SAMPLE 1

Synthesis of a Novel Small Molecule Inhibitor of D14-Type Strigolactone Receptors

Strigolactones are a class of plant hormones that can regulate shoot branching and stimulate germination of parasitic Striga hermonthica seeds. Since strigolactone signaling affects the growth of devastating parasitic weeds, plant height, and overall plant architecture, finding an effective way to regulate strigolactone receptors and inhibit strigolactone perception could lead to novel pathways to improving crop yields and controlling agricultural pests. Recently, the Itami Group discovered a novel small molecule inhibitor, named as DL1, which binds to the DWARF14 (D14) receptor and inhibits further strigolactone hydrolysis and signaling. This study was derived from their recent discovery, and had two specific aims: 1) to investigate the structure-activity relationship (SAR) of DL1, and 2) based on the SAR, design a new, stronger inhibitor. To research the effect of the adamantyl moiety on inhibitor efficacy, derivatives of the original DL1 molecule with various carbon scaffolds such as cubane, cyclohexane, and benzene in place of the adamantyl were synthesized. Derivatives of DL1 with different hydrocarbon branches on the indole moiety were also synthesized. The binding activity and dose-dependent hydrolysis inhibition efficacy of all derivatives were studied through a competition bioassay using Yoshimulactone Green, a molecule that fluoresces when hydrolyzed by uninhibited D14 receptors. Preliminary bioassay results revealed that replacing the adamantyl moiety with a simple aromatic group yielded a surprisingly strong inhibitor, which disputed the original idea that the polycyclic cage nature of the adamantyl moiety would play a key role in inhibition activity. Based on these results, new families of derivatives, like those having ortho, meta, para, and disubstituted phenyl moieties, were systematically designed, synthesized, tested, and modified to create more effective inhibitors. The structures of these new inhibitors were characterized with 1H NMR and X-ray crystallography. This systematic approach ultimately led to the discovery of a new potent inhibitor of D14-mediated strigolactone hydrolysis that is nearly 4.5x more effective than the original DL1 molecule. The IC50 value (half-maximum inhibitory concentration) of the new compound is 0.29 micromolar while that of DL1 is 1.3 micromolar. This new small molecule inhibitor has great potential as an agrochemical to control strigolactone signaling in crops, particularly because DL1 and its derivatives enhance shoot branching in crops such as Arabidopsis thaliana and rice.