K14 Conformational Considerations of Ethylenediamine Opioids AH-7921 and U-47700

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After attending this presentation, attendees will be able to recognize potentially confounding spectra attributable to conformational preference or slow conformation interchange of the amide bond in the AH- and U-series opioids.

This presentation will impact the forensic science community by informing attendees regarding spectroscopic issues that arise from conformational aspects seen in the related AH-7921 and U-7700 series opioids.

The published Structure Activity Relationships (SAR) for the AH-7921 series opioids demonstrate a preference for N-monosubstituted benzamides with hydrogen attached to the amide nitrogen. These types of analogs should favor a *trans* amide bond preference.[1] Conversely, U-47700 analog (SAR) indicates a preference for a methyl group on the corresponding amide nitrogen, which allows for *cis* and *trans* amide conformations.[2] The hypothesis is that this preference may be due to each series having the opposite amide bond configuration when bound to the mu-opioid receptor. Preliminary molecular modeling studies that explore this hypothesis by looking at preferred conformations for examples for each of the series and the potential for overlap of key functional groups between the AH-series and the U-series compounds will be presented.

The studies presented will highlight issues that an analyst may encounter that may cause confusion due to data that could be misinterpreted as a mixture. For example, peak doubling in the Nuclear Magnetic Resonance (NMR) due to slow interchange between *cis* and *trans* amide conformations may mislead one into thinking the sample is impure. It has long been documented in the literature that unsymmetrically N,N-disubstituted alkyl amides can exhibit both *cis* and *trans* amide bond conformations due to the lower barrier for rotation and diminished steric preference compared to N-monosubstituted alkyl amides.[3]

Analogs within the AH-7921 and U-47700 series will be analyzed by a variety of methods, including NMR, Gas Chromatography/Mass Spectrometry (GC/MS), Infrared (IR), Raman, etc., particularly regarding indications of conformational preference and potential for rotational interchange. It is well known that simple N-monosubstituted amides that are not conformationally restrained prefer the *trans* amide configuration. The AH-7921 analogs fall into this category. The U-47700 analogs are N,N-disubstituted alkyl amides and demonstrate both *cis* and *trans* configurations as evidenced in their NMR spectra, since the rotational interchange of the amide bond is slower than the NMR time scale. The conditions and the degree to which this phenomenon is observed will be described. The binding of the respective *cis* vs *trans* isomers to the mu-opioid receptor is not known, but it is likely one of the isomers would be preferred by the receptor over the other just as any flexible drug molecule binds to its receptor with a preferred conformation. Also, it is known from structure activity relationships for the U-series analogs that small changes in structure can lead to significant changes in receptor selectivity (e.g., phenylacetamides as kappa-receptor agonists vs. benzamides as mu-receptor agonists).[2]

In conclusion, occasionally even simple compounds can present the analyst with potentially confusing data, so awareness of not only stability issues (e.g., UR-144 degradation in the GC), but also conformational influences on chromatography and spectroscopy is important.

Reference(s):

1. Harper N.J., Veitch B.A. 1-(3,4-dichlorobenzamidomethyl)cyclohexyldimethylamine. *U.S. Patent* 3,975,443, Aug. 17, 1976.
2. Szmuszkovicz J., VonVoigtlander P.F. Benzeneacetamide amines: Structurally novel non-mu opioids. *J. Med. Chem.* 1982, 25 (10), 1125-1126.
3. Isbrandt L., Tung W.C.-T., Rogers M.T. An NMR study of hindered internal rotation in some unsymmetrically N,N-disubstituted acetamides. *J. Magn. Reson. (1969)*, 1973, 9 (3), 461-466.

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