.