Investigating the Potential of Resveratrol Synthase Inhibition in Management of Japanese knotweed

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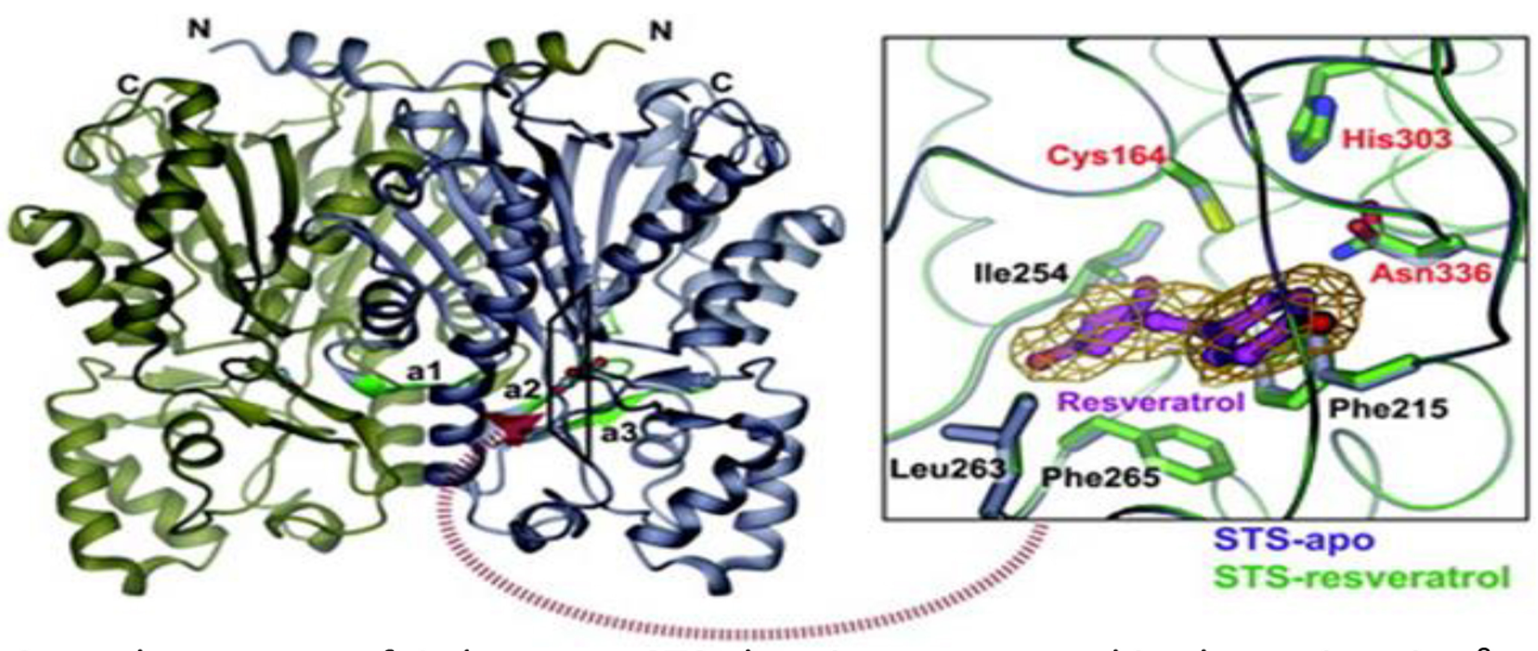
1. Japanese Knotweed; An invasive Species

Fallopia japonica (Houtt.) Ronse Decr. (Japanese Knotweed) is a rhizomatous, perennial geophyte, native to Japan, originally introduced mid-nineteenth century to the UK and USA as an ornamental plant.[1] It is highly invasive in most European countries including Ireland. [1] To date only female plants have been reported in Ireland.[2] The major cause of spread is by deliberate or accidental movement of rhizome fragments or cut stems.[2] Japanese knotweed has economic and ecological impacts in Ireland.[3] In invasive regions it outcompetes native plants for sunlight.[4] Production of secondary products with allochemical properties, alter the mineral availability in soil which leads to suppression of the growth or fitness of native plants.[5] The rhizomes penetrate foundations and asphalt, and damage riparian structures including flood defence systems.[4] Current methods involve the repeated use of glyphosate, a systemic herbicide, which has been categorised as a 2A probable carcinogen to humans by the International Agency for Research on Cancer (IARC). [6] The aim of this project is to synthesize inhibitory analogues of the enzyme substrate and to investigate if inhibiting resveratrol production affects the invasiveness of Japanese Knotweed when exposed to biological controls. Specific species of Fungi and psyllids that are natural enemies of the plant in Japan and not found in invasive regions have been suggested as potential biological controls.[3,7]

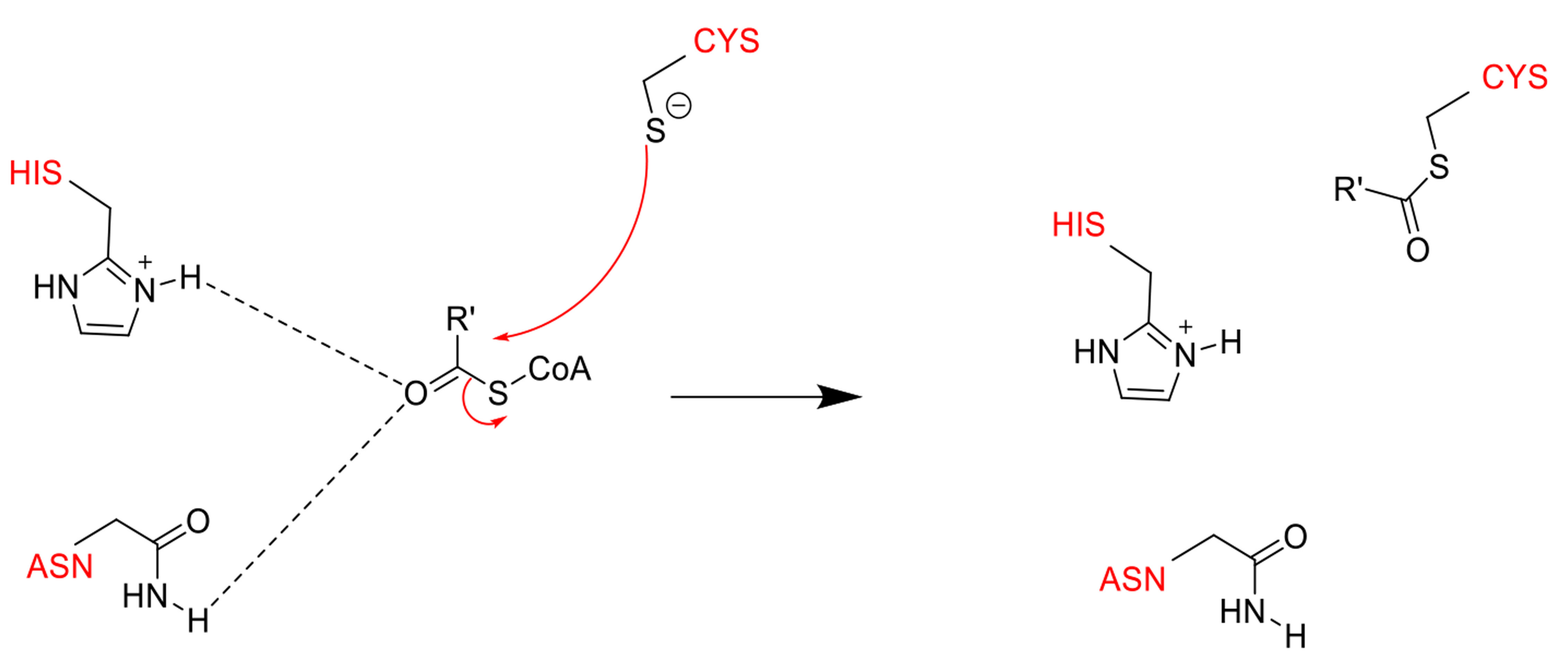
2. Resveratrol Synthase

Resveratrol synthase is a member of the type III polyketide synthase (PKS) family of enzymes.[8] Resveratrol is a phytoalexin; a chemical produced in certain plant species as part of a defence mechanism in response to biotic and abiotic stimuli including; UV irradiation, mechanical stresses, heat stimuli and pathogen infections.[8] Resveratrol synthases contains a conserved Cys-His-Asn catalytic triad.[8]



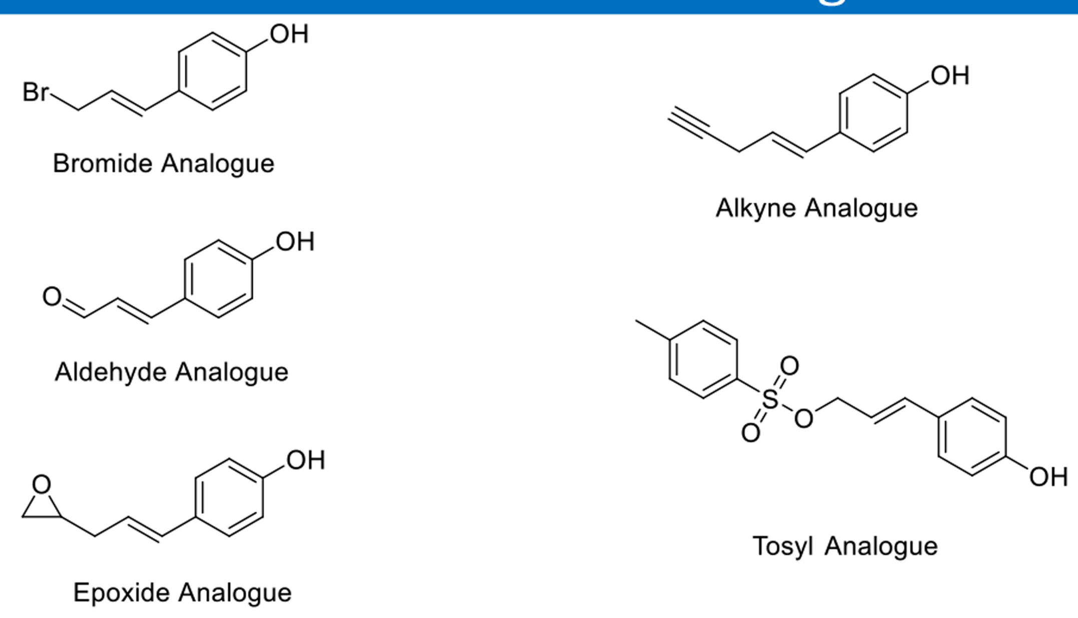
Crystal structure of *A. hypogae* STS showing resveratrol in the active site.[9]

3. Catalytic Mechanism of Action:

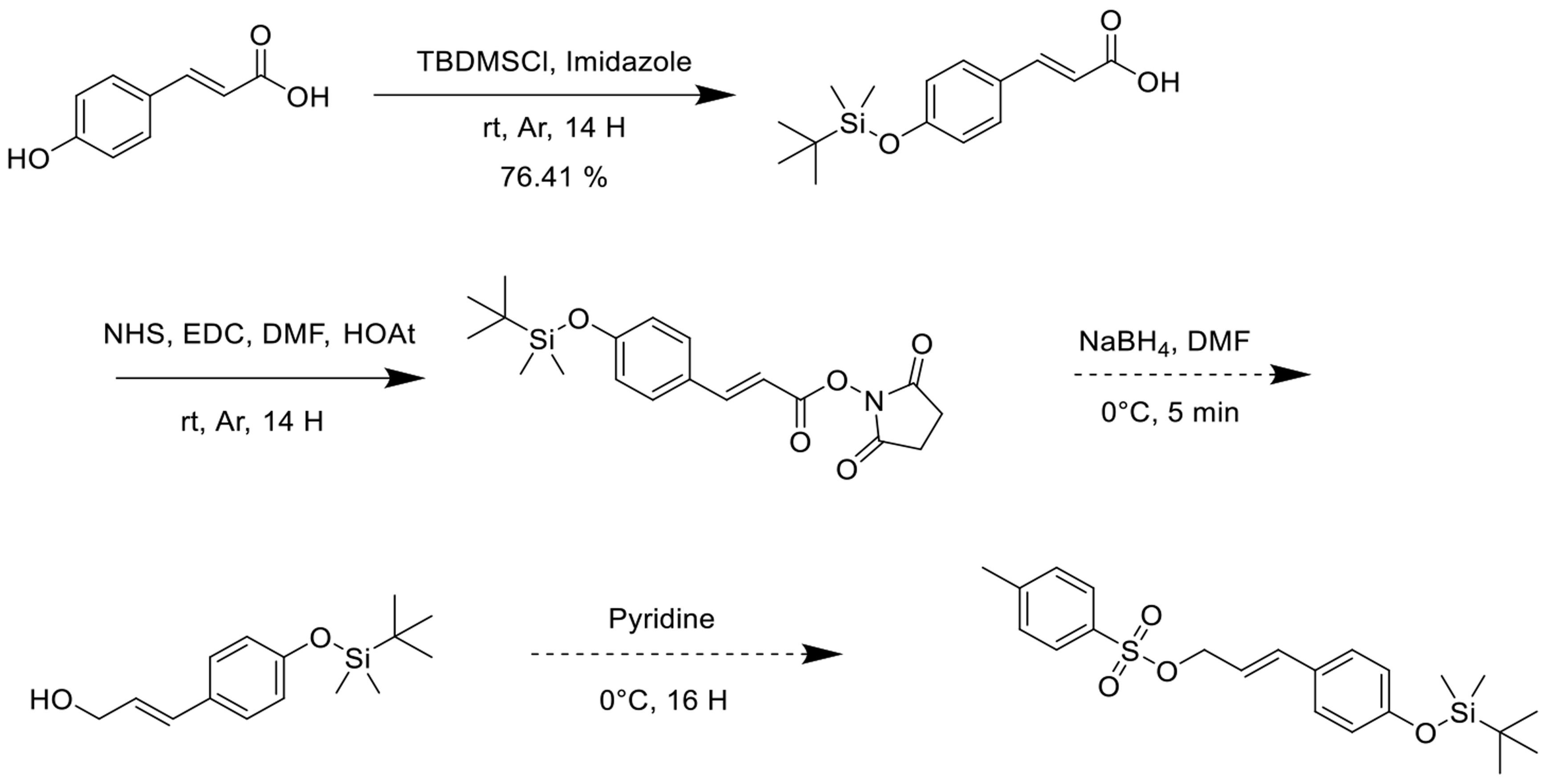


Nucleophilic attack of *P*-Coumaryl CoA substrate by catalytic cysteine residue. Followed by chain lengthening via successive condensation of 3 acetyl units, derived from the decarboxylation of malonyl CoA, with a CoA tethered phenyl propanoic starter molecule to form a linear polyketide follows.[10] A subsequent C2 to C7 intramolecular aldol condensation produces Resveratrol.[10]

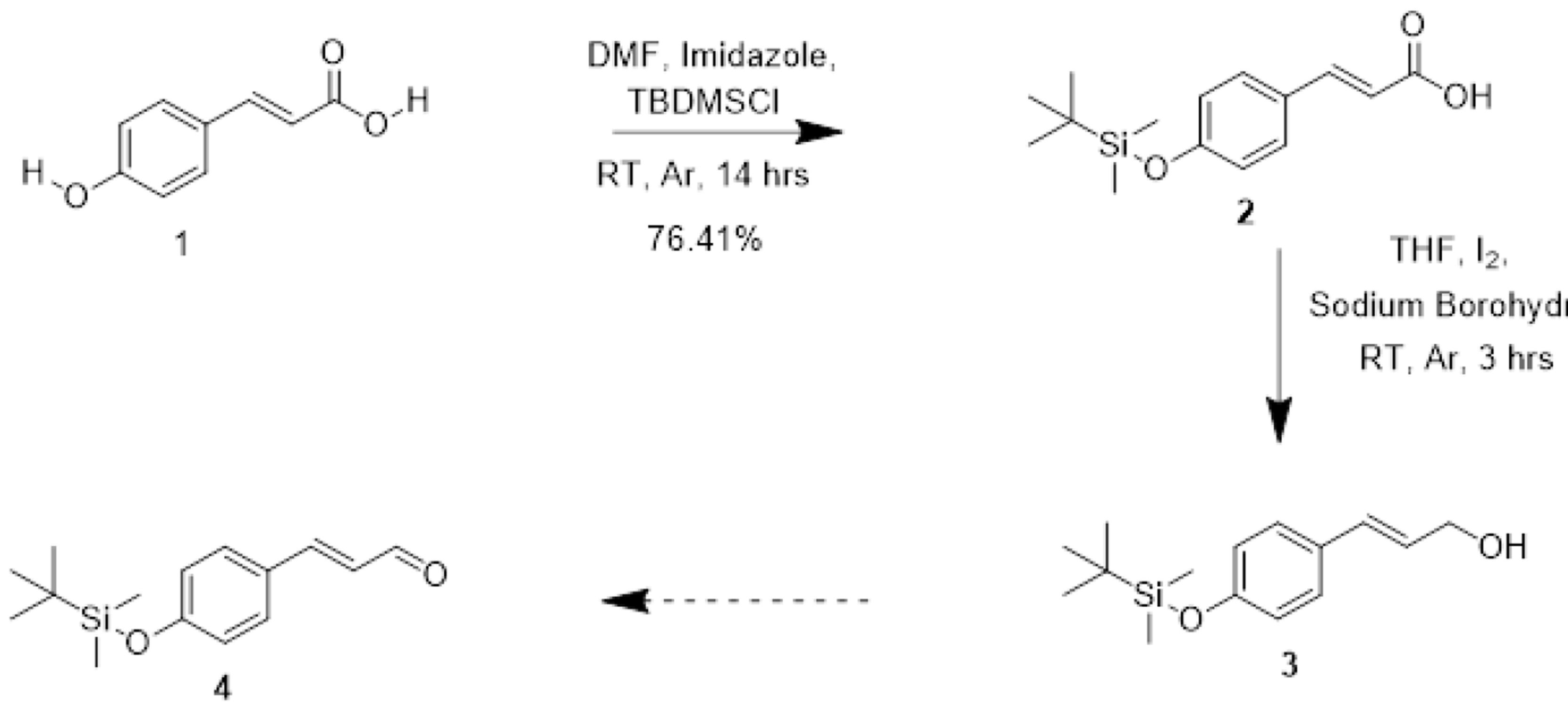
4. First Generation Analogues



5. Synthesis of a Tosyl Analogue



6. Synthesis of an Aldehyde Analogue



7.Future Work

Future work should focus on the synthesis of epoxide, aldehyde and alkyne analogues of P-Coumaric acid. Synthesis of second generation analogues would include the CoA part of the molecule to improve specificity. Biological evaluation of the inhibitors should include kinetic studies.

8. Acknowledgements

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9. References

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