Synthesis and Biological Evaluation of Guanylhydrazone Coactivator Binding Inhibitors for the Estrogen Receptor

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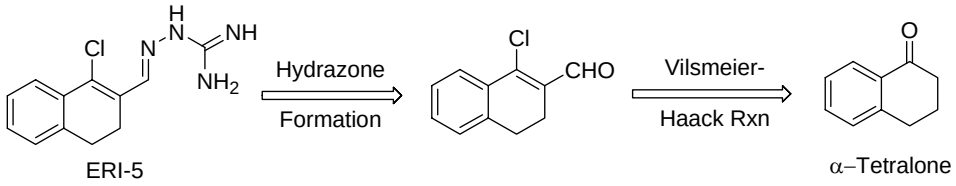
In 2004 Wyeth Pharmaceuticals reported a compound, ERI-5, which showed anti-estrogen activity in an *in vivo* assay, but appeared to work by a different mechanism than traditional estrogen receptor (ER) antagonists. Inspired by their claims, we prepared ERI-5 and 14 derivatives for testing in our labs using both *in vitro* (fluorescence polarization) and *in vivo* (reporter gene) assays. The compounds were prepared from a variety of aryl ketones via the Vilsmeier reaction followed by hydrazone formation. One of the derivatives we prepared performed better than ERI-5 and had an IC_{50} of 0.6 μM in a MCF-7 cell reporter gene assay and did not displace ^{3}H-estradiol in a radiometric competition assay, indicating a new form of antagonism. We are currently testing the lead compound in a mammalian two hybrid assay and will publish the results in the near future.



ERI-5 α–Tetralone