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Aryl-propionamide-derived selective androgen receptor modulators: Liquid chromatographic-tandem mass spectrometric characterization of the *in vitro* synthesized metabolites for doping control purposes

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Abstract

Selective androgen receptor modulators (SARM) are a prominent group of compounds for being misused in sports owing to their advantageous anabolic properties and reduced side effects. To target the preventive doping control analysis in relevant compounds, the challenge is to predict the metabolic fate of a new compound.

For aryl-propionamide-derived SARM, an in vitro assay employing microsomal and S9 human liver enzymes was developed to simulate phase-I and phase-II metabolic reactions. *In vitro* metabolic profiles and the structure-metabolic relationship were compared between four structurally modified substrates. Accurate mass measurements were used to characterize the synthesized metabolites, and also collision-induced dissociation was examined to suggest the methodological approach to monitor the prohibited use of aryl-propionamide-derived drug candidates.

Subsequent phase-I and phase-II metabolic reactions were successfully combined in one *in vitro* assay. The main routes of phase-I modifications involved the hydrolysis of ether linkage, monohydroxylation, and hydrolytic cleavage of the amide bond. Nitro-reduction and

deacetylation were reactions observed for substrates possessing the corresponding functionality. SARM metabolites were analyzed in negative ion electrospray ionization and detected as deprotonated species $[M-H]^-$. The main metabolic modifications were observed to occur in the B-ring side, and collision-induced dissociation resulted in the product ions originating from the A-ring side of the compound. These structure-specific ions may be monitored as target ions in the routine doping control.

For the complete paper, please, see the following reference:

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