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The Network developing forensic applications of stable isotope mass spectrometry

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Forensic Isotope Ratio Mass Spectrometry

A Preliminary Multi-Stable Isotopic Evaluation of Three Synthetic Pathways of *Topiramate*

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Pharmaceutical products can be characterized or “fingerprinted” by measuring and comparing their highly-specific stable isotopic ratios via isotope-ratio mass spectrometric analysis (Jasper, 2004; Jasper *et al.*, 2004, and refs. therein). The isotopic composition observed is dependent on both the reactants used and the manufacturing process employed. A change in either of these variables produces a drug product having a different isotopic profile. Recent work has shown that when both the source of the starting materials and the manufacturing process are presumably held relatively constant during manufacture of the bulk drug substance, similar product isotopic-ratios are observed (Jasper *et al.*, 2004). By measuring the isotopic ratios for suspect samples in cases such as drug counterfeiting and process patent infringement, it may be possible to obtain useful information about the process and origin of raw materials used.

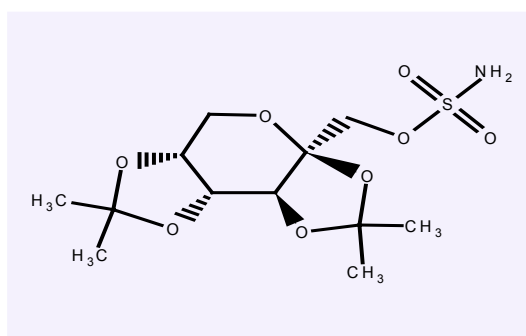


Fig.1. Structure of Topiramate (C₁₂H₂₁NO₈S).

To test the utility of the natural stable-isotopic differentiation of batch samples produced by different pathways, multi-stable isotopic analyses ($\delta^{13}\text{C}$, $\delta^{15}\text{N}$, $\delta^{18}\text{O}$, and δD) of 53 Topiramate samples produced by three different synthetic pathways (designated “A,” “B,” and “C”) were performed (Fig. 1). Examination of the data via the six possible bivariate isotope plots, reveals distinct data clustering, though in some cases with some overlapping within standard errors. In general, the isotopic composition of Topiramate from the C pathway is distinct from those of the A and B pathways. The isotopic data from the A and B pathways typically abut each other, sometimes partially overlapping. The hydrogen/deuterium- (δD) and oxygen ($\delta^{18}\text{O}$) isotopic compositions of Topiramate are each significantly linearly correlated with the paired carbon ($\delta^{13}\text{C}$) isotopic composition (Fig. 2). Given that H and O largely derive from meteoric water, the linear correlations with $\delta^{13}\text{C}$ indicate that a mixture of carbon sources (*viz.*, perhaps terrestrial C3

photosynthetic organic carbon and marine C3 organic carbon) were used in the production of the batches tested. If the H and O analyzed derived from meteoric water, then an elementary comparison of the span of the δD ($\Delta\delta D = 54.6 \pm 2.1\text{‰}$) and $\delta^{18}O$ ($\Delta\delta^{18}O = 4.71 \pm 0.26\text{‰}$) values in the Topiramate samples to the global isotopic gradients indicates that the water retained in the samples spanned from as much as 11° of latitude (or, ~ 760 statute miles north to south). The present isotope results ($\delta^{13}C$, $\delta^{15}N$, $\delta^{18}O$, and δD) form a database against which future samples can be compared to infer specific synthetic pathways.

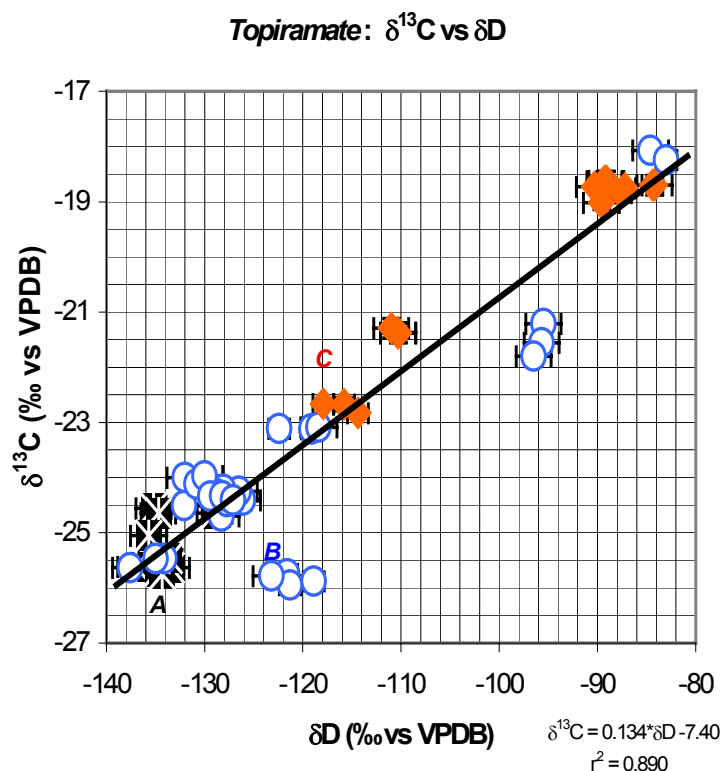


Fig. 2. A bivariate isotope plot ($\delta^{13}C$ vs. δD) of 53 Topiramate samples produced by three different synthetic pathways.

References

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