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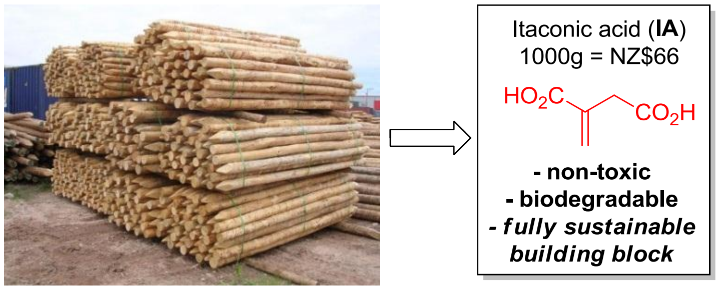
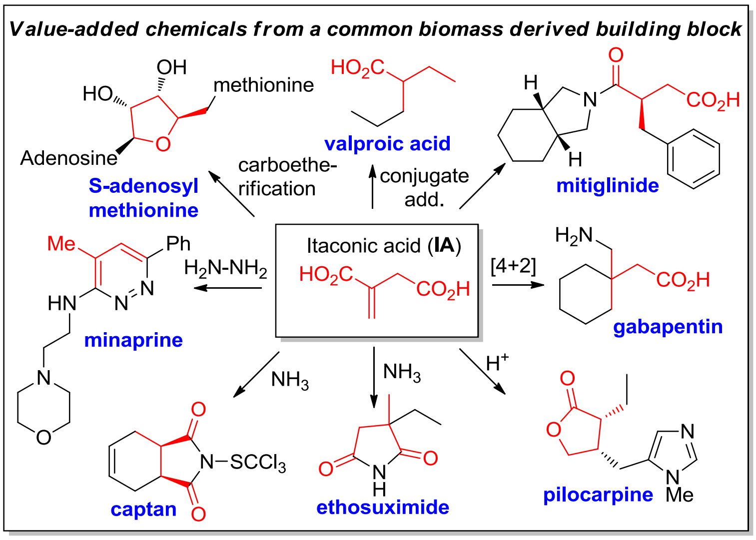
# Blockbusters from Biomass: Sustainable Pharmaceutical Synthesis from Itaconic Acid

A major recommendation in the vision 2020 catalysis report is the improved use of renewable feedstocks (biomass) in the production of valuable chemicals.[1] One area that has struggled to rise to the challenge is chemical synthesis, a discipline that relies heavily on fossil fuel-derived building blocks in stoichiometric routes with poor atom-economy,[2] unavoidably leading to large waste streams.[3] In a deviation from this theme, a unique sustainable synthesis programme proposed herein will demonstrate that several commodity and speciality chemicals can be obtained from the biomass-derived building block itaconic acid (IA) using synthetic pathways devoid of toxic solvents and reagents. This proposal presents a clear opportunity to contribute to a paradigm shift in chemical synthesis, stimulating the use of biomass-derived platform chemicals in the production of pharmaceuticals and other value-added products.




Itaconic acid (IA) is readily obtained by fermentation of sugars extracted from hardwood and agricultural residues.[4] It is a fully sustainable chemical building block that features on the U.S. DOE National Renewable Energy Laboratory's Top 12 list of renewable chemicals attainable from biomass.[5] Furthermore, the low cost, negligible toxicity and structural characteristics (C=C double bond and an unsymmetrical 1,4-diacid) make it an excellent candidate for a sustainable synthesis programme. Indeed, the potential of IA has not gone unnoticed; it is a valuable precursor in the polymer industry[6] and the IA scaffold has been explored for its biological properties[7] but surprisingly, the use of IA in the synthesis of complex value-added products is unexplored.




As alluded to above, the C=C bond and 1,4-diacid present in IA provide excellent handles with which to introduce molecular complexity. Conjugate addition to the C=C bond will provide to key step in the synthesis of valproic acid, used in the treatment of epilepsy and bipolar disorder and the type 2 diabetes drug mitiglinide. The C=C bond should readily participate in [4+2]-cycloadditions, facilitating access to cyclohexanes bearing a quaternary centre such as gabapentin, a GABA analogue used to treat epilepsy and neuropathic pain. Oxidative lactonization will provide facile access to butyrolactones such as the glaucoma drug pilocarpine. The 1,4-diacid will readily react with ammonia to furnish cyclic imides, structures present in the anticonvulsant ethosuximide and the pesticide captan. Similarly, the 1,4-diacid will react with hydrazine to provide pyridazines, a medicinally important heterocycle seen in the antidepressant minaprine. Finally, intramolecular carboetherification provides the basis for the synthesis of tetrahydrofurans, as observed in *S*-adenosylmethionine, a nutraceutical used in the treatment of depression, liver failure and osteoarthritis.

It is of note that all of the proposed syntheses show high atom economy, with the entire five carbon framework of itaconic acid (red) incorporated into the final products. Although detailed synthetic schemes are not priovided herein, toxic reagents and solvents will only be employed as an absolute last resort and particular emphasis placed on eradicating chromatography. This project will not only involve novel synthetic steps that contribute to the development of synthetic methodology, but also validate wood biomass as a viable platform for value-added chemicals. By demonstrating the efficient, renewable and economically viable synthetic approaches to the aforementioned compounds, we hope to emphasize to the organic chemistry community (both academic and industrial) that biomass derived building blocks are viable alternatives for synthetic chemistry research.

## References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