Structure Characterization and Analysis of Drugs Relevant to Sports Drug Testing by GC-Q/TOF

Mario Thevis
The Drive to Win and Never Grow Old

The Risks of Anabolic Steroid Abuse, an Update for the Clinical Nurse Specialist

PATRICIA ANNE O’MALLEY, PhD, RN, CNS
1771: Testicular implantation to capons

Castrated roosters recovered some of their loss of maleness after testicular implantation.

John Hunter (1728 – 1793)
1849: On the importance of the testes

On August 2 I caponized six cockerels...The dewlaps and combs were left intact. Two cockerels had both testes removed; these cockerels later exhibited the typical nature of capons, behaved cowardly, agreed only rarely to shiftless fights with other cockerels...
1889: Misinterpretation and placebo effects...

The Lancet,] Dr. Brown-Séquard: Injections of Testicular Liquid. [July 20, 1889. 105

NOTE ON

THE EFFECTS PRODUCED ON MAN BY SUB-CUTANEOUS INJECTIONS OF A LIQUID OBTAINED FROM THE TESTICLES OF ANIMALS.

By Dr. Brown-Séquard, F.R.S. &c.
1935: The synthesis of Testosterone

Leopold Ruzicka (1935)
Anabolic-Androgenic Steroids – unlimited

ANDROGENS AND ANABOLIC AGENTS
CHEMISTRY AND PHARMACOLOGY

JULIUS A. VIDA

1969
ACADEMIC PRESS New York and London
# Anabolic-Androgenic Steroids – unlimited

## Table 1. Major doping substances used in high-performance sport of the GDR.

<table>
<thead>
<tr>
<th>Trivial name</th>
<th>Alternative or International name</th>
<th>Code name</th>
<th>Chemical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgenic-anabolic steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral-Turinabol (tablets)</td>
<td>—</td>
<td>OT, M1</td>
<td>Dehydrochloromethyltestosterone, 4-chlor-1-dehydro-17α-methyltestosterone</td>
</tr>
<tr>
<td>Steroid substance 646</td>
<td>Mestanolone</td>
<td>STS 646, M2</td>
<td>17α-Methyl-17β-hydroxy-5α-androstane-3-one</td>
</tr>
<tr>
<td>Steroid substance XII</td>
<td>—</td>
<td>SXII, U2</td>
<td>11β-Hydroxy-OT</td>
</tr>
<tr>
<td>Steroid substance 482</td>
<td>—</td>
<td>STS 482</td>
<td>4-Chlor-17α-methyl-17β-hydroxy-5α-androst-4-en-3-one</td>
</tr>
<tr>
<td>Steroid substance 648</td>
<td>—</td>
<td>STS 648</td>
<td>4-Chlor-17α-methyl-17β-hydroxy-5α-androstane-3-one</td>
</tr>
<tr>
<td>Dianabol</td>
<td>Methandienone, methandrostenolone</td>
<td>—</td>
<td>17α-Methyl-17β-hydroxy-1.4-androstandien-3-one</td>
</tr>
<tr>
<td>Injectable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone-Ampullen</td>
<td>Testosterone propionate</td>
<td>TP</td>
<td>—</td>
</tr>
<tr>
<td>Testosterone-Depot-Ampullen</td>
<td>Testosterone enanthate</td>
<td>TD</td>
<td>—</td>
</tr>
<tr>
<td>Testo-Tropin-Ampullen*</td>
<td>Nandrolone phenylpropionate, Durabolin</td>
<td>TT</td>
<td>—</td>
</tr>
<tr>
<td>Turinabol-Ampullen</td>
<td>Nandrolone decanoate, Deca-Durabolin</td>
<td>TA</td>
<td>Phenylpropionate ester of 17β-hydroxy-19-norandrost-4-en-3-one</td>
</tr>
<tr>
<td>Turinabol-Depot-Ampullen</td>
<td></td>
<td></td>
<td>Decanoate ester of the same compound</td>
</tr>
<tr>
<td>Nasal spray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone esters</td>
<td>—</td>
<td>AD</td>
<td>—</td>
</tr>
<tr>
<td>Androstendione</td>
<td>—</td>
<td></td>
<td>—</td>
</tr>
</tbody>
</table>

Fig. 1.
Effects of an androgenic-anabolic steroid, Oral-Turinabol, on the shot-put performance (in meters, y-axis) of a female athlete (code identification 1/68).
Anabolic-Androgenic Steroids – Stanozolol
Numerous challenges for sports drug testing laboratories

- utmost comprehensiveness
- speed / turn-around times
- broad spectrum of physico-chemical properties of analytes
- etc.
The World Anti-Doping Code

THE 2013 PROHIBITED LIST

INTERNATIONAL STANDARD
**S1. ANABOLIC AGENTS**

Anabolic agents are prohibited.

1. **Anabolic Androgenic Steroids (AAS)**

   a. Exogenous AAS, including:

   1-androstendiol (5α-androst-1-ene-3β,17β-diol); 1-androstendione (5α-androst-1-ene-3,17-dione); bolandiol (19-norandrostenediol); bolasterone; boldenone; boldione (androst-1,4-diene-3,17-dione); calusterone; closebol; danazol (17α-ethynyl-17β-hydroxyandroster-4-enol[2,3-d]isoxazole); dehydrochlormethyltestosterone (4-chloro-17β-hydroxy-17α-methylandrosta-1,4-dien-3-one); desoxymethyltestosterone (17α-methyl-5α-androst-2-en-17β-ol); drostanolone; ethylestrenol (19-nor-17α-pregn-4-en-17-ol); fluoxymesterone; formebolone; furazabol (17β-hydroxy-17α-methyl-5α-androstano[2,3-c]-furazan); gestrinone; 4-hydroxytestosterone (4,17β-dihydroxyandroster-4-en-3-one); mexitanolone; mesterolone; metenolone; methandienone (17β-hydroxy-17α-methylandrosta-1,4-dien-3-one); methandriol; methasterone (2α, 17α-dimethyl-5α-androstane-3-one-17β-ol); methylidenolone (17β-hydroxy-17α-methylestra-4,9-dien-3-one); methyl-1-testosterone (17β-hydroxy-17α-methyl-5α-androst-1-en-3-one); methylnortestosterone (17β-hydroxy-17α-methylestr-4-en-3-one); methyltestosterone; metribolone (methyltrienolone, 17β-hydroxy-17α-methylestra-4,9,11-trien-3-one); mibolerone; nandrolone; 19-norandrostenedione (estr-4-ene-3,17-dione); norboletone; norclostebol; noresandrolone; oxabolone; oxandrolone; oxymesterone; oxymetholone; prostanozol (17β-hydroxy-5α-androstano[3,2-c] pyrazole); quinbolone;
stanozolol; stenbolone; 1-testosterone (17β-hydroxy-5α-androst-1-en-3-one); tetrahydrogestrinone (16α-homo-pregna 4,9,11 trien-17β-ol-3-one); trenbolone and other substances with a similar chemical structure or similar biological effect(s).

b. Endogenous** AAS when administered exogenously:

androstenediol (androst-5-ene-3β,17β-diol); androstenedione (androst-4-ene-3,17-dione); dihydrotestosterone (17β-hydroxy-5α-androstan-3-one); prasterone (dehydroepiandrosterone, DHEA); testosterone
and the following metabolites and isomers:

5α-androstane-3α,17α-diol; 5α-androstane-3α,17β-diol; 5α-androstane-3β,17α-diol; 5α-androstane-3β,17β-diol; androst-4-ene-3α,17α-diol; androst-4-ene-3α,17β-diol; androst-4-ene-3β,17α-diol; androst-4-ene-3β,17β-diol; androst-5-ene-3α,17α-diol; androst-5-ene-3α,17β-diol; androst-5-ene-3β,17α-diol; androst-5-ene-3β,17β-diol; 4-androstenediol (androst-4-ene-3β,17β-diol); 5-androstenedione (androst-5-ene-3,17-dione); epi-dihydrotestosterone; epitestosterone; 3α-hydroxy-5α-androstan-17-one; 3β-hydroxy-5α-androstan-17-one; 19-norandrosterone; 19-noretiocholanolone.

2. Other Anabolic Agents, including but not limited to:

Clenbuterol, selective androgen receptor modulators (SARMs), tibolone, zeranol, zilpaterol.
SARMs structures

Arylpropionamide

Bicyclic hydantoins

Quinolines

Tetrahydroquinolines
JAAA awaits result of Wilkins drug hearing

BY DANIA BOGLE Observer staff reporter
Wednesday, July 14, 2010

THE Jamaica Amateur Athletic Association (JAAA) is expecting a result soon from the disciplinary hearings being held into the positive drugs test result returned by quarter-miler Bobby-Gaye Wilkins, Dr Warren Blake told the Observer.

Wilkins tested positive for the Selective Androgen Receptor Modulator (SARM) Andarine, which is listed by the World Anti-Doping Agency (WADA) as an anabolic agent, at the 13th IAAF World Indoor Championships (WIC) in Doha, Qatar in March.
Canadian bobsledder Chris Korol suspended for doping infraction
Nets 15-month ban for presence of androgen
The Canadian Press, Posted: May 14, 2013 2:23 PM ET

Canadian bobsled pilot Chris Korol has been given a 15-month suspension by the Canadian Centre for Ethics in Sport after testing positive for a prohibited anabolic agent. The substance was detected in a urine sample collected during in-competition doping control on Oct. 21 at the Canadian bobsled championships in Calgary. The sample was found to contain SARM S-22, which the CCES classifies as a new drug with presumed anabolic properties.

In its decision, the CCES said "the mere presence of SARM S-22 in an athlete's sample is an anti-doping rule violation."

Korol, from Hamilton, piloted sleds in both the two-men and four-men competitions at the Canadian championships, finishing third in both races.
Enobosarm seizure

- confiscated in 2012 at German customs
- 1 kg pure Enobosarm (MK-2866)
...SARMs structures

Tropanol derivatives (ACP-105)

Phenyloxadiazole derivative (RAD140)
Tropanol derivative ACP-105

\[ -N + Si(CH_3)_3 \]

\[
\begin{align*}
\text{Cl} & : 73.0467 \\
\text{NC} & : 108.0803 \\
\text{CH}_3 & : 131.0886 \\
\text{Cl} & : 170.0992 \\
\text{Si(CH}_3)_3 & : 185.1227 \\
\text{CH}_3 & : 216.0445 \\
\text{Si(CH}_3)_3 & : 217.0532 \\
\text{CH}_3 & : 231.0677 \\
\text{Si(CH}_3)_3 & : 257.0835 \\
\text{CH}_3 & : 273.1145 \\
\text{Si(CH}_3)_3 & : 332.1582 \\
\text{M}^+ & : 347.1345 \\
\text{M}^+ & : 362.1582
\end{align*}
\]

Relative abundance (%)
Tropanol derivative ACP-105

For Forensic Use.


MS/MS \( m/z \) 347
\[ \text{NC} \quad m/z 362 \]
\[ \text{Cl} \quad \text{NC} \quad \text{N} \quad \text{CH}_3 \]
\[ \text{Cl} \quad \text{NC} \quad \text{N} \quad \text{CH}_3 \]
\[ \text{Cl} \quad \text{NC} \quad \text{N} \quad \text{CH}_3 \]
\[ \text{m/z 198} \]
\[ \text{m/z 108} \]
\[ \text{m/z 216} \]
\[ \text{m/z 257} \]
\[ \text{m/z 273} \]
\[ \text{m/z 347} \]
\[ \text{m/z 362} \]

For Forensic Use.

Tropanol derivative ACP-105 – monohydroxylated metabolite

For Forensic Use.
Tropanol derivative ACP-105 – monohydroxylated metabolite

$m/z$ 450

$m/z$ 435

$m/z$ 361

$m/z$ 305
Tropanol derivative ACP-105 – monohydroxylated metabolite

For Forensic Use.
Phenyloxadiazole derivative RAD140

For Forensic Use.

Phenyloxadiazole derivative RAD140

\[ \text{NC} - \text{C} - \text{H}_3 \text{C} - \text{Si(CH}_3)_3 \]

\[ m/z \, 465 \]

\[ \text{NH} \]

\[ \text{NC} - \text{C} - \text{Cl} - \text{CH}_3 \]

\[ m/z \, 421 \]

\[ \text{Si(CH}_3)_3 \]

\[ \text{NC} - \text{C} - \text{Cl} - \text{CH}_3 \]

\[ m/z \, 291 \]
PDE4: A Novel Target in the Treatment of Chronic Obstructive Pulmonary Disease

JM Michalski\textsuperscript{1}, G Golden\textsuperscript{1}, J Ikari\textsuperscript{1} and SI Rennard\textsuperscript{1}

Phosphodiesterases (PDEs) are important modulators of inflammation and wound healing. In this capacity, specific targeting of PDEs for the treatment of many diseases, including chronic obstructive pulmonary disease (COPD), has been investigated. Currently, treatment of COPD is suboptimal. PDE4 modulates the inflammatory response of the lung, and inhibition of PDE4 may be a novel, COPD-specific approach toward more effective treatment strategies. This review describes the state of PDE4-inhibitor therapy for use in COPD treatment.

Expert Opinion

1. Introduction
2. Status of PDE4 inhibitors in clinical development
4. New developments in PDE4 research and their implications
5. Conclusion and expert opinion


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\textsuperscript{1}Almirall R\&D Centre, Department of Medicinal Chemistry, Lauro de Miro 408-410, 08980 Sant Feliu de Llobregat, Barcelona, Spain

Background: Despite the sound preclinical database and some promising data from clinical trials, development of PDE4 inhibitors for the treatment of inflammatory or neurological diseases has been hampered by dose-limiting class-related side effects. Objective: In the past years, companies opted for different approaches to improve the therapeutic window of their compounds including topical administration of PDE4 inhibitors with the goal of minimizing systemic exposure. This change in strategy is reflected by the disclosure
Resveratrol Ameliorates Aging-Related Metabolic Phenotypes by Inhibiting cAMP Phosphodiesterases

Sung-Jun Park,1 Faiyaz Ahmad,2 Andrew Philp,4 Keith Baar,4 Tishan Williams,5 Haibin Luo,6 Hengming Ke,6 Holger Rehmann,7 Ronald Taussig,8 Alexandra L. Brown,1 Myung K. Kim,1 Michael A. Beaven,3 Alex B. Burgin,9 Vincent Manganiello,2 and Jay H. Chung1,*

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*Correspondence: chungj@nhlbi.nih.gov
DOI 10.1016/j.cell.2012.01.017
Resveratrol Ameliorates Aging-Related Metabolic Phenotypes by Inhibiting cAMP Phosphodiesterases

**SUMMARY**

Resveratrol, a polyphenol in red wine, has been reported as a calorie restriction mimic with potential antiaging and anti-diabetogenic properties. It is widely consumed as a nutritional supplement, but its mechanism of action remains a mystery. Here, we report that the metabolic effects of resveratrol result from competitive inhibition of cAMP-degrading phosphodiesterases, leading to elevated cAMP levels. The resulting activation of Epac1, a cAMP effector protein, increases intracellular Ca^{2+} levels and activates the CamKKβ-AMPK pathway via phospholipase C and the ryanodine receptor Ca^{2+}-release channel. As a consequence, resveratrol increases NAD^{+} and the activity of Sirt1. Inhibiting PDE4 with rolipram reproduces all of the metabolic benefits of resveratrol, including prevention of diet-induced obesity and an increase in mitochondrial function, physical stamina, and glucose tolerance in mice. Therefore, administration of PDE4 inhibitors may also protect against and ameliorate the symptoms of metabolic diseases associated with aging.

To test whether rolipram can reproduce the metabolic effects of resveratrol in vivo, we determined the effect of rolipram (2 mg/kg/day) on C57BL6/J mice fed with an HFD. After 12–14 weeks of treatment, we isolated skeletal muscle and measured the mRNA levels of genes that are known to be induced by resveratrol and AMPK, such as eNOS, PGC-1α, and others important for mitochondrial biogenesis. We found that rolipram consistently increased the mRNA levels of these genes (Figure 5I). In agreement with this, treatment with resveratrol, rolipram, or cAMP induced mitochondrial biogenesis in myotubes to comparable levels (Figure 5J). Rolipram and resveratrol also increased mitochondrial content to similar levels in mouse skeletal muscle (Figure 5K). To determine whether increased mitochondrial function improved exercise tolerance, we exercised rolipram-treated mice on a treadmill. Rolipram-treated mice ran a significantly greater distance on a treadmill before exhaustion than control mice (445 ± 19 m versus 268 ± 50 m) (Figure 5L). Taken together, these findings indicate that rolipram and resveratrol have very similar effects on mitochondrial biogenesis in skeletal muscle.
Natural and synthetic PDE4-inhibitors

- Resveratrol
- Roflumilast
- Rolipram
- Cilomilast

For Forensic Use.
Roflumilast

For Forensic Use.
AMPK and PPARδ Agonists Are Exercise Mimetics

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DOI 10.1016/j.cell.2008.06.051
Police find unlicensed drugs after trawling bins of Tour de France cyclists

One drug that cyclists are thought to be using increased exercise performance in mice by 44%

Paul Benkimoun PARIS
France’s antidoping agency has uncovered “a surprising therapeutic arsenal,” including two drugs that are not yet licensed, after scrutinising bins in the wake of the 2009 Tour de France.

Michel Rieu, the scientific adviser of the French Agency Against Doping (Agence Française de Lutte Contre le Dopage), said at a press conference on 7 October, “These are incongruous products in a milieu where people are supposed to be in good health.”

Professor Rieu said that this “surprising therapeutic arsenal” had been reported to the World Anti-Doping Agency in July.

The agency said it suspected that some cyclists were using blood transfusions and two unlicensed substances.

Pierre Bordry, head of the agency, told the French daily Le Monde on 28 July that he was “convinced that two new products have been used during the [2009] tour, two drugs that are not yet on the market.”

The first is a “third generation” erythropoietin called Hematile, which helps maintain stable haemoglobin concentrations—fluctuating haemoglobin being a sign that an athlete has taken banned substances. Hematile is still in phase III clinical trials for the treatment of anaemia and is not expected to reach the market before 2011.

The second compound, known as Aicar, increases performance of endurance exercise and decreases adiposity.

Exercise performance in sedentary mice treated with Aicar is 44% better than that in control mice, as if they had undergone training (Cell 2008;134:405-15).

A spokeswoman for Affymax, which makes Hematile, said it was unaware of the drug being used to enhance athletic performance and that it was working with the World Anti-Doping Agency to ensure that the drug is used only for its intended purpose.

She said, “We share its [the agency’s] founding principle that doping endangers the health of athletes and undermines the integrity of sports. We place a top priority on patient safety.”

The French antidoping agency wanted to run another round of tests on some samples collected from cyclists during the 2009 Tour de France, but the samples “belong” to the International Cycling Union, which did not grant it authorisation. Mr Bordry expressed his frustration with the International Cycling Union. “We can have questions, but we can’t go beyond that,” he said.

Cite this as: BMJ 2009;339:b4201
Monday, March 19, 2012

**Colombian doctor Beltrán Niño arrested with AICAR and TB-500 doping products**

by Shane Stokes at 8:48 AM EST
Categories: Pro Cycling, Doping

**Previously worked with several cycling teams**

Reports that the doping substances AICAR and TB-500 are being used by some in the peloton have gained weight with the news that a doctor linked to cycling was arrested earlier this month with both substances in his possession.

According to El Pais, Alberto Beltrán Niño was arrested on March 7th in Barajas airport in Madrid, from where he was due to fly to Colombia. The two substances were seized, as were his laptop plus flash drives.

These will presumably be screened in order to try to determine who he was supplying products to. Beltrán has been in the Soto del Real prison since March 8th.
First cycling positive for GW501516, Rusvelo’s Valery Kaykov provisionally suspended

By Shane Stokes @ 9:07 AM, April 11, 2013

Following a recent WADA warning concerning the substance GW501516, banned under its rules since 2009 and linked to potentially lethal health issues, the first case in cycling has been announced today by the UCI.

The governing body has stated that the Rusvelo rider Valery Kaykov is provisional suspended in relation to the black market substance, which was never cleared for human use.

“The decision to provisionally suspend this rider was made in response to a report from the WADA accredited laboratory in Köln indicating an Adverse Analytical Finding of metabolite GW1516 sulfone – Metabolic Modulator in a urine sample collected from him in an out of competition test on 17th March 2013,” stated the UCI in an announcement.

It added that Kaykov would remain suspended until such time as a hearing panel of the Russian Cycling Federation ruled on his case, and that the rider could request and attend the analysis of his B sample.

He has been racing with the Rusvelo team for the past two seasons. Last year he finished third in the Russian time trial championships, one minute and ten seconds behind Denis Menchov (Katusha). He was also 22nd in the 1.1-ranked Coppa Bernocchi.

Responding today, the Rusvelo said that it had terminated his contract and insisted that its main ideology “is zero tolerance to doping in cycling. We do support clean cycling and we will stick firmly to our policy,” it said.

A little over two weeks ago WADA issued a rare warning to all athletes, speaking about severe consequences of using GW501516 [also known as GW1516 - ed.].

“The side effect of this chemical compound is so serious that WADA is taking the rare step of warning “cheats” to ensure that there is complete awareness of the possible health risks to athletes who succumb to the temptation of using GW501516 for performance enhancement,” it stated then.

“GW501516 was a developmental drug that was withdrawn from research by the pharmaceutical company and terminated when serious toxicities were discovered in pre-clinical studies. Clinical approval has not, and will not be given for this substance.” It is understood that the substance has been linked to the spread of tumours. According to New Scientist, the original manufacturers GlaxoSmithKline abandoned its development in 2006 after serious effects were detected in rats used as the first test subjects. It was determined that in all doses, the drug quickly caused tumours in a number of organs, including the liver, bladder, stomach, skin, thyroid, tongue, testes, ovaries and womb.
GW501516 positives confirmed, three out of 4 riders are from the same BCR Pizza Hut team
By Shane Stokes @ 3:10 PM Monday, April 15, 2013

UCI confirms Vargas Barrantes, Mudarra Segura, Morales Castillo, Villalobos Azofeifa, and Miguel Ubeto provisionally suspended

Sergej Lisin arguably first athlete tested positive with GW1516 (2012)
GW1516

For Forensic Use.
Established substances – new long-term metabolites?

Exploiting the sniffer-dog quality of GC/C/IRMS and identification capability of GC-Q/TOF

![Chemical structure image]
Established substances – new long-term metabolites?
Established substances – new long-term metabolites?

8 hours

PD


For Forensic Use.
Established substances – new long-term metabolites?

141 hours

PD

Established substances – new long-term metabolites?

477 hours

PD

Established substances – new long-term metabolites?

-> structure characterization by GC-Q/TOF

6β-OH-metandienone-acetate standard

6β-OH-\(^2\)H\(_3\)-metandienone-acetate after administration
Established substances – new long-term metabolites?

-> structure characterization by GC-Q/TOF
Established substances – new long-term metabolites?

-> structure characterization by GC-Q/TOF

18-nor-17α-trideuteromethyl-17β-methyl-5β-androst-1,13-diene-3α-ol (3-acetate)

Summary

- Utmost comprehensiveness of detection assays in sports drug testing desirable – necessitates targeted AND non-targeted approaches
  - GC-HRMS/(MS) complements existing LC-HRMS/(MS) methods

- Metabolism studies and structure characterization enabled/supported by GC-HRMS/MS with MS/MS feature being essential

- Extensive analytical data allow for retrospective data mining, which facilitates estimation of prevalences of substances and/or their abuse in sport
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Manfred-Donike Institute for Doping Analysis