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Identification and Characterization of in Vivo, in Vitro and Reactive Metabolites of Zorifertinib Using Liquid Chromatography Lon Trap Mass Spectrometry

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Abstract : Zorifertinib is a novel, potent, oral, a small molecule used to treat non-small cell lung cancer (NSCLC). zorifertinib is an Epidermal Growth Factor Receptor (EGFR) inhibitor and has good blood–brain barrier permeability for (NSCLC) patients with EGFR mutations. zorifertinibis currently at phase II/III clinical trials. The current research reports the characterization and identification of in vitro, in vivo and reactive intermediates of zorifertinib. Prediction of susceptible sites of metabolism and reactivity pathways (cyanide and GSH) of zorifertinib were performed by the Xenosite web predictor tool. In-vitro metabolites of zorifertinib were performed by incubation with rat liver microsomes (RLMs) and isolated perfused rat liver hepatocytes. Extraction of zorifertinib and it's in vitro metabolites from the incubation mixtures were done by protein precipitation. In vivo metabolism was done by giving a single oral dose of zorifertinib(10 mg/Kg) to Sprague Dawely rats in metabolic cages by using oral gavage. Urine was gathered and filtered at specific time intervals (0, 6, 12, 18, 24, 48, 72,96and 120 hr) from zorifertinib dosing. A similar volume of ACN was added to each collected urine sample. Both layers (organic and aqueous) were injected into liquid chromatography ion trap mass spectrometry(LC-IT-MS) to detect vivozorifertinib metabolites. N-methyl piperizine ring and quinazoline group of zorifertinib undergoe metabolism forming iminium and electro deficient conjugated system respectively, which are very reactive toward nucleophilic macromolecules. Incubation of zorifertinib with RLMs in the presence of 1.0 mM KCN and 1.0 Mm glutathione were made to check reactive metabolites as it is often responsible for toxicities associated with this drug. For in vitro metabolites there were nine in vitro phase I metabolites, four in vitro phase II metabolites, eleven reactive metabolites(three cyano adducts, five GSH conjugates metabolites, and three methoxy metabolites of zorifertinib were detected by LC-IT-MS. For in vivo metabolites, there were eight in vivo phase I, tenin vivo phase II metabolitesofzorifertinib were detected by LC-IT-MS. In vitro and in vivo phase I metabolic pathways wereN- demthylation, O-demethylation, hydroxylation, reduction, defluorination, and dechlorination. In vivo phase II metabolic reaction was direct conjugation of zorifertinib with glucuronic acid and sulphate.

Keywords : in vivo metabolites, in vitro metabolites, cyano adducts,GSH conjugate
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