Review of: "Synthesis and Antibacterial Screening of Cefradine Schiff Bases and Their Metal Salts"

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Potential competing interests: No potential competing interests to declare.

Ali et al. report the synthesis of the Schiff base condensation products of substituted benzaldehydes, acetophenone, and benzophenone. These products are formulated successively as their sodium, potassium, silver, calcium, and barium salts (with respect to the carboxylic acid of the cephem). The different salts were evaluated qualitatively for their antimicrobial activity by disk diffusion assay against *S. aureus* and *E. coli*. All are less active than the parent. Some are inactive.

•One prior Schiff base derivative of cefradine, with a 2-[[(2-hydroxyphenyl)methylene] substitution [CAS 879281-13-7], is known in the literature. The bibliography cites correctly its first synthesis, but not a second manuscript reporting additional microbiological data: Anacona, Juan R.; Marquez, Victoria. Latin American Journal of Pharmacy (2013), 32(6), 887-891. This specific structure was not re-synthesized by Ali et al. for use as a positive control. This failure is unfortunate.

•The failure of the authors' Scheme 1 to depict the stereochemistry of cefradine is not acceptable. The stereochemistry of the imine was not determined for CAS 879281-13-7 from its synthesis by others. The imine stereochemistry of these new structures also is not addressed.

•The compounds of this manuscript are characterized by IR and 1H NMR. The 1H NMR data are interpreted superficially (for example, the coupling constants of the coupled methine resonances of the beta-lactam are not given). The 1H NMR spectra are not given for assessment of the compound purity. It is remarkable, given the low electrophilicity of the benzophenone carbonyl, that imine formation is claimed for benzophenone, using the same reaction conditions (AcOH, MeOH) as is successful with benzaldehyde (1H NMR data correct for 8?). The successful reaction of acetophenone is also remarkable (albeit less so). More rigorous characterization of the ketone-derived imine structures would be highly desirable.

•An important aspect of the chemistry which is not discussed is the aqueous solubility of the salts. For example, while monovalent (Na, K) salts are generally regarded as having aqueous solubility, divalent (Ba, Ca) salts are generally regarded as insoluble in water. Here, it is a pleasant surprise for one of the more active structures (the 2-[[(4-methoxyphenyl)methylene] imine) that its Ba and Ca salts (26, 27) are equally active to its sodium salt (23). The claimed complete inactivity of the potassium salt (24) is, however, inexplicable, especially since the Na and K salts of a different imine (18, 19) are equally active. Specific comment as to the possibility of aqueous solubility/insolubility as an influencing factor on the biological activity is desirable.

•The terse conclusion statement—that the poorer microbiological activity of these imines reflects the unavailability of the

(protonated) amine (presumably, for target recognition)—is unsatisfactory. Are these imines pro-drugs? The formation of imine derivatives from related compounds, such as cephalexin, is not well explored. However, such structures appear in the patent literature (for example, CAS 42286-22-6 & 67834-16-6) and are claimed as having antimicrobial activity. Does a broader examination of Schiff base derivatives, such as these latter two cephalexin-derived structures, support the assertion that the formation of these derivatives correlates strongly with the diminution of antimicrobial activity?