

Synthesis and physicochemical characterization of the process-related impurities of olmesartan medoxomil. Do 5-(biphenyl-2-yl)-1-triphenylmethyltetrazole intermediates in sartan syntheses exist?

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Streszczenie

During the process development for multigram-scale synthesis of olmesartan medoxomil (OM), two principal regioisomeric process-related impurities were observed along with the final active pharmaceutical ingredient (API). The impurities were identified as N-1- and N-2-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl derivatives of OM. Both compounds, of which N-2 isomer of olmesartan dimedoxomil is a novel impurity of OM, were synthesized and fully characterized by differential scanning calorimetry (DSC), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) and high-resolution mass spectrometry/electrospray ionization (HRMS/ESI). Their ^1H , ^{13}C and ^{15}N nuclear magnetic resonance signals were fully assigned. The molecular structures of N-tritylomesartan ethyl (N-tritylomesartan ethyl) and N-tritylomesartan medoxomil, the key intermediates in OM synthesis, were solved and refined using single-crystal X-ray diffraction (SCXRD). The SCXRD study revealed that N-tritylated intermediates of OM exist exclusively as one of the two possible regioisomers. In molecular structures of these regioisomers, the trityl substituent is attached to the N-2 nitrogen atom of the tetrazole ring, and not to the N-1 nitrogen, as has been widely reported up to the present. This finding indicates that the reported structural formula of N-tritylomesartan ethyl and N-tritylomesartan medoxomil, as well as their systematic chemical names, must be revised. The careful analysis of literature spectroscopic data for other sartan intermediates and their analogs with 5-(biphenyl-2-yl)tetrazole moiety showed that they also exist exclusively as N-2-trityl regioisomers.

Typ publikacji

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Słowa kluczowe

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