Journal of Medicinal Chemistry

Editorial

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Absolute Quantitative ^{1}H NMR Spectroscopy for Compound Purity Determination

We encourage our authors to consider the use of absolute quantitative ^{1}H NMR spectroscopy to determine the purity of biologically tested research compounds. The Perspective by Pauli et al. (DOI: 10.1021/jm500734a) in this issue provides an excellent overview of quantitative ^{1}H NMR spectroscopy methods and their use for purity determination. The major advantages of these techniques are that they can be used for very small samples, are nondestructive to the sample, are fast, and provide high accuracy and precision. NMR spectroscopy is commonly employed in medicinal chemistry laboratories for the determination of compound identity, and therefore, adaptation of absolute quantitative ^{1}H NMR spectroscopy should be straightforward and can be incorporated readily into the normal workflow of compound identification by NMR. In the Perspective two methods are discussed, the 100% percent method and the absolute quantitative ^{1}H NMR method. We consider the latter one as the most suitable for compounds used in biological assays; thus, we are recommending this technique to our authors. In collaboration with the Pauli group, we have developed a detailed procedure that will ensure that absolute quantitative ^{1}H NMR purity analyses can be performed correctly. The protocol that details the calibration, the NMR data acquisition, and the processing of the NMR data with specific examples can be found in the Guidelines for Authors (http://pubs.acs.org/page/jmcmar/submission/authors.html).

The *Journal of Medicinal Chemistry* requires purity of >95% for all tested compounds to ensure that the observed effect is accurate and not related to highly active impurities present in the test sample. According to the Guidelines for Authors, compound purity can be established by HPLC, elemental analysis, or any other "scientifically established method". We do not accept other spectral data as evidence of purity. Both of the major methods that our authors typically employ, HPLC and elemental analysis, have certain drawbacks. Analysis by HPLC will typically not detect materials such as solvent residues, water, inorganic impurities, or an impurity that has the same retention time as the sample under the conditions employed. While elemental analysis is considered to be superior to HPLC analysis, fractional amounts of water or solvent are impurities that are not easy to identify and quantify and therefore require orthogonal analytical methods to determine their presence. Also, molecules of similar composition, such as isomers, may not affect the elemental analysis and may therefore not be detected by this method. As a primary analytical method, absolute quantitative ^{1}H NMR spectroscopy offers certain advantages for purity determination. As samples and the standards are accurately weighed, inorganic impurities and other nonobservables will be detected and most solvent residues and water will be identified in the NMR spectrum. Another advantage is that the method is orthogonal to HPLC, which is often employed for compound purification. Overlapping NMR peaks from impurities can be detected by employing 2D NMR techniques.

We hope that the Perspective by Pauli and collaborators and our detailed procedure that gives guidance on the acquisition and purity calculation using absolute quantitative ^{1}H NMR spectroscopy will promote the use of this method for purity determination. Absolute quantitative ^{1}H NMR spectroscopy that follows the protocol provided in the Guidelines for Authors will henceforth be an accepted method for the establishment of compound purity for papers published in the *Journal of Medicinal Chemistry* in addition to HPLC and elemental analysis methods.

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