Alkaloid-like Molecules for Drug Discovery

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1. Introduction

The biological activities of several alkaloid-like compounds containing the 3-aza-bicyclo[3.3.1]nonane core structure (**1**) have been investigated due to the prevalence of this structure in several bio-active natural products, such as the *Aristotelia* alkaloids (**2**, **3**, **4**).[1]

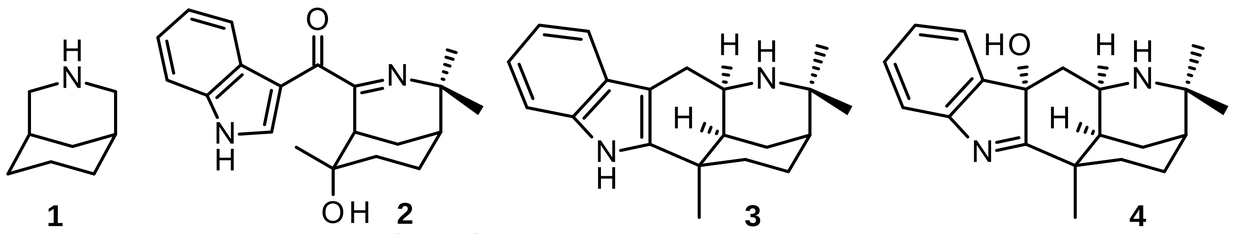
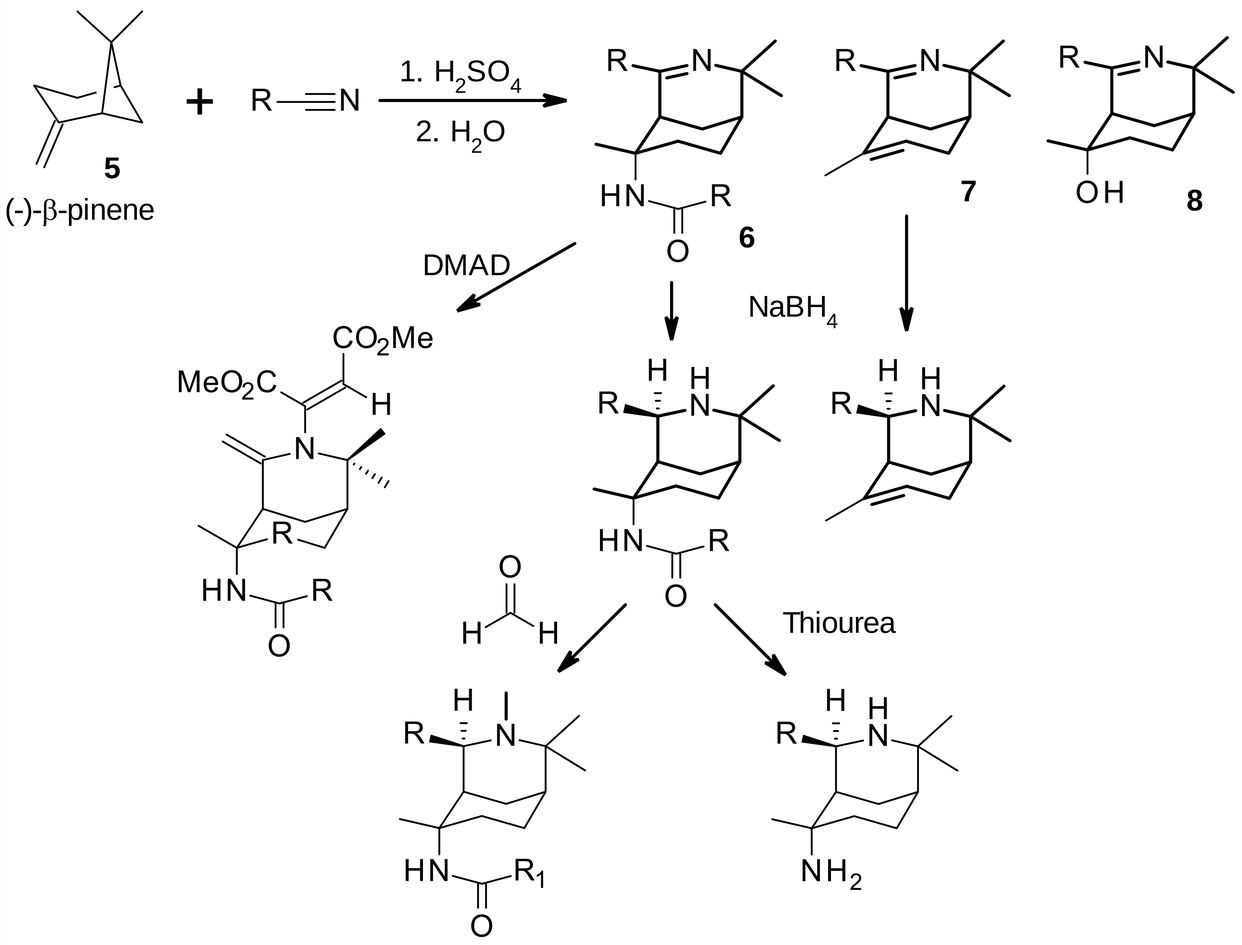


Figure 1. 3-aza-bicyclo[3.3.1]nonane core structure and Aristotelia alkaloids.

The 3-aza-bicyclo[3.3.1]nonane architecture was achieved synthetically *via* the bridged Ritter reaction between (-)-β-pinene (**5**) and various nitriles. This reaction generates optically pure imino amides (**6**) imino alkenes (**7**) and imino alcohols (**8**) in a single step.[2] In addition to using a wide range of nitriles to vary the –R functionality, several derivatisation reactions were also attempted as shown in Scheme 1.



Scheme 1. The general scheme for bridging Ritter reaction with (-)-β-pinene and nitriles of functionality –R, with subsequent derivatisation.

2. Results

2.1 Chemistry

A library of 35 alkaloid-like compounds was successfully synthesised, isolated and characterised, most of which were then assessed for their biological properties. The acetylcholine esterase (AChE) inhibition properties and cytotoxicity against the MDA-MB-231 breast cancer cell line were screened in-house, while broad screening against therapeutic targets in areas including oncology, neuroscience, endocrine/cardiovascular, diabetes and immunology and musculoskeletal, is currently being undertaken through the Lilly open innovation drug discovery program.

2.2 Biology

Cytotoxic activity

Cytotoxicity against MDA-MB-231 cells was assessed using the MTS assay.[3] Initial screening showed that three compounds caused significant reduction in cell viability (Figure 2). The IC_{50} values for these three compounds was also assessed, the IC_{50} value and corresponding structures are shown in Figure 3.

The apoptotic nature of cells treated with compound **10** can be seen in Figure 4, compare to the healthy control cells.

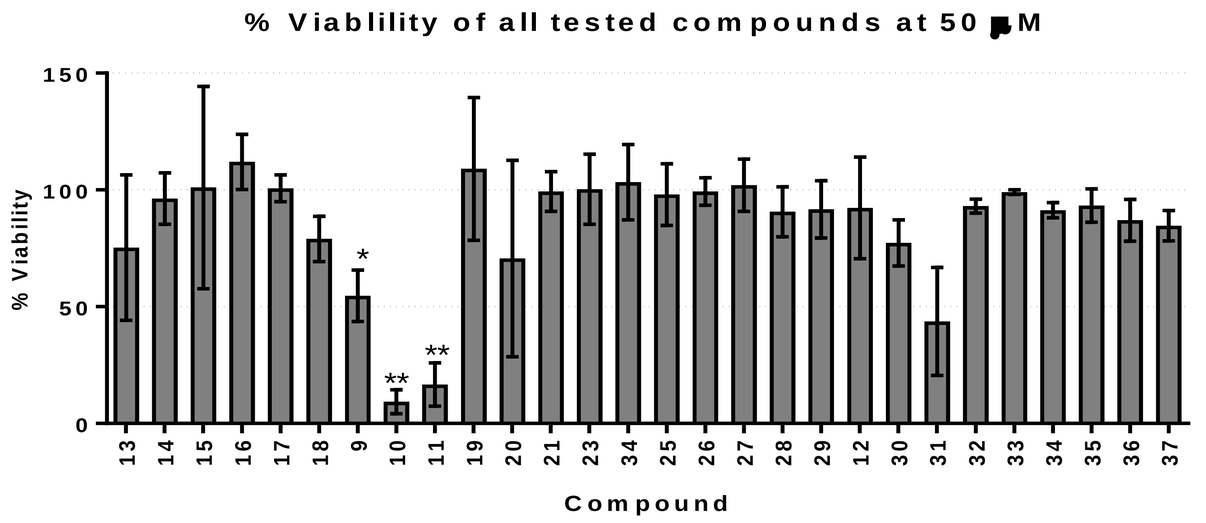
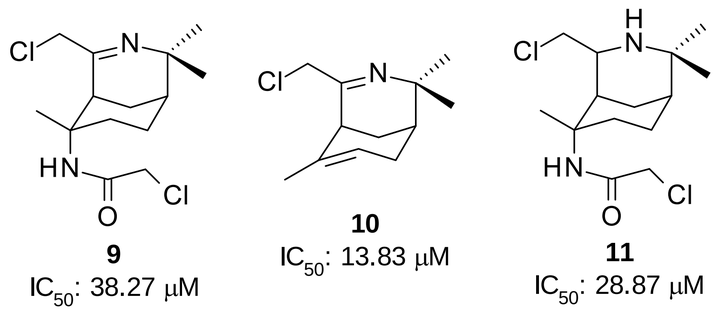


Figure 2. MDA-MB-231 % viability screening results.



9 IC_{50}: 38.27 µM

10 IC_{50}: 13.83 µM

11 IC_{50}: 28.87 µM

Figure 3. Structure and IC_{50} values for alkaloid-like compounds cytotoxicity against MDA-MB-231.

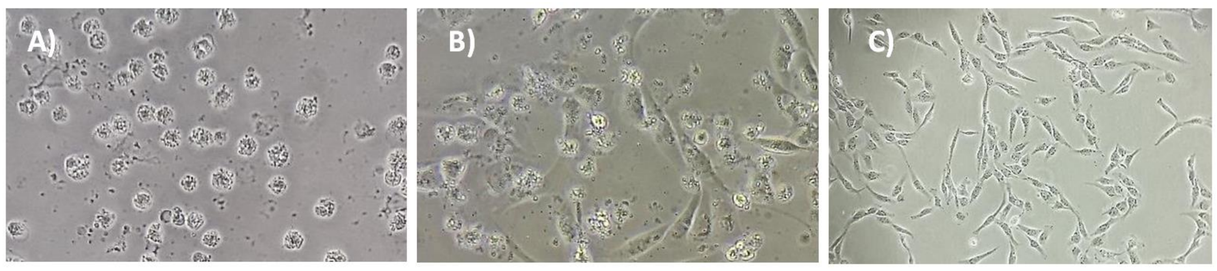


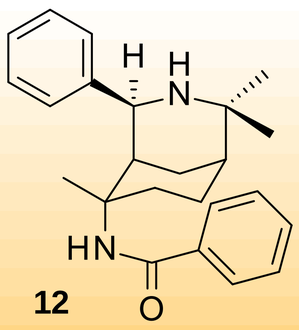
Figure 4. The effects of **10** on MDA-MB-231 cells after 48 h. Images were viewed at 10 x magnification using light microscopy. A) **10** at 50 µM; B) **10** at 10 µM; C) healthy untreated control cells.

AChE inhibition

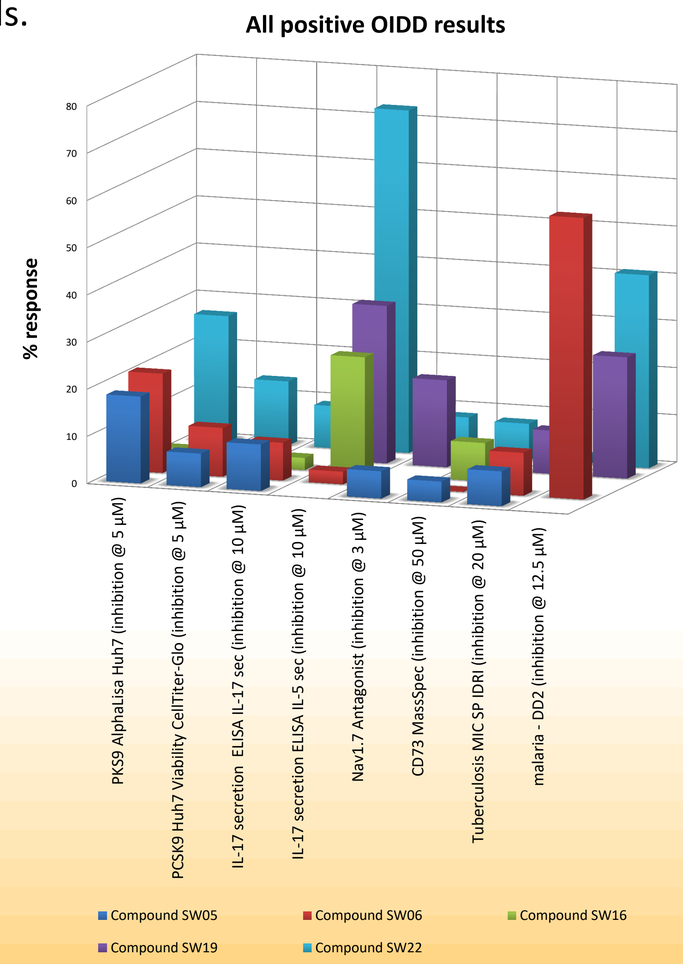
AChE inhibitors are currently the front line of drugs used for relieving the symptoms of Alzheimer's disease. Inhibition properties were assessed using the TLC bioautograph[4] and Ellman[5] assays. This library of compounds showed only a few compounds with weak inhibition activity at the maximum tested concentration and therefore do not make viable AChE inhibitors. Computer aided drug design is currently being used to develop the potency of these compounds.

Broad Screening

Of the 35 compounds submitted for *in silico* screening, 21 passed and were submitted for *in vitro* screening. The results currently obtained are shown in Figure 5. Most significant is the 72.6 % inhibition of IL-17 secretion by compound **12**.



12



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