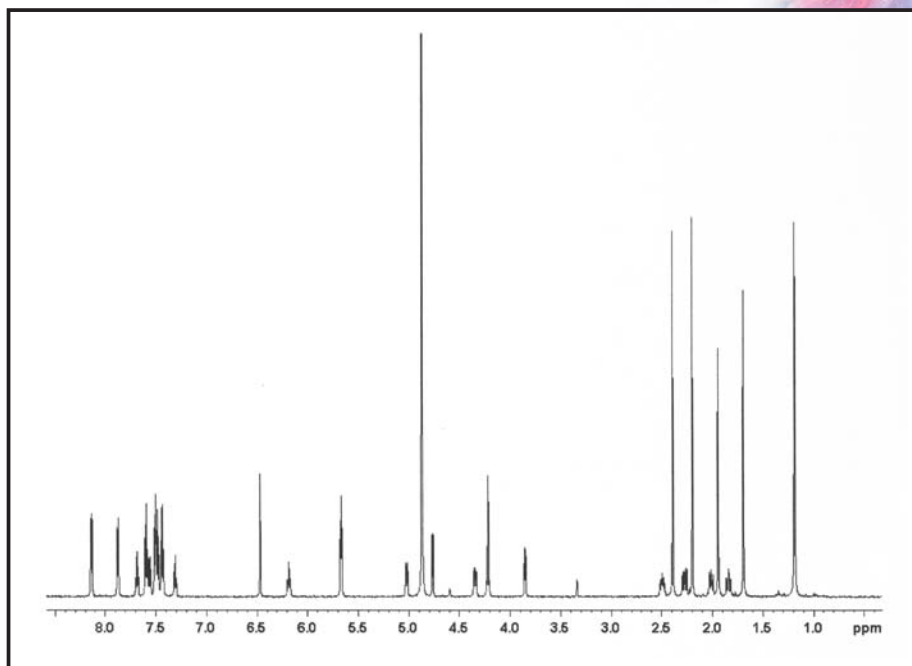


Natural Product Analysis: Rapid Dereplication, Taxol

Natural products have been a major source for the generation of lead compounds for drug discovery research and approximately 30% of all current drug sales are direct descendants of natural products. Currently, about 60 % of the anti-tumour and anti-infective agents commercially available or in the later stages of clinical trials are of natural product origin.



50 μg of Taxol in MeOD

Bruker Avance 600 MHz Spectrometer
CapNMR $^1\text{H}/^{13}\text{C}$ probe 1.5 μl active volume
pump rate 5 $\mu\text{l min}^{-1}$,
load volume 3 μl
64 scans
5 min acquisition time

Advances in combinatorial chemistry have allowed the rapid synthesis of large libraries of compounds that have tended to focus lead discovery efforts toward the production and screening of combinatorial compound libraries. These same advances coupled with conventional natural product chemistry has allowed for the creation of large libraries of purified fractions of small molecule natural products that are suitable for high-throughput screening formats. HTS methods using microflow NMR combined with conventional techniques is a powerful tool for this process and can accelerate drug discovery from natural resources.

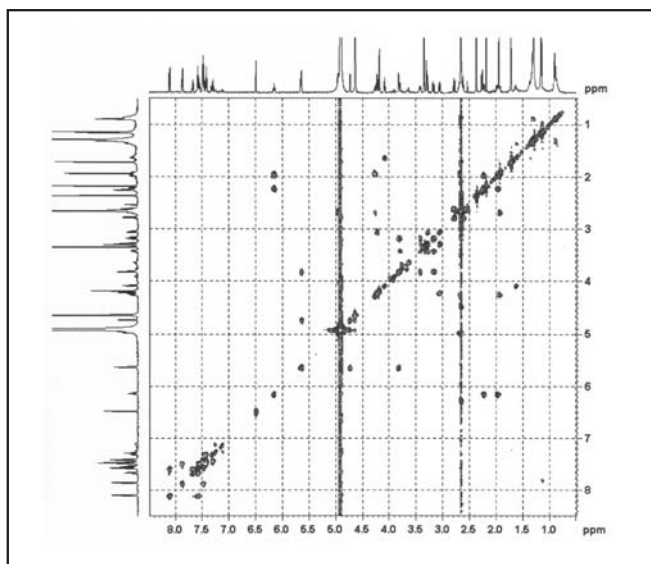
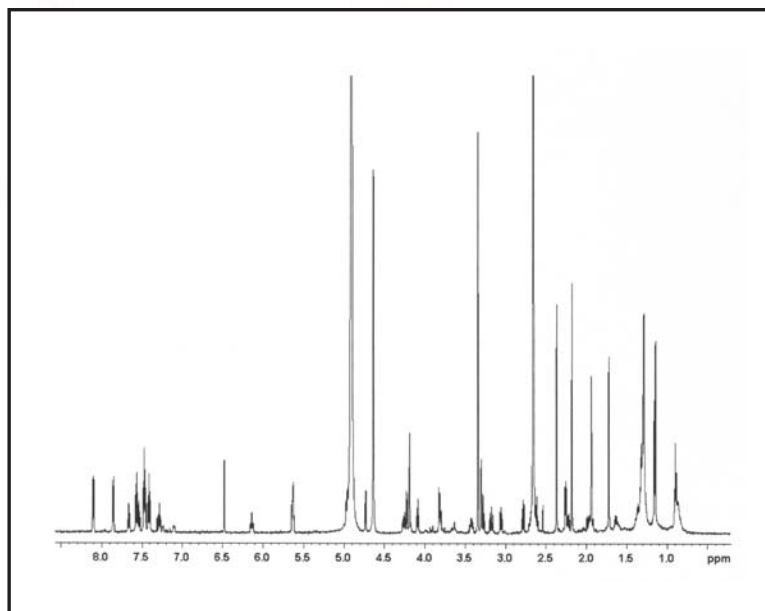
The example shown is a compound from the stem bark of *Taxus brevifolia*, the pacific yew tree, containing paclitaxel (Taxol) and its 300 plus derivatives. The active compounds, 7-(β -xylosyl)taxol A, 7-(β -xylosyl)taxol C and 7-(β -xylosyl)-10-deacetylaxol C were rapidly dereplicated using their molecular weights as determined by LC-ELSD-MS analysis and the structures were characterised using a Protasis/MRM CapNMR probe for ^1H and COSY NMR experiments. Data was gathered using only 20 μg of sample and minimal acquisition times.

Natural Product Analysis

Since conventional NMR employs either 5 or 3 mm tubes, most laboratories need low milligram quantities of sample to acquire all of the necessary homo- and heteronuclear correlations for full structure elucidation. If compounds are mass limited, as is the case in natural products drug discovery, obtaining low-milligram quantities of sample requires multiple steps of separation needing weeks or even months of time. With a capillary based microlitre volume flow cell, the acquisition of NMR spectra on the samples in trace quantities is dramatically improved.

20 µg of 7-(β-xylosyl)taxol A in MeOD

*Bruker Avance 600 MHz Spectrometer
CapNMR ¹H/¹³C probe 1.5 µl active volume
pump rate 5 µl min⁻¹, load volume 3 µl
64 scans
5 min acquisition time*



20 µg of 7-(β-xylosyl)taxol A in MeOD

*Bruker Avance 600 MHz Spectrometer
CapNMR ¹H/¹³C probe
1.5 µl active volume
pump rate 5 µl min⁻¹, load volume 3 µl
16 scans per t1 increment
256 increments
1.75 hr acquisition time*

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In summary, structure elucidation was achieved within a fraction of the time needed as compared to conventional natural products chemistry.

The possibility of working with such small quantities is an important step forward in utilising natural products in drug discovery research.

This technique will open doors enabling chemists to readily discover bioactive components among the minor constituents of natural resources.

Data courtesy of Mark O'Neil-Johnson, Sequoia Sciences Inc., San Diego, CA, USA.

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