General European OMCL Network
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé
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# Official Medicines Control Laboratories (OMCL)

## Market Surveillance of Suspected Illegal Products (MSSIP)

## MSSIP006: SARMs, metabolic modulators and small molecule growth hormone secretagogues used as performance enhancing substances

| | |
|---|---|
| Type of substances analysed: | SARMs (selective androgen receptor modulators), metabolic modulators and small molecule growth hormone secretagogues used as performance enhancing substances |
| Countries involved: | 13 |
| Participating laboratories: | 14 |
| Scientific advisor: | Magnolia Mendoza Barrios (AEMPS, Agencia Española de Medicamentos y Productos Sanitarios, Spain) |
| Number of samples analysed: | 324 samples |

## Summary Report

### 1. Introduction

Fourteen OMCLs from 11 European countries as well as Australia and Canada participated in the sixth Market Surveillance Study on Suspected Illegal Products (**MSSIP006**).

For this study, the General European OMCL Network (GEON) initially decided to focus exclusively on SARMs. Shortly thereafter, the scope of the study was widened to also cover metabolic modulators and small molecule growth hormone secretagogues, which are often advertised as SARMs and also used as performance enhancing substances.

The goal of this study was to raise awareness of the fact that there are products circulating on the European market and beyond, either on the legal or illegal market, that contain these substances and that are used to boost physical performance. These performance enhancing substances are sometimes promoted as "miracle products" for building muscle mass, but they have not been approved for medical use, since clinical studies performed up till now have not demonstrated their safety/efficacy. These substances are generally taken orally (e.g. tablets, liquid), although some illegal websites also promote their use for parental administration.

These products can be associated with acute life-threatening reactions, including liver toxicity or an increased risk of heart attack and stroke. Consequently, they can be considered as a potential threat to the consumer's health.

## 2. Scope of study

The participating OMCLs were asked to provide data on any product (medicines, herbal preparations, food supplements, cosmetics, medical devices, etc.) tested in their laboratories between January 2018 and September 2023 that contained mainly non-steroidal compounds, such as:

- SARMs, e.g. andarine, ligandrol, LGD-3033, LGD-3303, ostarine, RAD140, S-23, TT-701;
- metabolic modulators, e.g. acadesine (adenosine monophosphate-activated protein kinase (AMPK) activator), cardarine (peroxisome proliferator-activated receptor delta (PPARδ) agonist) and SR9009 (REV-ERB agonist);
- small molecule growth hormone secretagogues, e.g. ibutamoren;
- steroidal SARMs e.g. YK-11.

If quantitative data were available, the laboratories were asked to report them.

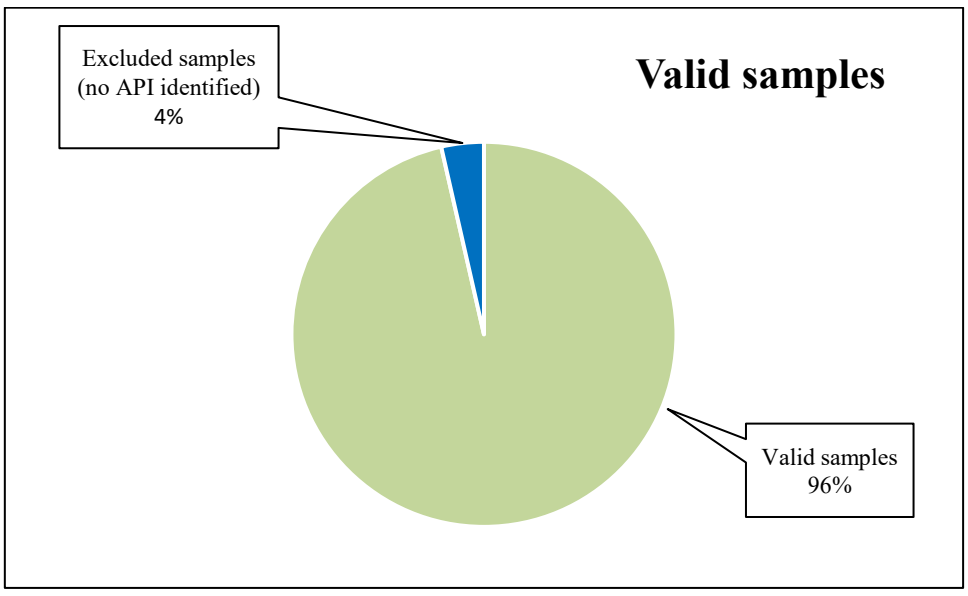
Products containing the following substances were out of scope of the study:

- anabolic androgenic steroids (e.g. trenbolone acetate, boldenone, drostanolone), with the exception of steroidal SARMs;
- GHRP-2 growth hormone secretagogues and similar substances (illegal peptides).

## 3. Collection of results

Test results for 336 samples were reported, although 12 samples (4%) were excluded from the study since no active pharmaceutical ingredient (API) was identified in them.

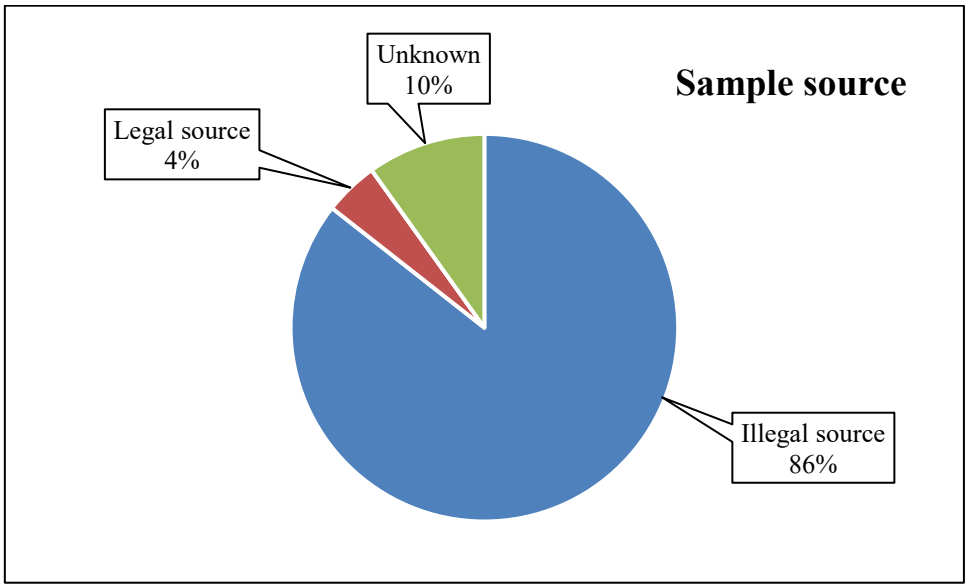
In total, **324 samples** were considered for the report.



Some samples contained more than one substance; thus, for those samples, more than one result was provided. Overall, a total of **354 results** were considered as valid.

### 4. Origin of the tested samples

Most of the samples were obtained from the illegal supply chain.
For 35 results (10%) included in this study, the participants could not confirm whether the corresponding samples had been obtained from a legal or illegal source.



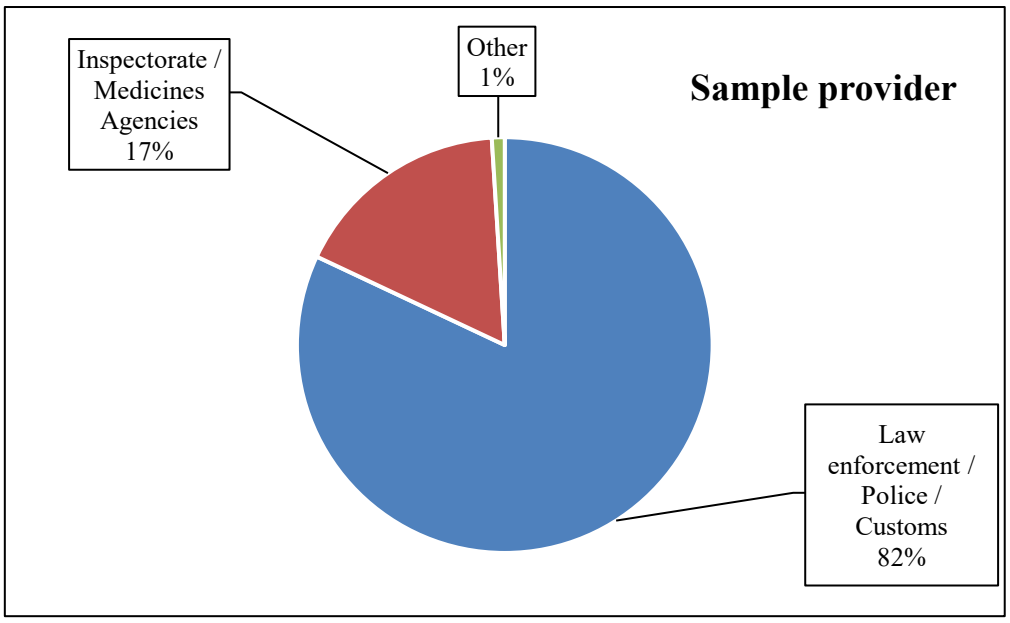

Overall, the origin of the samples was reported as follows:

| Sample origin | Number of test results reported in this category | Percentage |
|---|---|---|
| Targeted police/customs operation | 185 | 52% |
| Police/customs | 84 | 24% |
| Internet | 36 | 10% |
| Unknown | 29 | 8% |
| Other | 10 | 3% |
| Commercial shop | 9 | 2.5% |
| Fitness centre | 1 | 0.3% |

The vast majority of results (around 76%) were obtained for samples that had been seized by **customs or police**, which is to be expected considering these substances are illegal.
Most of the samples classified as "Other" with respect to the sample origin were food supplements seized from the legal market by health inspectors.

## 5. Providers of the tested samples

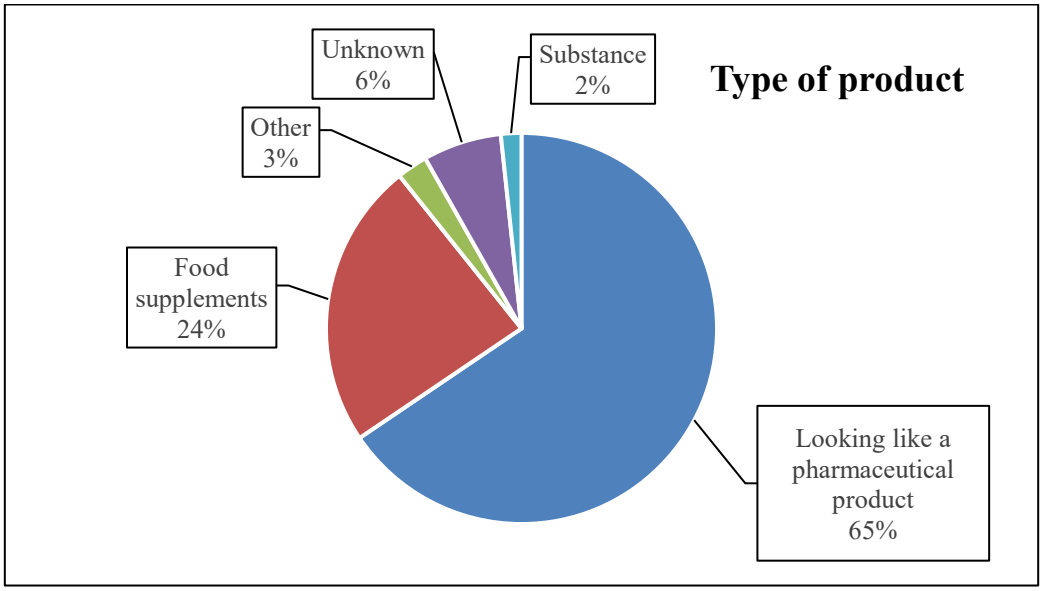
The providers of the test samples were reported as follows:




The chart above shows that most of the results (82%) were obtained from samples provided by the police or other law enforcement bodies.
Two of the samples classified as "Other" with respect to the sample provider were received from a hospital, after adverse reactions had been reported.

## 6. Types of products

The following main product types were reported:



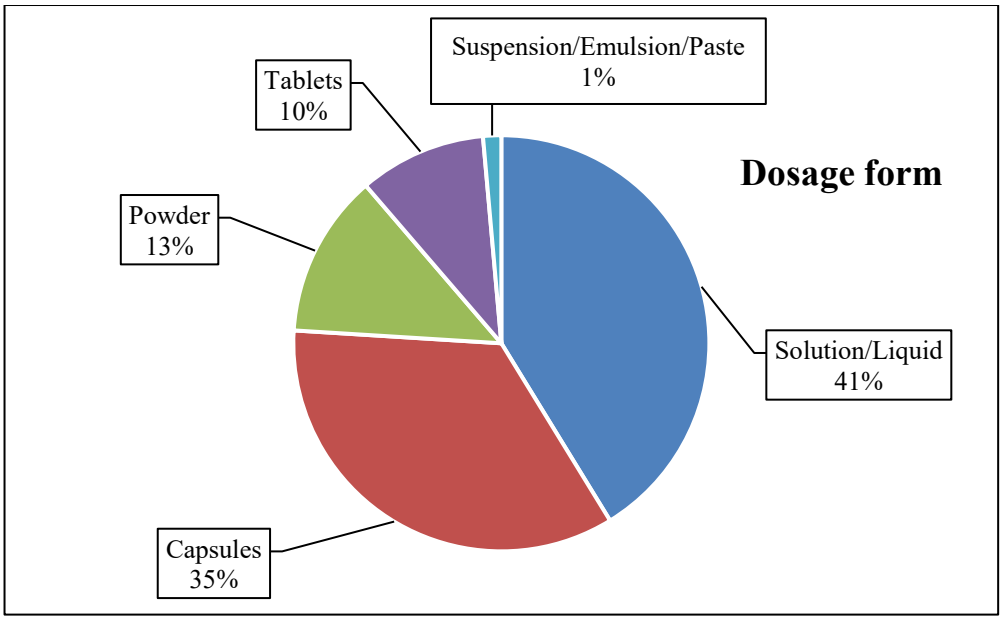
The chart above shows that most of the samples had the appearance of a **pharmaceutical product**. It is assumed that most consumers were aware of what they were taking, considering most products had an indication of their actual content. However, they probably did not know that neither toxicological nor clinical data were available for some of these substances or, in cases where such studies had been carried out, they were not aware that serious adverse effects had been observed, which sometimes resulted in the studies being discontinued.

Furthermore, a high proportion of products were sold as **food supplements**. In this case, some consumers might not have been aware that they were taking a non-approved substance. This could have resulted in side effects that could not immediately be linked to the product by either the patient or health professionals.

Five samples classified as "Other" with respect to the product type were labelled as being "for research purposes only".

**7. Dosage form of the tested samples**

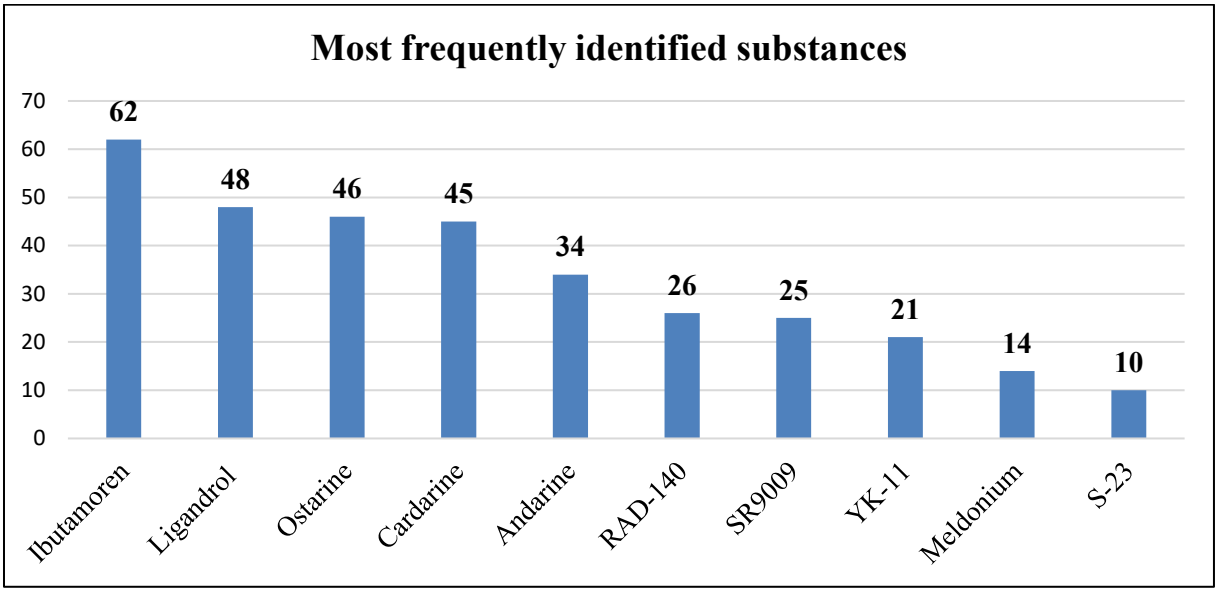
The tested samples were presented in different dosage forms. The test results obtained corresponded to the following types:




The chart above shows that 41% of the results were obtained from **liquid** samples, whether intended for oral administration (e.g. food supplements or oral drops) or presented as solutions for injection. A higher percentage of results (58%) was obtained from samples in **solid** form (capsules, powders or tablets).

## 8. Detected substances

Thirty different substances were identified, of which 18 were within the scope of the study. The chart below shows the most frequently reported substances, in decreasing frequency of detection.




**Ibutamoren** (**Oratrope, Nutrabol, MK-677**) was the most frequently reported substance. This substance mimics the endogenous hormone ghrelin, which stimulates the secretion of growth hormone, and it was identified as a potential treatment for growth hormone deficiency. Clinical studies have shown that this substance resulted in only a small increase in muscle mass and bone mineral density. However, several drawbacks were noted, including transient elevation of liver enzymes, hypertension and heart failure in older adults. For this reason, clinical trials were halted, and this substance is currently not approved for human consumption. As is the case for all SARMs, ibutamoren is included in the World Anti-Doping Agency (WADA) list of prohibited substances.

**Ligandrol** is a SARM that acts as an agonist of the androgen receptor. It has been reported to improve lean body mass and muscle strength during preliminary clinical trials, but it is still under development and has not been approved for any medical use.

**Ostarine** (**Enobosarm**) is a SARM under development for the treatment of androgen receptor-positive breast cancer in women. Ostarine is currently undergoing phase IIb clinical studies for its properties to inhibit muscle loss caused by the use of GLP-1 (glucagon-like peptide-1) receptor agonists. This substance is not yet approved.

**Cardarine** (**Endurobol**) is a metabolic modulator, acting as a selective agonist of the PPAR-delta receptor, which governs a variety of biological processes. Cardarine was intended to be developed as a medicine for metabolic diseases (e.g. obesity, diabetes) and cardiovascular

diseases; however, considering the serious adverse effects observed during animal testing (development of cancers in several organs), the development was halted.

**Andarine** is a SARM that was used in clinical trials as potential treatment for osteoporosis, benign prostatic hypertrophy and muscle atrophy; however, development was discontinued for all indications.

**RAD-140 (Testolone, Vosilasarm)** is a SARM under development for the treatment of hormone-sensitive breast cancer. However, it is not yet approved for any medical use and is not available as a licensed medicine.

**SR9009** (**Stenabolic**) is a metabolic modulator. It is an investigational medicinal product that was found to increase metabolic activity in skeletal muscle (resulting in increased muscle mass) as well as reducing obesity in mice. Stenabolic is included in the WADA list of prohibited substances.
The substance **SR9011**, which is also a metabolic modulator and is related to SR9009, was also identified by some participants, but at a lower frequency (six cases).

**YK-11** (**Myostop**) is a steroidal SARM, a selective partial agonist of the androgen receptor, which acts as inhibitor of the protein myostatin. This leads to muscle growth and increases athletic performance. It has been investigated in animal studies because of its preventive effects to bacterial sepsis-induced muscle atrophy.

**Meldonium** (**Mildronate, Quaterine)** is a metabolic modulator, acting as a fatty acid oxidation inhibitor. It is the API of an approved anti-ischaemia medicine. It is mostly prescribed to treat cardiovascular diseases. Meldonium is included in the WADA list of prohibited substances.

**S-23** is an investigational SARM, developed as a potential male contraceptive due to its ability to suppress spermatogenesis (reversible once treatment is stopped).

It is important to highlight that different combinations of substances were identified in this study, such as the combination of two or more performance enhancing substances within the scope of the study (e.g. ibutamoren + ostarine + rad-140) or combinations of these substances with other components outside the scope, for example with substances with an anabolic effect (e.g. cardarine + stanozolol) or combinations with substances used for erectile dysfunction (e.g. ibutamoren + yohimbine or meldonium + sildenafil).

## 9. Analytical methods

The OMCLs were allowed to use the analytical method(s) of their choice for identification and/or quantification purposes, e.g. liquid chromatography (LC), gas chromatography (GC), mass spectrometry (MS) or nuclear magnetic resonance (NMR) spectrometry.

The following methods and detectors were used by the participating laboratories for identification and/or quantification purposes:

- **LC-MS**: UHPLC-MS/QTOF, LC-MS/ESI-QTOF, LC-MS/MS, UPLC-MS/MS-ESI-QTOF, LC/MS-UV, LC-MS (QDa), LC-MS (Orbitrap), HPLC/RI-MS.
- **GC-MS**.
- **LC**: LC-PDA, HPLC-DAD, UPLC-DAD.
- **qNMR**.

## 10. Conclusions and perspectives

Unlicensed products containing SARMs, metabolic modulators and small molecule growth hormone secretagogues are being sold in the European market and beyond and consumed as performance enhancing substances.

Some of the substances covered in this study had originally been identified as potential treatments for a variety of medical conditions, and toxicological/clinical trials had been initiated. However, with the exception of meldonium, none of these substances has received authorisation for medical use in humans, mainly due to their serious adverse effects.

Most of the tested products were seized from the illegal market, and it should be noted that because SARMs found on the black market are often taken at much higher doses than those used during clinical trials, the safety impact is not known.

In addition, these illegal substances can interfere with other medicines or have consequences for the development or treatment of diseases that have already manifested in the consumer, thus representing a real danger to health.

In conclusion, a continued effort is needed to control and screen illegal and suspect products for their composition. The results of this study should be used to raise awareness among the public and policymakers regarding the dangers posed by these substances and, more generally, to raise awareness and discourage the purchase of products (whether medicines, food supplements or life-style products) from suspect websites that are not reputable and/or that conceal their physical identity.

*Appendix 1: Identified valid substances (within the scope) and corresponding number of reported results.*

| Reported substance | No. of reported results | CAS number | Synonyms |
|---|---|---|---|
| Ibutamoren | 62 | 159634-47-6 | MK-677, L-163,191, Oratrope, Nutrabol |
| Ligandrol | 48 | 1165910-22-4 | LGD-4033, VK5211 |
| Ostarine | 46 | 841205-47-8 | MK-2866, Enobosarm, S-22 |
| Cardarine | 45 | 317318-70-0 | Endurobol, GW 501516, GW 1516, GW-501,516, GSK-516 |
| Andarine | 34 | 401900-40-1 | GTX-007, S-4 |
| RAD-140 | 26 | 1182367-47-0 | Testolone, Vosilasarm |
| SR-9009 | 25 | 1379686-30-2 | REV-ERB Agonist II, Stenabolic |
| YK-11 | 21 | 1370003-76-1 | Myostop |
| Meldonium | 14 | 76144-81-5 | Mildronate, Quaterine, MET88, THP |
| S-23 | 10 | 1010396-29-8 | Sarmbolone |
| SR-9011 | 6 | 1379686-29-9 | Recardin |
| GW-0742 | 5 | 317318-84-6 | Supercardarine, Cardabol, GW610742 |
| LGD-3303 | 3 | 917891-35-1 | |
| RU-58841 | 3 | 154992-24-2 | PSK-3841, HMR-3841 |
| Acadesine | 2 | 2627-69-2 | Aicar, AICA-Riboside, NSC 105823 |
| 5α-hydroxy laxogenin* | 2 | 56786-63-1 | |
| AC-262 | 1 | 870888-46-3 | Accadrine, AC-262536 |
| ACP-105 | 1 | ---- | |

*5α-hydroxy laxogenin is not a SARM; however, it is considered within the scope because it is a partial agonist of androgen receptors (PAAR) used as a performance enhancing substance.

The following substances were identified in the tested products by some participants. In some cases, they were used in combination with other substances. The following substances were outside the scope of this study and were not included in the above table: 2,4-dinitrophenol, caffeine, clomiphene, epimethandienone, letrozole, niacinamide, sildenafil, stanozolol, tadalafil, tamoxifen, testosterone and yohimbine.