

Hot Topics in Pharmacognosy: Acutumine, An Old Alkaloid With New Potential

By ASP President David Newman

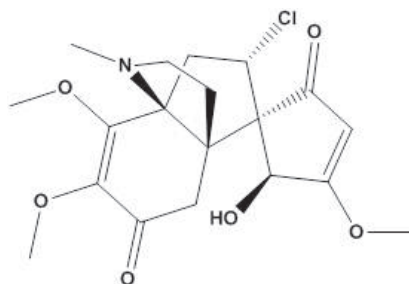
There are many, many unsolved mysteries in the mammalian immune system, to say nothing of the manifold differences and similarities between the human system and comparative processes in the other domains of life. Even the simple metazoan (the marine sponge) has an immune system of sort, to say nothing of more complex invertebrates and the plant kingdom.

In 1929, a group in Japan (Goto, K. and Sudzuki, H., *Bull. Chem. Soc. Jpn.* **1929**, 4, 220) reported the isolation of what we now know to be an unusual alkaloid, with an empirical formula of $C_{20}H_{27}O_8N$ or $C_{21}H_{27}O_8N$, together with a suggestion of a ketone, a carboxyl, an N-methyl and three methoxyl groups in the structure; we now know this to have an unusual tetracyclic structure.

The compound, together with others was isolated from a species of Menispermaceae, *Sinomenium acutum* Rehd. et Wils, with the Japanese name of Oh-tsuzurafuji. There the story languished until a report from the original scientist and colleagues in two papers in *Tetrahedron Letters* in 1967, where they demonstrated that the compound was also isolable from *Menispermum dauricum* DC (Japanese name Kohmori-kazura) in addition to the original source (Tomita et al., *Tet. Lett.* **1967** (25), 2421 and 2425).

With the improved analytical techniques available in comparison to those in 1926, a novel tetracyclic structure was proposed which included a chlorine atom in the molecule and a revision of the empirical formula to $C_{19}H_{24}O_6NCl$. These papers were followed by a much fuller report in 1971 (Tomita et al., *Chem. Pharm. Bull.* **1971**, 19, 770).

The story might have finished there, with the report of a novel chlorine-containing tetracyclic alkaloid, coupled to some further studies of a phytochemical nature. However, this plant was well known in Traditional Chinese Medicine as a source of antipyretic and analgesic activities. Thus in 2002, Chinese scientists in Shanghai and Hong Kong reported on the biological activity of acutumine and four closely related alkaloids (two being the des-chloro derivatives).



Acutumine structure as of today.

What was found was not expected. Of the five closely related compounds, only acutumine demonstrated cytotoxic activity against T-cells with no activity against other cell types (Yu et al., *Phytochem.* **2002**, 61, 439). It also was reported in a patent in 2006 to “improve object and social recognition in a Wistar rat model” (Qin

et al., US 2006/0167076 A1, 27JUL2006).

A number of groups have reported various routes to synthesis of this molecule with the first synthesis by Castle's group in 2009 (Li et al., *J. Amer. Chem. Soc.* **2009**, 131, 6674 & *J. Org. Chem.* **2009**, 74, 9082), and then in 2013, Herzon's group at Yale reported the synthesis of both acutumine and the first reported synthesis of the des chloro analogue (King et al., *Angew. Chem. Int. Ed.* **2013**, 52, 3642), a follow-on from their 2011 paper describing the parent molecule's synthesis (Herzon et al., *Angew. Chem. Int. Ed.* **2011**, 50, 8863).

Thus, 85 years after the original report and 11 years after its identification as a potential lead for treatment for T-cell malignancies, the compound is now accessible, using some very elegant catalytic chemistry and stereo-control of addition of various substituents. A much more thorough evaluation can now be performed as to the biological activities of this class of alkaloids.

A take-home lesson from this story may well be that “there are many rough diamonds” in the phytochemical literature from tens of years ago that have interesting structures but whose structures, availability and biological activities are still waiting for “stardom!” ■

ASP Election Results

By Dr. Amy Keller

The results of the recent ASP elections determined Dr. Phil Crews to be the Vice President during 2013-2014 with 144 votes, and Dr. Barry O'Keefe will be the Executive Committee Member with 146 votes. The incoming Secretary will be Dr. Bill Keller, and there were no constitution or bylaws amendments in this election.

According to the report compiled by the ASP Tellers Committee, chaired by Dr. Bill Keller, from 1,001 ballots sent to ASP members in April, 2013, 261 were sent back, resulting in voting participation by 26% of membership. ■