How tropolones synthesized in fungi: 70-year-old chemical mystery solved

April 16 2012

Chemists and biologists from the University of Bristol have finally cracked one of the longest standing chemical mysteries. In a paper published today in the *Proceedings of the National Academy of Sciences*, the team demonstrate exactly how an unusual class of compounds known as tropolones are synthesized in fungi.

In 1942, an 'unidentifiable' aromatic compound known as stipitatic acid was first isolated from fungi. By 1945 the structure was solved but it was so unique that it caused a revolution in the understanding of organic chemistry.

Stipitatic acid is very unusual as it displays similar aromatic properties to the six-membered rings in benzene-based compounds, but is a seven-membered carbon ring known as a tropolone. New theoretical models developed to understand tropolones now underpin our understanding of structure and bonding in organic chemistry.

However it remained a mystery as to how fungi are able to synthesise such a product under biological conditions – until now.

Using a combination of genetic and chemical methods, Dr Andy Bailey and Professor Russell Cox and colleagues were able to identify the genes responsible for this process, blocking the synthetic pathway at different steps and thus demonstrating how, on a molecular scale, the tropolone structure is produced. This is the core of a number of fungal compounds including stipitatic acid, the xenovulenes which are antidepressants and

the antimalarial compound puberulic acid.

Knowledge of tropolone biosynthetic pathway is in itself very interesting to chemists, but it may also lead to the discovery of new drugs.

Professor Russell Cox of Bristol's School of Chemistry, who led the project, said: "Members of this class of compound are well known as having antibacterial properties and some have promise as antimalarial treatments – we now plan to engineer fungi to produce these new compounds."

It is hoped that identification of the enzymes responsible for tropolone synthesis will help in generating a wider range of compounds for evaluation.

More information: 'The Genetic, Molecular and Biochemical Basis of Fungal Tropolone Biosynthesis' by Jack Davison, Ahmed al-Fahad, Menghao Cai, Zhongshu Song, Samar Yehia, Colin M. Lazarus, Andrew M. Bailey, Thomas J. Simpson and Russell J. Cox in *Proceedings of the National Academy of Sciences* (2012).

Provided by University of Bristol