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Abridging Pharmaceutical Analysis and Drug Discovery via LC-MS-TOF, NMR, in-silico Toxicity-Bioactivity Profiling for Therapeutic Purposing Zileuton Impurities: Need of Hour

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Abstract : The need for investigations protecting against toxic impurities though seems to be a primary requirement; the impurities which may prove non - toxic can be explored for their therapeutic potential if any to assist advanced drug discovery. The essential role of pharmaceutical analysis can thus be extended effectively to achieve it. The present study successfully achieved these objectives with characterization of major degradation products as impurities for Zileuton which has been used for to treat asthma since years. The forced degradation studies were performed to identify the potential degradation products using Ultra-fine Liquid-chromatography. Liquid-chromatography-Mass spectrometry (Time of Flight) and Proton Nuclear Magnetic Resonance Studies were utilized effectively to characterize the drug along with five major oxidative and hydrolytic degradation products (DP's). The mass fragments were identified for Zileuton and path for the degradation was investigated. The characterized DP's were subjected to In-Silico studies as XP Molecular Docking to compare the gain or loss in binding affinity with 5-Lipooxygenase enzyme. One of the impurity of was found to have the binding affinity more than the drug itself indicating for its potential to be more bioactive as better Antiasthmatic. The close structural resemblance has the ability to potentiate or reduce bioactivity and or toxicity. The chances of being active biologically at other sites cannot be denied and the same is achieved to some extent by predictions for probability of being active with Prediction of Activity Spectrum for Substances (PASS) The impurities found to be bio-active as Antineoplastic, Antiallergic, and inhibitors of Complement Factor D. The toxicological abilities as Ames-Mutagenicity, Carcinogenicity, Developmental Toxicity and Skin Irritancy were evaluated using Toxicity Prediction by Komputer Assisted Technology (TOPKAT). Two of the impurities were found to be non-toxic as compared to original drug Zileuton. As the drugs are purposed and repurposed effectively the impurities can also be; as they can have more binding affinity; less toxicity and better ability to be bio-active at other biological targets.

Keywords : UFLC, LC-MS-TOF, NMR, Zileuton, impurities, toxicity, bio-activity
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