QSPR Prediction of Retention Times of Methylxanthines and Cotinine by Bioplastic Evolution

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ABSTRACT

High-performance liquid-chromatographic retention times of methylxanthines and cotinine in human plasma and urine are modelled by structure–property relationships. Bioplastic evolution is an evolutionary perspective conjugating the effect of acquired characters, and relations that emerge among the principles of evolutionary indeterminacy, morphological determination and natural selection. It is applied to design co-ordination index, which is used to characterize retentions of methylxanthines, etc. Parameters used to calculate co-ordination index are formation enthalpy, molecular weight and surface area. Morphological and co-ordination indices provide strong correlations. Effect of different types of features like thermodynamic, fractal, etc., are analyzed. The molar formation enthalpy, fractal dimensions, etc. distinguished methylxanthines and cotinine in linear fits. Different behaviour depends on number of C+N+O atoms.

KEYWORDS

Biological Plastic Evolution, Caffeine, Clinical Analysis, Co Ordination Index, Formation Enthalpy, Fractal Dimension, Metabolite, Morphological Index, Nicotine, Solvation Parameter Model

INTRODUCTION

The determination of purine derivative alkaloid methylxanthines (caffeine, and its metabolites theobromine, paraxanthine and theophylline, cf. Figure 1e,b–d) in human plasma or urine is based on liquid chromatography (LC) coupled to ultraviolet (UV) spectrophotometric detection or mass spectrometry (MS). Sensing UV provides low selectivity since endogenous compounds present in biofluids interfere with the target analytes. The LC coupled to single MS (LC–MS) (Arinoubu et al., 2009; Wang et al., 2008) or tandem MS (LC–MS–MS) (Ptolemy et al., 2010; Schneider et al., 2003) were applied for the analysis of oxopurine methylxanthines in human biofluids. The LC–MS–MS provides better sensitivity and selectivity than LC–MS. Published LC–MS and LC–MS–MS methods are based on direct sample injection before LC column-switching, or centrifugation and filtration followed by sample dilution to reduce matrix impact on the chromatographic determination. The most frequently used technique for the determination of cotinine (an alkaloid nicotine metabolite), Figure 1a,g, in human fluids is gas chromatography coupled to MS (GC–MS). The LC–MS and LC–MS–MS were successfully applied for the analysis of cotinine in biomatrices (Llaquet et al., 2010). Feyer et al. (2009) reported photoionization (PI) MS and valence PI of hypoxanthine, xanthine and caffeine. Caffeine content decayed during green/black-teas fermentation process (Kim, et al.,

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2013; Lee et al., 2011; Maria John et al., 2014). Harsa et al. (2014) informed quantitative structure–activity relationships of caffine by similarity cluster prediction. Bossi and Bech (2014) developed and validated a multi-residue method for the analysis of methylxanthines and cotinine in human plasma. Their method involved off-line solid-phase extraction (SPE) and analysis by LC–MS–MS with electrospray ionization (ESI) in positive ion (PoI) mode. Their developed and validated method was fast, selective and convenient for the simultaneous determination of cotinine, caffeine and its metabolites in human plasma, which was useful to assess human exposure to tobacco smoke and coffee consumption. They successfully applied the method to the analysis of 500 samples from pregnant women in a clinical study.

Grapefruit juice did not interact with alkaloid theophylline, which is not unexpected since this presents complete oral bioavailability (Fuhr et al., 1995). Theophylline is not substrate for cytochrome P450 (CYP)3A4. However, grapefruit juice did prolong the systemic elimination half-life of caffeine, a probe for CYP1A2 activity, and theophylline is metabolized by CYP1A2 (Fuhr et al., 1993; Maish et al., 1996), which discrepancy may be resolved by a report, suggesting that grapefruit juice decreased caffeine elimination by inhibition of flavin-containing monoxygenase (FMO), a CYP-independent system, which does not metabolize theophylline (Chung et al., 1997). Some small, lipid-soluble drugs cross the blood–brain barrier (BBB) simply by diffusion via the cell membrane and others, e.g., caffeine, enter successfully via specialized transporter proteins. Kim et al. (2015) reported urine and serum metabolite profiling of rats fed with a high-fat diet and anti-obesity effects of caffeine consumption. Not only lipophilicity but also the position of alkyl groups in the purine ring affect the ability of caffeine and theobromine to cross biomembranes (Martínez-Piñilla et al., 2015). Although theobromine may have less affinity for receptors than caffeine, the efficacy of theobromine may become higher if it readily crosses membranes and reaches high interstitial concentrations.

Figure 1. Structures: (a) cotinine; (b) theobromine; (c) paraxanthine; (d) theophylline; (e) caffeine; (f) adenosine; (g) nicotine
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