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IDENTIFICATION AND CHARACTERIZATION OF IN VITRO AND REACTIVE METABOLITES OF VANDETANIB IN RLMS WITH METHOD QUANTIFICATION USING LC-MS/MS: APPLICATION TO METABOLIC STABILITY

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Vandetanib (VNT) is an oral inhibitor of vascular endothelial growth factor receptor. The current work reports the identification and characterization of *in vitro* and reactive metabolites of VNT. *In vitro* metabolites of VNT were generated by incubation with rat liver microsomes (RLMs). Extraction of vandetanib and its *in vitro* metabolites from the incubation mixtures were done by protein precipitation method. N-methyl piperidine ring of vandetanib, a cyclic tertiary amine, 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 idiosyncratic toxicities including phototoxicity and prolongation of QT interval. Six *in vitro* phase I metabolites, and four cyano conjugates of vandetanib were detected by LC-MS/MS. *In vitro* phase I metabolic pathways were N-demethylation, N-oxide formation, α-carbonyl formation and α-hydroxylation. All metabolic reactions occurred in N-methyl piperidine of vandetanib which causes its instability and toxicity. Validated LC–MS/MS was established for the determination of VNT in rat liver microsomes (RLMs) . This method was applied in metabolic stability investigation of VNT. Resolution of two analytes was 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 with injection volume of 5 µL. Ions were generated by ESI source and analyzed by multiple reaction monitoring mode (basis for quantification) in the Agilent 6410 QqQ analyzer. The linearity of the established method ranged from 5 to 500 ng/mL (r2 ≥ 0.9996) in RLMs. LOQ and LOD was 7.52 ng/mL, and 6.49 in RLMs matrices. The intra-day and inter-day precision and accuracy in RLMs matrix, ranged from 0.97 to 3.08% and 95.8 to 100.09% . *In vitro* half-life was 39.85 min and intrinsic clearance was 3.92±0.28 mL/min/kg.

Biography

Sawsan M Amer, starting higher school in 1972, obtained her Bachelors' in Pharmaceutical chemistry, 1977. She worked as Pharmaceutical Researcher in National Research Centre from 1977-1980 and obtained her MSc in 1980 from Cairo University, faculty of pharmacy, Egypt. She has joined as Assistant Lecturer 1980, became Lecturer in 1985 and Assistant Professor in Analytical Chemistry Department, Faculty of Pharmacy Cairo University in 1995. She has completed her PhD in 1985 from Cairo University. She is Full Professor from 2003-present and Head of Analytical Chemistry Department, Faculty of pharmacy, Cairo University from 2010- 2015. She has worked as a Lecturer in Faculty of Science in 1993 and 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 and Reviewer in *journal of Talanta, Analytical Chemica Acta, Spectrochemica Acta, Saudi Pharmaceutical Journal* & many others. She is a Member of the Syndicate of Pharmacists, the Professional Society of Pharmacists, Egypt, the Society of Analytical Chemistry, Egypt , and in the Society of Saudi Chemists. She has supervised about 30 Master and PhD theses. Also she was involved in judging committee for more than 25 theses.

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