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Profiling of in vitro & reactive metabolites of Ponatinib using LC-MS/MS method: metabolic stability and bioactivation pathway elucidation

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Abstract

Ponatinib (PNT) , marketed as (Iclusig™ tablets), is a drug taken orally for the management of some types of tumors including acute lymphoblastic leukemia and chronic myeloid leukemia . The current work reports the identification and characterization of in vitro & reactive metabolites of PNT. In vitro metabolites were generated by incubation with rat liver microsomes (RLMs). Extraction of ponetanib and its in vitro metabolites from the incubation mixtures were done by protein precipitation method. N-methyl piperazine ring of ponetanib, a cyclic tertiary amine ring , undergoes metabolism to form iminium intermediates that are reactive toward nucleophilic macromolecules. Incubation with RLMs in the presence of 1.0 mM KCN to check reactive metabolites as it is often responsible for observed toxicities including phototoxicity and prolongation of QT interval. Seven in vitro phase I metabolites, and four cyano conjugates of ponatinib were detected by LC-MS/MS. In vitro phase I metabolic pathways were N-demethylation, N-oxide formation, oxidation, reduction and hydroxylation . All metabolic reactions occurred in N-methyl piperazine ring of ponatinib which causes its instability and toxicity.

Validated LC–MS/MS method was established for the determination of PNT in RLMs . This method was applied in metabolic stability investigation of PNT. Resolution of PNT & VNT (IS) analytes were performed using C18 column and isocratic mobile phase composed of binary system of 10 mM ammonium formate (pH 4.1) and acetonitrile in a ratio of 1:1. The flow rate was set at 0.25 mL/min and total run time was 4 min . Ions were generated by ESI source and analyzed by multiple reaction monitoring mode (MRM) in the Agilent 6410 QqQ analyzer. The linearity of the established method ranged from 5 to 400 ng/ ml . LOD and LOQ was 0.44 ng/mL, and 1.32ng/ml , respectivly . The intra-day and inter-day precision and accuracy , ranged from 0.97 to 2.31% and -1.65 to -0.3% respectivly with mean % recovery of 100.09 ± 2.31% . In vitro half-life was 6.26 min and intrinsic clearance was 15.18 ± 0.47 mL/min/kg, indecates low bioavailability.

Biography:

Prof. Dr .Sawsan Mohamed Amer, starting higher school 1972 , obtained her B.Pharmaceutical chemistry 1977. She worked as Pharmaceutical researcher in National Research Centre from 1977 -1980 & M.Sc.1980 from Cairo University, faculty of pharmacy ,Egypt Assistant Lecturer 1980, Lecturer1985 & Assistant professor in Analytical Chemistry Department, Faculty of Pharmacy Cairo University 1995 She has completed her PhD at the age of 31 years in 1985 from Cairo University. She is Full Professor from 2003-present & Head of Analytical Chemistry Department Faculty of pharmacy Cairo University from 2010- 2015. She worked as a lecturer in Faculty of Science in 1993 & as a professor in college of Pharmacy , King Saud University , Saudi Arabia. She has published more than 65 papers in reputed journals and has been serving as an editorial board member of Bulletin faculty of pharmacy, Cairo University & reviewer in journal of Talanta , Analytical Chemica Acta, Spectrochemica Acta, Saudi Pharmaceutical Journal & many Others .

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