

NMR, GCMS and LCMS Metabolic Profiling Integrated with Toxicogenomics Analysis in the Investigation of Endocrine Toxicity of the CRF R1 Inhibitor DPC-904

Nelly Aranibar¹, Lois Lehman-McKeeman¹, David Nelson¹, Lloyd Lecureux¹, Karl-Heinz Ott², Jeff Vassallo¹, Michael Ford³, Joseph Cantone³, Petia Shipkova², Mark Sanders¹

¹Provinceline and Rt. 206, Princeton, NJ 08543

²311 Pennington-Rocky Hill Road, Hopewell, NJ 08534

³5 Research Parkway, Wallingford CT, 06492

Research and Development,
Bristol-Myers Squibb

DPC-904 is a potent and selective antagonist of corticotropin releasing factor receptor-1 (CRF-R1) and as such, an efficacious antianxiolytic in preclinical models. However, it causes endocrine toxicity in rats, which includes altered thyroid homeostasis. The mechanism of DPC-904-induced alterations in hormone levels was experimentally investigated using different metabonomics analytical platforms (NMR, LCMS and GCMS) and the results were analyzed in conjunction with clinical chemistry parameters and transcriptional profiling experiments. Biofluids used for NMR and MS based metabonomics measurements included urine, serum and extracts of different tissues (adrenal, liver, testes). The expression data were obtained for liver and testis of male Sprague Dawley rats, Wistar and Wistar TR^{-/-} rats (deficient in Multidrug transport protein 2) treated subchronically with the compound. Specific changes in serum lipid ratios as well as products from fatty acid beta-oxidation and other endogenous metabolites could be correlated between the metabonomics and transcriptomics data sets, providing mechanistic insights to the mode of action of DPC-904.