

A Femtomolar-Range Suicide Germination Stimulant for the Parasitic Plant *Striga hermonthica*

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Striga hermonthica (Striga), a parasitic plant commonly called “Witchweed”, represents a major threat to food security in Africa; however, despite its scale, the problem is not well recognised by the general public. *Striga* is an obligate root hemiparasitic plant that makes a host plant wither. Although tiny *Striga* seeds are difficult to remove directly from the soil in order to protect crops, they can be killed by inducing their germination in the absence of host plants, which is known as a suicide germination strategy. Since the strigolactones (SLs), a group of a plant hormones produced by host plant roots, were discovered as germination stimulants of *Striga* in 1966, they have been attractive lead molecules for designing *Striga* suicide germinators and major efforts have been made to develop synthetic SLs by modifying their structures. However, none has had the high potency, target (plant) selectivity and low synthetic costs required for further development. An interdisciplinary team led by researchers at Nagoya University (Japan) has tackled the *Striga* infection problem and found a highly potent SL mimic as a candidate of an ideal suicide germination stimulant.

Plant biologist Dr. Yuichiro Tsuchiya (now at Nagoya University, Japan) had reasoned that the major issue in SL research for tackling the *Striga* infection is a lack of basic information,

such as the identity of SL receptors, which hinders development of suicide germination molecules through rational molecular design. He said: “Because I had experience in identifying a receptor of Arabidopsis through chemical screening to find its seed germinators, we had a strong belief that we might be able to identify SL receptors in *Striga* as well.” His team had decided to investigate and collect basic information about how *Striga* senses SLs and germinates. However, this turned out to be a very challenging task because, in *Striga*, it is impossible to conduct conventional biological assays using genetics, such as mutational studies, transformations, and gene editing. Dr. Tsuchiya explained: “A breakthrough came when I moved to the Institute of Transformative Bio-Molecules (WPI-ITbM) at Nagoya University, where chemists and biologists work together to crack unsolved issues.” His team in Nagoya was eventually able to determine 11 SL receptors in *Striga* (ShHTLs) in 2015, by means of a synthetic SL with fluorescence turn-on property, now called Yoshimulactone green (YLG), which was designed and synthesized by two ITbM chemists, Drs. Shinya Hagihara and Masahiko Yoshimura.

The fluorescence probe made it extremely easy to analyze SL receptors biochemically and understand their biological functions, and indeed, the discovery of YLG enabled the

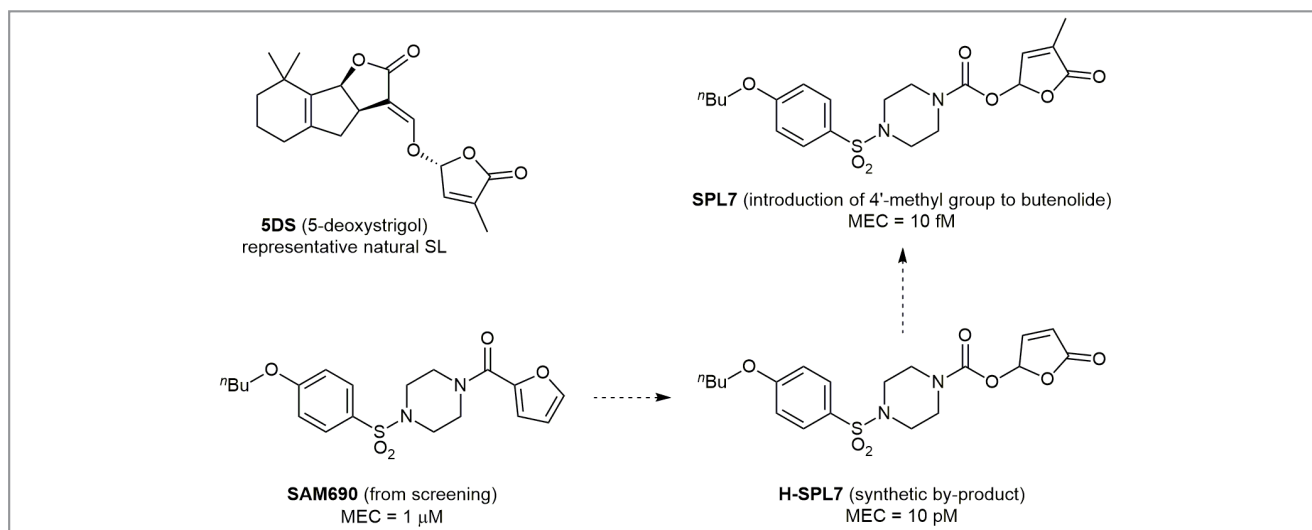


Figure 1 Natural and synthetic suicide germination stimulants; MEC = minimum effective concentration for *Striga* seed germination

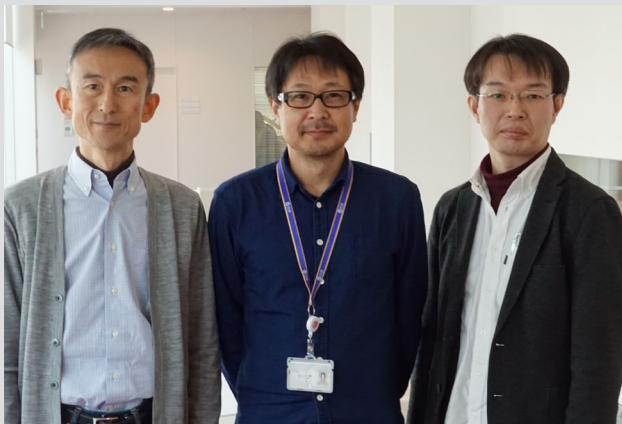
team to develop, for the first time, suicide germination molecules based on the ligand–receptor interactions. The present research was initiated by the chemical screening of small molecules to find receptor-selective *Striga* germinators, and subsequent structural modification of hit molecules by the Ooi group led to the serendipitous discovery of a femtomolar-range suicide germination stimulant for *Striga*, sphynolactone-7 (SPL7). “The development of SPL7 as a highly potent germination stimulant is a monument to the efforts we have made over 15 years and now one of my dreams is coming true!” exclaimed Dr. Tsuchiya, with feeling.

Organic chemist Prof. Takashi Ooi took up the tale: “My research group (Daisuke Uruguchi, Sathiyarayanan AM, and Rie Yamaguchi) introduced chemical viewpoints to Yuichiro’s study on parasitic plants, specifically *Striga*, and helped open up a new avenue to understand and combat the *Striga* infection.” Dr. Daisuke Uruguchi (organic chemist) echoed this statement: “I believe that our experience with homogeneous catalysis in organic chemistry really helped the investigation of biological reaction mechanisms relating to the *Striga* germination process.” For instance, their approach enabled an investigation into how *Striga*’s SL receptors (ShHTLs), having hydrogenase activity, recognize and react with ligands and transmit germination signaling through the alteration of their three-dimensional structures, which finally led them to propose a cumulative activation scenario. Dr. Uruguchi described: “A cumulative model for switching-on the germination signaling was proposed through monitoring the intermediate of the process by LC-MS, which is somewhat similar to the mechanistic study of organic transformations.” Furthermore, during structure–activity relationship studies of *Striga* germinators, the group found that an impurity of a synthetic germinator (H-SPL7) was an unprecedentedly potent molecule, providing a basis for development of the key molecule named sphynolactone-7 (SPL7). “We did not neglect inconsistencies in the data from biological experiments – namely, in the evaluation of the activity of germination stimulants – and hypothesized this could be due to contamination by a trace amount of a highly potent molecule. We had this idea thanks to our experience in catalysis, where the influence of a small amount of impurity can cause a lot of trouble!” he said. On the basis of the experimental results, they realized that the contaminant (H-SPL7) seemed to be generated via autooxidation of the target molecule (one of the SAM molecules), which was a derivative of the hit molecule in the initial chemical screening. Dr. Uruguchi continued: “I feel that Nature suitably derivatized our molecule on our behalf and then we serendipitously found it as a gift from Nature!” The process of identifying the contaminant was similar to the isolation of natural products and

its actual structure convinced the group of its extraordinary potency. The core skeleton of the SAM molecules was hybridized with a butenolide ring, which has been regarded as a critical part of SLs for stimulating *Striga* germination. “This structural characteristic motivated us to name it sphynolactone-7 (SPL7), whose pronunciation is derived from ‘sphinx’, the hybrid of a human head and a lion body, guardian of a pyramid in Africa, and specifically in Egypt,” he said. Prof. Ooi further noted: “Since SPL7 selectively activates/binds one of the ShHTLs, ShHTL7, we believe it will be a powerful tool for elucidating the biological systems behind germination signaling.” Dr. Uruguchi followed: “Hereafter, by taking advantage of the receptor selectivity of SPL7, we will further tackle the mysteries of *Striga*; for example, how the germination signal is transmitted and why *Striga* has many SL receptors. Through this challenge, I hope that our study will eventually contribute to solving the current serious *Striga* problems for African food security.” Prof. Ooi continued: “More importantly, SPL7 is a promising candidate for a *Striga* herbicide, relying on the suicide germination process.” Since the danger to food security in Africa originates largely from the damage to food production caused by *Striga* infection – as detailed in United Nations documents – if SPL7 provides a definitive solution to this problem, this work would have an enormous impact on society. He concluded: “We are going to pursue a field test of SPL7 as a *Striga* suicide germinator in Africa (Kenya) and hope to develop an agrochemical for ensuring food security in Africa within the next decade. For us, as chemists, the collaboration with biochemists has been a real pleasure.”

Mattias Hansson

About the authors



From left: Prof. T. Ooi, Dr. Y. Tsuchiya, Dr. D. Uraguchi

Yuichiro Tsuchiya (middle), born in 1974 in Hokkaido (Japan), initiated his career as a plant scientist in Eiji Nambara's group while he was an undergraduate at Hokkaido University (Japan). He earned his PhD in agriculture in 2002 under the supervision of Peter McCourt at the University of Toronto (Canada) and Satoshi Naito at Hokkaido University. After experiences as a postdoctoral researcher in Peter McCourt's laboratory, Yuji Kamiya's group in Riken (Japan) and Toshinori Kinoshita's group at Nagoya University (Japan), he became a designated associate professor at the Institute of Transformative Bio-Molecules (WPI-ITbM) at Nagoya University in 2015. His lab's research has focused on elucidating the mechanism of seed germination in the parasitic plant *Striga hermonthica* using small-molecule probes.

Takashi Ooi (left) is a professor at Nagoya University (Japan). He was born in 1965 in Nagoya and received his B.Eng. (1989) and Ph.D. (1994) degrees from Nagoya University under the supervision of Professor Hisashi Yamamoto. After working as a JSPS postdoctoral fellow with Professor Julius Rebek, Jr. at

the Massachusetts Institute of Technology (USA), he started his academic career as an assistant professor in Professor Keiji Maruoka's group at Hokkaido University (Japan) in 1995. In 2001, he was appointed as an associate professor at Kyoto University (Japan). He was then promoted to professor at Nagoya University in 2006. From 2012, he has been one of the principal investigators at the Institute of Transformative Bio-Molecules (WPI-ITbM) at Nagoya University. He has received several awards, including the Chugai Pharmaceutical Co., Ltd. Award in SSOCJ (1996), the CSJ Award for Young Chemists (1999), the Thieme Chemistry Journals Award (2006), the JSPS Prize (2010), the IBM Japan Science Prize (2011), the Inoue Prize for Science (2013), and the SSOCJ Daiichi-Sankyo Award for Medicinal Organic Chemistry (2017), and was named a Fellow of the RSC (FRSC) in 2014. His research interests are general synthetic organic chemistry.

Daisuke Uraguchi (right) is an associate professor at Nagoya University (Japan). He was born in 1974 in Hokkaido (Japan) and received his B.Sc. (1997) and Ph.D. (2002) degrees from Hokkaido University (Japan) under the guidance of Professor Keiji Maruoka. He gained substantial experience working as a JSPS postdoctoral fellow (2002–2004) with Professor P. Andrew Evans at Indiana University (USA) and with Professor Masahiro Terada at Tohoku University (Japan). Then, he moved to the Sagami Chemical Research Center (Japan, 2004–2006). In 2006, he became an assistant professor in the research group of Professor Takashi Ooi at Nagoya University, and was promoted to associate professor in 2008. He has received the Takeda Pharmaceutical Co., Ltd. Award in SSOCJ (2008), the CSJ Award for Young Chemist (2010), the Young Scientists' Prize from MEXT (2011), the Banyu Chemist Award (2012), the MBLA Lecture-ship Award (2013), and the Thieme Chemistry Journals Award (2014). His current research interests include the chemistry of organic ion-pair catalysis.