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Trafficking of drug candidates relevant for sports drug testing: Detection of non-approved therapeutics categorized as anabolic and gene doping agents in products distributed via the Internet

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Identifying the use of non-approved drugs by cheating athletes has been a great challenge for doping control laboratories. This is due to the additional complexities associated with identifying relatively unknown and uncharacterized compounds and their metabolites as opposed to known and well-studied therapeutics. In 2010, the prohibited drug candidates and gene doping substances AICAR and GW1516, together with the selective androgen receptor modulator (SARM) MK-2866 were obtained by the Cologne Doping Control Laboratory from Internet suppliers and their structure, quantity, and formulation elucidated. All three compounds proved authentic as determined by liquid chromatography – high resolution/high accuracy (tandem) mass spectrometry and comparison to reference material. While AICAR was provided as a colourless powder in 100 mg aliquots, GW1516 was obtained as an orange/yellow suspension in water/glycerol (150 mg/ml), and MK-2866 (25 mg/ml) was shipped dissolved in polyethylene glycol (PEG) 300. In all cases, the quantified amounts were considerably lower than indicated on the label. The substances were delivered via courier, with packaging identifying them as containing 'amino acids' and 'green tea extract', arguably to circumvent customs control. Although all of the substances were declared 'for research only', their potential misuse in illicit performance-enhancement cannot be excluded; moreover sports drug testing authorities should be aware of the facile availability of black market copies of these drug candidates.

Keywords: sport; doping; mass spectrometry; SARM; black market

Introduction

The legal and illegal commerce of (emerging) drugs, together with experimental compounds has received considerable attention during the last decade and represents a continuously growing (illicit) market. Substances that bear therapeutic properties that can be potentially misused as doping agents are to be monitored by sports drug testing authorities in a proactive and preventive context.[1] While the administration of several listed emerging drugs has been banned by the World Anti-Doping Agency (WADA) for many years, the expansion of the 2011 Prohibited List compared to its 2010 version by Section S0 is especially notable. Section S0 generally interdicts the use of non-approved drugs including those that were discontinued in their developmental stages. Among these, new anabolic agents such as selective androgen receptor modulators (SARMs, e.g. Andarine and MK-2866, Figure 1, **1** and **2**) and so-called gene doping drugs including the peroxisome proliferator-activated receptor (PPAR)-δ agonist GW1516 (Figure 1, **3**) as well as the 5′-adenosine monophosphate-activated protein kinase (AMPK) agonist 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR, Figure 1, **4**) have been the subject of various studies in relation to doping controls[2–7] due to their advanced status in clinical trials and assumed and confirmed availability. Selective androgen receptor modulators (SARMs; particularly the most advanced representatives bearing an arylpropionamide-derived nucleus such as Andarine and MK-2866) have demonstrated beneficial effects in various clinical studies and are considered for future treatments of cancer cachexia, sarcopenia, age-related functional decline, and geriatric frailty.[8,9] Clinical observations have reported the positive anabolic effects of these compounds combined with the absence of commonly reported undesirable effects of steroid (mis)use. As such, SARMs might pose a temptation to cheating athletes, especially since these compounds are yet to be approved and expected to be below doping control radars.

The first adverse analytical findings with Andarine uncovered in 2010 seem to corroborate this assumption.[10] The drug candidate GW1516 (Figure 1, **3**) is currently undergoing phase-II clinical trials; it is being developed and tested for the treatment of dyslipidaemia and the metabolic syndrome.[11–14] Administration studies with laboratory rodents not only significantly reduced the susceptibility of the animals to weight gain but also increased their physical performance when given a daily dosage of 2–5 mg/kg.[15,16] The result was an improved endurance performance exceeding control cohorts by approximately 70%.

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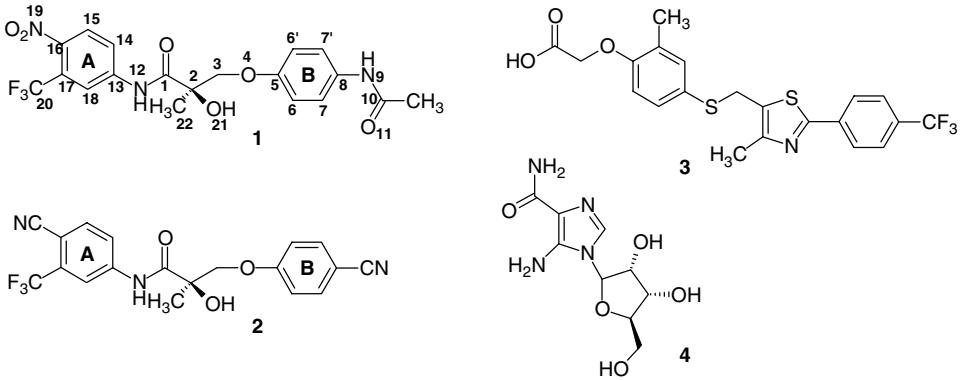

Figure 1. Chemical structures of the arylpropionamide-derived SARMs S-4 (**1**), MK-2866 (**2**), and the gene doping agents GW1516 (**3**) and AICAR (**4**).

Table 1. Characteristics of the obtained black-market products

Product	Outer Packaging	Inner Packaging		Content	Volume/Amount	Analytically identified compounds
		Container	Sealing			
MK-2866	Courier box, declaring 'Green Tea Extract'	Bluish pipette bottle	Screw cap dropper	Oily liquid	30 ml/25 mg/ml	MK-2866 (11 mg/ml)
		'SARM MK-2866'				PEG 300
GW1516	Courier box, declaring 'Amino Acids'	Glass vial	Orange crimp cap	Aqueous liquid	30 ml/150 mg/ml	GW1516 (30 mg/ml)
		'GW1516'				Glycerol
AICAR	Courier box, declaring 'Amino Acids'	Glass vial	Grey crimp cap with light-blue lid	Colorless powder	2 ml/100 mg	AICAR (45 mg)
		'AICAR'				

This was attributed specifically to the induction of oxidative genes as well as a modified substrate preference of skeletal muscles. Consequently, consideration of the therapeutic agent for illicit performance enhancement cannot be ruled out. Finally, AICAR was shown to activate the adenosine monophosphate (AMP)-activated protein kinase (AMPK), which contributes to skeletal muscle gene expression, oxidative metabolism and in particular, to mitochondrial biogenesis.[17] The use of this natural and cell-permeable activator of AMPK at 500 mg/kg/day effectively triggered the AMPK signaling pathway and caused an improved endurance performance of untrained mice by 23–44% by up-regulating 32 genes associated with oxidative metabolism without exercise.[15] Here anecdotal evidence has been received that the drug candidate undergoing phase-II clinical trials has been the subject of recent misuse in sports.

In the present case study, the characterization of products containing the SARM MK-2866, the PPARδ agonist GW1516, and the AMPK agonist AICAR, which were purchased via the Internet, is described. Ordered over the Internet, the drug candidates were delivered via courier in packaging labelled to contain 'amino acids' and 'green tea extract' to circumvent customs control. The vials and ampoules carried amateurishly prepared stickers declaring the content (compound and amount) while outlining the fact that the substances are 'for research/laboratory use only' or at least 'not for human consumption'. Further details on the obtained products are summarized in Table 1.

Experimental

Reference material and black-market products

The reference compound MK-2866 was purchased from Selleck Chemicals (Houston, TX, USA), GW1516 (>98%) was purchased from AXXORA (Lörrach, Germany), and AICAR (>98%) was purchased from Sigma (Deisendorf, Germany).

The black-market products MK-2866, GW1516, and AICAR were obtained from two different Internet suppliers with the characteristics listed in Table 1. The product supposedly containing MK-2866 was delivered in a bluish pipette bottle with screw-cap dropper, containing approx. 30 ml of an oily liquid. The label stated 'SARMS, MK-2866, 25 mg/ml, 30 ml' and the warning 'Not for Human Consumption'. The suspension of GW1516 was provided in a glass vial sealed with an orange crimp cap, containing approximately 30 ml of an orange aqueous liquid with yellowish sediment. The label declared 'GW1516, 150 mg/ml, 30 ml vial' and a comprehensive warning and handling recommendation: 'GW501516 is a very potent chemical. This form is for research/laboratory use only. Not intended for human use. Accidental ingestion could cause increased body temperature, heart palpitations, vomiting, shaking, or even death. Keep out of the reach of children. Protect from light. Store at room temperature.' AICAR was sent as a colourless powder in a 2 ml glass vial sealed with a grey crimp cap and a light-blue lid. A printed sticker lettered with 'AICAR, 100 mg/2 ml, Research Use Only' was wrapped around the bottle.

Sample preparation

The content of the AICAR bottle was dissolved in 1 ml of deionized water, and the total of three liquid specimens (AICAR, MK-2866, and GW1516) was prepared for liquid chromatography-mass spectrometry (LC-MS) or LC-tandem mass spectrometry (LC-MS/MS) analysis by diluting aliquots (10 µl) with 10 ml of acetonitrile, 1 ml of which was transferred to autosampler vials. For gas chromatography-mass spectrometry (GC-MS), 20 µl of the diluted samples were placed in a glass tube, concentrated to dryness under reduced pressure, and reconstituted in 100 µl of *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA). After heating for 10 min at 60 °C, the solution was transferred into autosampler vials for analysis.

Liquid chromatography – (tandem) mass spectrometry

Characterization and quantitation of the compounds detected in the obtained products was accomplished by means of high resolution/high accuracy (tandem) mass spectrometry using a Thermo Scientific Accela liquid chromatograph (Bremen, Germany) equipped with a Hypersil Gold analytical column (50 × 2.1 mm, 1.9 µm particle size) interfaced to a Thermo Scientific Exactive mass spectrometer using electrospray ionization (ESI) in positive and negative modes. LC solvents were 0.1% formic acid (A) and acetonitrile (B). The flow rate was set to 250 µl/min, and gradient elution was conducted starting at 90% A, decreasing to 0% A in 8 min, maintaining 0% A for a further 2 min followed by re-equilibration at 90% A. The ionization voltage was +3.5 kV or −3.0 kV, the capillary temperature was set to 290 °C, and three MS settings were used throughout the analytical runs: (1) full scan MS from *m/z* 50–2000 at a resolution of 50 000 (FWHM), (2) full scan MS (*m/z* 50–2000, resolution set to 25 000) with higher energy collision-induced dissociation (HCD) set to 20 V, and (3) full scan MS (*m/z* 50–2000, resolution set to 25 000) with HCD set to 50 V. Gas supplied to the curved linear ion trap (CLT) was nitrogen obtained from a CMC nitrogen generator (CMC Instruments, Eschborn, Germany). Elemental compositions of protonated and deprotonated analytes were determined with mass accuracies <5 ppm ensured by external calibration.

Product ion mass spectra were recorded using an Applied Biosystems API4000 QTrap mass spectrometer (Darmstadt, Germany) using identical chromatographic conditions employing an Agilent 1100 Series LC (Waldbronn, Germany). Also here, the MS was operated in positive and negative ionization mode, using ionization voltages of +5.0 and −4.2 kV and collision energies between 15 and 25 eV.

Quantitative LC-MS measurements were achieved by preparing calibration curves of all corresponding reference compounds in acetonitrile (0.1–5 µg/ml, 5-point calibration) and analyzing the 1/100 000 dilutions of the black-market products. All aliquots were assayed in triplicate.

Gas chromatography - mass spectrometry

GC-MS measurements of the liquid samples (MK-2866 and GW1516) to identify the solvents were conducted on an Agilent 6890 gas chromatograph interfaced to a 5973 mass selective detector. The GC was equipped with a HP-5 MS column (inner diameter 0.2 mm, film thickness 0.2 µm, length 17 m), and a temperature program starting at 100 °C increasing by 30 °C/min to 320 °C was employed. Helium was used as carrier gas (0.8 ml min^{-1}, constant pressure), and the injector temperature was set to 300 °C, the interface temperature to 320 °C and the ion source temperature to 230 °C. Two µl of the derivatized sample were injected in split mode (1 : 10), and spectra were recorded after electron ionization (EI) at 70 eV over the range *m/z* 40–800.

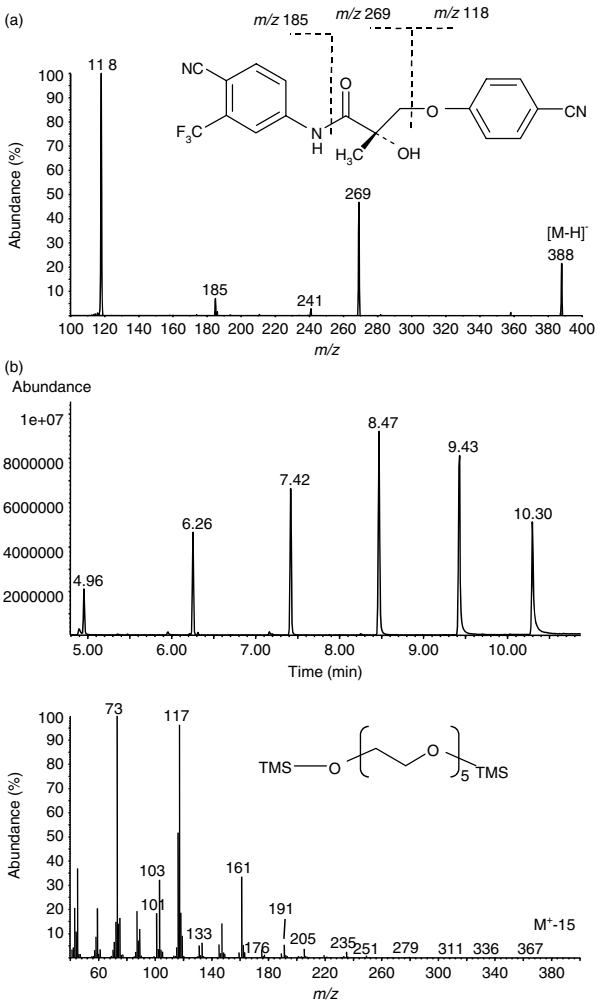

Figure 2. (A) ESI product ion mass spectrum of the deprotonated molecule $[M-H]^-$ at *m/z* 388 of MK-2866 as determined in the product supplied via Internet order; (B) chromatogram of the trimethylsilylated aliquot of the MK-2866 product and EI mass spectrum of the bis-TMS derivative of 2-(2-{2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethanol $[HO-(C_2H_4O)_5-H]$ at 8.47 min representing a major constituent of PEG 300.

Results and Discussion

MK-2866 is a SARM drug candidate comprising an arylpropionamide-based structure (Figure 1, **2**). Several representatives of this class of therapeutics have been studied in-depth concerning their metabolism and pharmacokinetic behavior[18–21] but none has yet received full clinical approval. Nevertheless, the former drug candidate Andarine (Figure 1, **1**), (the development of which was discontinued several years ago) was recently found in products advertised and sold via the Internet[22] as well as in doping control samples,[10] highlighting the need for inclusion of compounds that have not completed or have not undergone clinical trials at all into routine controls. The product supposedly containing MK-2866 was tested for its active ingredients and MK-2866 was

detected at a concentration of approximately 11 mg/ml of the oily solution (contravening the statement on the label claiming a concentration of 25 mg/ml) as determined using authentic reference material. The product ion mass spectrum of MK-2866 as measured from the received specimen is illustrated in Figure 2A, and accurate masses of the precursor ion (*m/z* 388) as well as diagnostic product ions (*m/z* 269, 241, 118, Table 2) were in agreement with earlier studies and the reference material.[3] In contrast to earlier findings of black-market SARMs, byproducts, for example, from synthesis were not detected. The oily liquid was identified as polyethylene glycol (PEG) 300 by means of GC-MS after trimethylsilylation of the diluted solution. The typical distribution of the PEG 300 constituents and the EI mass spectrum of a representative analyte, the trimethylsilylated 2-(2-{2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethanol [HO-$(C_2H_4O)_5$-H] at 8.47 min, are depicted in Figure 2B. The use of PEG 300 as solvent was probably adopted from canine metabolism and disposition studies with Andarine, where the drug was intravenously and orally delivered as PEG 300 solution.[19]

In animal experiments, the potential of GW1516 (Figure 1, **3**) to increase physical performance has been shown during studies of fat metabolism, obesity, and metabolic syndrome.[13,14] Still requiring an exercise stimulus, a dosage of 2–5 mg/kg/day[15,16] was sufficient for inducing oxidative genes[15] as well as shifting the substrate preference of skeletal muscles from carbohydrate to lipid consumption.[14] Due to the resulting overall improvement of endurance performance among laboratory rodents, PPARδ agonists such as GW1516 were added to the Prohibited List effective from January 2009 and categorized as gene doping agents.[23] The product obtained in the course of this case study claiming to contain 150 mg/ml of GW1516 was found to consist of a water/glycerol mixture and approximately 30 mg/ml of the PPARδ agonist. The ESI product ion mass spectrum of the detected active ingredient GW1516 and the EI mass spectrum of the trimethylsilylated glycerol as observed in the aqueous solution are shown in Figures 3A and 3B, respectively. The elemental compositions of the diagnostic product ions at *m/z* 257, 256, and 188 of GW1516 were in agreement with those determined from the reference substance (Table 2). To the best of our knowledge, the availability of authentic gene doping substances such as GW1516 via Internet providers has not been reported before and it demonstrates the facile supply of these emerging drug candidates, presumably also to cheating athletes. Even though pharmaceutically unapproved, trafficking under the umbrella of 'research chemicals' has proved possible.

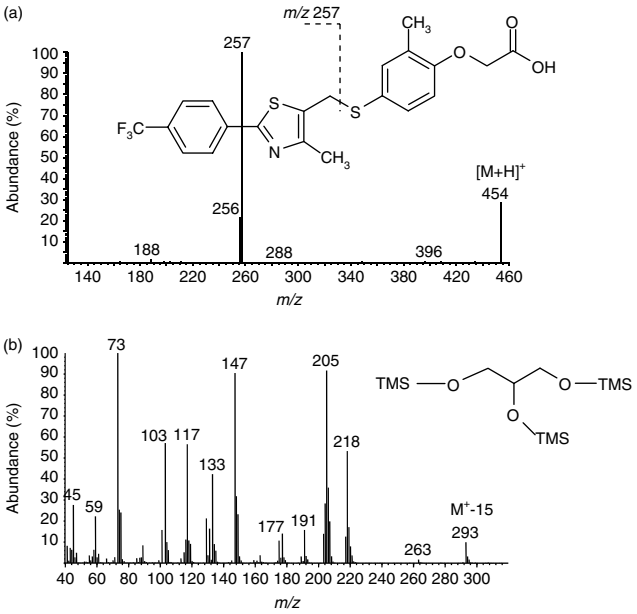

Figure 3. (A) ESI product ion mass spectrum of the protonated molecule $[M+H]^+$ at *m/z* 454 of GW1516 as determined in the product supplied via Internet order; (B) EI mass spectrum of the tris-TMS derivative of glycerol used in the solvent mixture of the same product.

In the same context of gene doping agents, the use of the experimental compound AICAR has been prohibited in sports since January 2009. In contrast to GW1516, the misuse of the AMPK agonist AICAR has been suspected during great sporting events supported by police findings[24] and studies to define a reference value were initiated.[7] While GW1516 is an entirely non-natural substance, AICAR is produced endogenously and excreted into urine in considerable amounts, which requires a robust and reliable tool to differentiate a case of misuse from naturally elevated levels. The experimental drug candidate AICAR was also obtained from an Internet supplier (Table 1) claiming to sell 100 mg of the drug per ampoule as a crystalline powder on

Table 2. Elemental compositions of precursor and diagnostic product ions obtained from negative or positive ESI and CID using high resolution/high accuracy MS/MS experiments

Cmp.	Precursor ion (*m/z*) MS^2	elemental comp. (exp.)	error (ppm)		Product ion (*m/z*)	elemental comp. (exp.)	error (ppm)	cleaved species
MK-2866	388.0905	$C_{19}H_{13}O_3N_3F_3$	−2.3	25	269.0540	$C_{12}H_8O_2N_2F_3$	−1.1	C_7H_5NO
					241.0590	$C_{11}H_8ON_2F_3$	−1.8	C_7H_5NO, CO
					185.0326	$C_8H_4N_2F_3$	−3.0	$C_{11}H_9NO_3$
					118.0294	C_7H_4ON	−3.6	$C_{12}H_9O_2N_2F_3$
GW1516	454.0747	$C_{21}H_{19}O_3NF_3S_2$	−1.2	25	257.0478	$C_{12}H_{10}NF_3S$	−1.2	$C_9H_9O_3S$
					256.0398	$C_{12}H_9NF_3S$	−1.5	$C_9H_{10}O_3S$
					188.0526	$C_{11}H_{10}NS$	−1.6	$C_{10}H_9O_3F_3S$
AICAR	259.1030	$C_9H_{15}O_5N_4$	−2.5	25	242.0766	$C_9H_{12}O_5N_3$	−2.1	NH_3
					188.0452	$C_9H_6O_2N_3$	−1.3	NH_3, 3 × H_2O
					152.0454	$C_6H_6O_2N_3$	−0.3	NH_3, $C_3H_6O_3$
					127.0616	$C_4H_7ON_4$	1.5	$C_5H_8O_4$
					110.0351	$C_4H_4ON_3$	1.6	NH_3, $C_5H_8O_4$

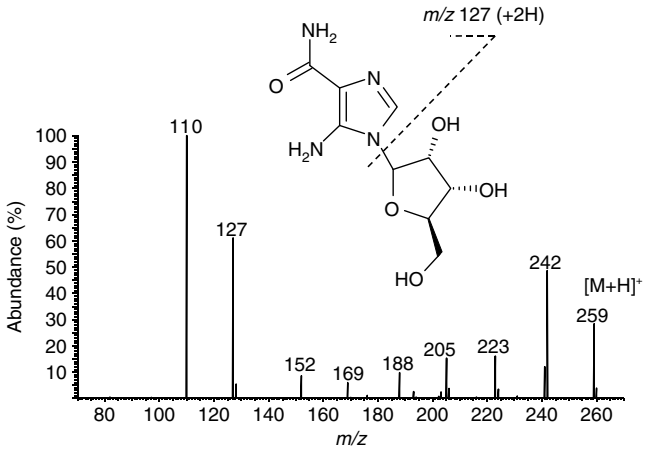

Figure 4. ESI product ion mass spectrum of the protonated molecule $[M+H]^+$ at *m/z* 454 of AICAR as found in the product supplied via Internet order.

a 'buy one get one free' basis. The quantitative analysis of the bottles revealed 45 mg of pure AICAR in each. The ESI product ion mass spectrum of the target compound is shown in Figure 4. The elemental composition of the protonated molecule as well as those deduced from characteristic product ions at *m/z* 242, 188, 152, 127, and 110 were in agreement with the reference substance and published data (Table 2).[7]

Conclusion

The availability of non-approved drug candidates, including a non-steroidal anabolic agent of the SARM's class and two compounds defined as gene doping agents, was demonstrated and their authenticity proven by state-of-the-art mass spectrometric techniques. While SARMs are potent drugs that are effective as such, the combined supply of AICAR and GW1516 appears noteworthy as the synergistic effect of their co-administration was specifically described for laboratory rodents. Major concerns result from these findings for anti-doping authorities, in particular the simple process of procuring these substances online at comparably low costs. This underlines the importance of proactive and preventive measures against the misuse of emerging therapeutics as further promoted by WADA's 2011 Prohibited List. While SARMs and the abovementioned gene doping agents are explicitly listed as banned compounds, the new section S0 generally outlaws all substances and drug candidates that have not completed clinical trials from being used in elite sport.

Acknowledgments

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References

[1] M. Thevis, A. Thomas, M. Kohler, S. Beuck, W. Schänzer. Emerging drugs: mechanism of action, mass spectrometry and doping control analysis. *J. Mass Spectrom.* **2009**, *44*, 442.

[2] T. Kuuranne, A. Leinonen, W. Schänzer, M. Kamber, R. Kostiainen, M. Thevis. Aryl-propionamide-derived selective androgen receptor modulators: LC-MS/MS characterization of the in vitro synthesized metabolites for doping control purposes. *Drug Metab. Dispos.* **2008**, *36*, 571.

[3] M. Thevis, E. Gerace, A. Thomas, S. Beuck, H. Geyer, N. Schlörer, J. D. Kearbey, J. T. Dalton, W. Schänzer. Characterization of in vitro generated metabolites of the selective androgen receptor modulators S-22 and S-23 and in vivo comparison to post-administration canine urine specimens. *Drug Test. Analysis* **2010**, *2*, 589.

[4] M. Thevis, W. Schänzer. Mass spectrometry of selective androgen receptor modulators. *J. Mass Spectrom.* **2008**, *43*, 865.

[5] M. Thevis, A. Thomas, G. Fusshöller, S. Beuck, H. Geyer, W. Schänzer. Mass spectrometric characterization of urinary metabolites of the selective androgen receptor modulator andarine (S-4) for routine doping control purposes. *Rapid Commun. Mass Spec.* **2010**, *24*, 2245.

[6] M. Thevis, I. Möller, A. Thomas, S. Beuck, G. Rodchenkov, W. Bornatsch, H. Geyer, W. Schänzer. Characterization of two major urinary metabolites of the PPARdelta-agonist GW1516 and implementation of the drug in routine doping controls. *Anal. Bioanal. Chem.* **2010**, *396*, 2479.

[7] A. Thomas, S. Beuck, J. C. Eickhoff, S. Guddat, O. Krug, M. Kamber, W. Schänzer, M. Thevis. Quantification of urinary AICAR concentrations as a matter of doping controls. *Anal. Bioanal. Chem.* **2010**, *396*, 2899.

[8] M. L. Mohler, C. E. Bohl, A. Jones, C. C. Coss, R. Narayanan, Y. He, D. J. Hwang, J. T. Dalton, D. D. Miller. Nonsteroidal selective androgen receptor modulators (SARMs): dissociating the anabolic and androgenic activities of the androgen receptor for therapeutic benefit. *J. Med. Chem.* **2009**, *52*, 3597.

[9] S. Bhasin, R. Jasuja. Selective androgen receptor modulators as function promoting therapies. *Curr. Opin. Clin. Nutr. Metab. Care.* **2009**, *12*, 232.

[10] D. Bogle, JAAA awaits result of Wilkins drug hearing. *Jamaica Observer* 14 July **2010**.

[11] U.S. National Institutes of Health Regulation of Lipoprotein Transport in Metabolic Syndrome. Available at: www.clinicaltrials.gov [21 September 2009].

[12] Y. X. Wang, C. H. Lee, S. Tiep, R. T. Yu, J. Ham, H. Kang, R. M. Evans. Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. *Cell* **2003**, *113*, 159.

[13] D. K. Krämer, L. Al-Khalili, B. Guigas, Y. Leng, P. M. Garcia-Roves, A. Krook. Role of AMP kinase and PPARdelta in the regulation of lipid and glucose metabolism in human skeletal muscle. *J. Biol. Chem.* **2007**, *282*, 19313.

[14] B. Brunmair, K. Staniek, J. Dorig, Z. Szocs, K. Stadlbauer, V. Marian, F. Gras, C. Anderwald, H. Nohl, W. Waldhausl, C. Furnsinn. Activation of PPAR-delta in isolated rat skeletal muscle switches fuel preference from glucose to fatty acids. *Diabetologia* **2006**, *49*, 2713.

[15] V. A. Narkar, M. Downes, R. T. Yu, E. Embler, Y. X. Wang, E. Banayo, M. M. Mihaylova, M. C. Nelson, Y. Zou, H. Juguilon, H. Kang, R. J. Shaw, R. M. Evans. AMPK and PPARdelta agonists are exercise mimetics. *Cell* **2008**, *134*, 405.

[16] Y. X. Wang, C. L. Zhang, R. T. Yu, H. K. Cho, M. C. Nelson, C. R. Bayuga-Ocampo, J. Ham, H. Kang, R. M. Evans. Regulation of muscle fiber type and running endurance by PPARdelta. *PLoS Biol.* **2004**, *2*, e294.

[17] R. M. Reznick, G. I. Shulman. The role of AMP-activated protein kinase in mitochondrial biogenesis. *J. Physiol.* **2006**, *574*, 33.

[18] W. Gao, J. Kim, J. T. Dalton. Pharmacokinetics and pharmacodynamics of nonsteroidal androgen receptor ligands. *Pharm. Res.* **2006**, *23*, 1641.

[19] M. A. Perera, D. Yin, D. Wu, K. K. Chan, D. D. Miller, J. Dalton. In vivo metabolism and final disposition of a novel nonsteroidal androgen in rats and dogs. *Drug Metab. Dispos.* **2006**, *34*, 1713.

[20] D. Wu, Z. Wu, J. Yang, V. A. Nair, D. D. Miller, J. T. Dalton. Pharmacokinetics and metabolism of a selective androgen receptor modulator (SARM) in rats–implication of molecular properties and intensive metabolic profile to investigate ideal pharmacokinetic characteristics of a propanamide in preclinical study. *Drug Metab. Dispos.* **2006**, *34*, 483.

[21] D. Yin, H. Xu, Y. He, L. I. Kirkovsky, D. D. Miller, J. T. Dalton. Pharmacology, pharmacokinetics, and metabolism of acetothiolutamide, a

novel nonsteroidal agonist for the androgen receptor. *J. Pharmacol. Exp. Ther.* **2003**, *304*, 1323.
[22] M. Thevis, H. Geyer, M. Kamber, W. Schänzer. Detection of the arylpropionamide-derived selective androgen receptor modulator (SARM) S-4 (Andarine) in a black-market product. *Drug Test. Analysis* **2009**, *1*, 387.
[23] World Anti-Doping Agency. *The 2009 Prohibited List*. Available at: http://www.wada-ama.org/rtecontent/document/2009_Prohibited_List_ENG_Final_20_Sept_08.pdf [2 January 2009].
[24] P. Benkimoun. Police find unlicensed drugs after trawling bins. *Brit. Med. J.* **2009**, *339*, b4201.