Reviewer’s report

Title: The 4-aminopiperidine series has limited anti-tubercular and anti-staphylococcus aureus activity

Version: 1 Date: 30 November 2014

Reviewer: Courtney Aldrich

Reviewer’s report:

This manuscript describes the antibacterial screening of a focused series of aminopiperidines against M. tuberculosis and S. aureus based on the promising reported anti-tubercular activity of compounds 1, 4, and 9 (Tuberculosis (2009), 89, 334-353 (ref#3 in the manuscript). The authors performed systematic SAR by commerce and examined the substituent at N-1 (11 compounds in Table 1) as well as modification at C-4 (11 compounds in Table 2). These studies showed the archetypical molecule 1 was the most potent and almost any additional alteration completely obliterated activity. The conclusion is that compound 1 represents an isolated hit with modest potency that cannot be further improved upon, and therefore the aminopiperidine series is not worthy of further investigation in regards to antitubercular activity. These types of negative results are in fact quite useful for the research community since they will prevent duplication of efforts. The manuscript is written by leaders in the field and is technically sound, but the authors should address the following minor comments below.

Minor Essential Revision.

1. The author’s state on page 4 (bottom) that compounds 3 and 4 had previously been reported as having antitubercular activity with MIC of 3 uM and 4 uM, respectively. This is incorrect. The reported values from ref 3 were in ug/mL and thus the MIC in uM of indole 3 is 9.4 uM. Similarly, the pyridyl analog 4 demonstrated 82% inhibition at 10 ug/mL, which corresponds to 26 uM.

2. The authors should compare their results for compound 1 with the literature values. Note: the reported activity of (5-norbornen-2yl)methyl analog 1 is 1.6 ug/mL, which corresponds to 4 uM. Note this is an MIC value that results in 90% inhibition, so the concentration that would result in complete growth inhibition would be a bit higher, in close agreement with the authors observations of an MIC equal to 10 uM.

3. Data for compound 9 was also reported in ref#3 (MIC of 3.3 ug/mL or 7.4 uM). For this compound, the authors do not observe any activity, thus this value is discordant with the literature value. This result should be mentioned.

4. The purity and verification of compound structure was only done by LC-MS analysis. The authors should specify the wavelength of detection used to determine purity (Ideally this should be a relatively non-specific wavelength like
220 nM that would pick up impurities more readily). If purity is based on the integrated peaks from MS, then this may be misleading since potential impurities are unlikely to ionize as well as the piperidines. Also, the retention times of many compounds are very small. What is the void volume and hence k’ value for these samples.

Discretionary Reviews:

1. Ideally, 1H NMR of samples should be obtained to confirm structure.

2. Elaboration of the olefin (via hydrogenation, halogenation, dihydroxylation, Pd-catalyzed insertion reactions, etc…) of the (5-norbornen-2yl)methyl analog 1 would be relatively straightforward and might produce some interesting analogs.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.