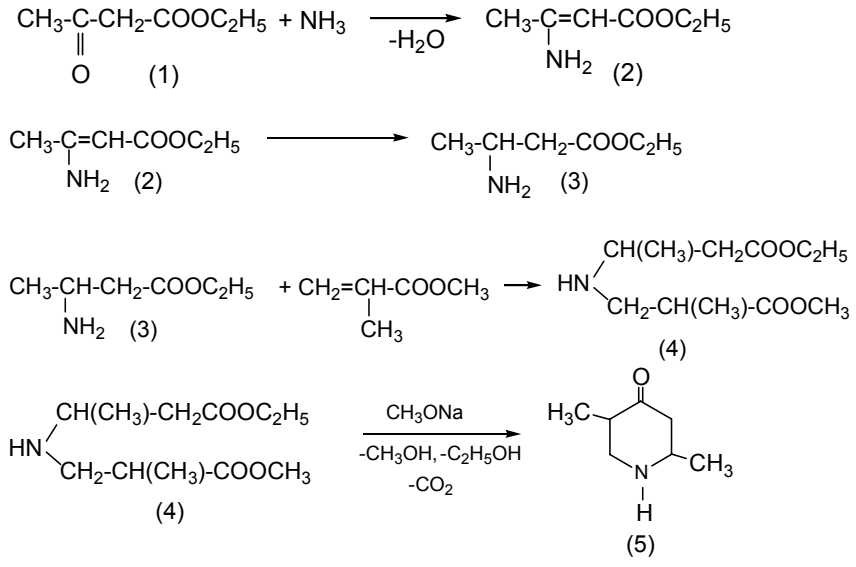
SCIENTIFIC BASES FOR DEVELOPMENT OF TECHNOLOGY OF KEY SEMI-PRODUCTS IN PRODUCTION OF MEDICINAL PREPARATIONS OF PIPERIDIN

Kunnaz Murzagulova *and Murgul Turmukhanova*

Derivatives of piperidine-4-ones are the key products for synthesis and search of new vital effective medicinal preparations such as analgetics, anticancer, anti-AIDS, and antidiabetes medicines. Up to the present time on the territory of CIS countries the method of academician I.N. Nazarov realized in the production of analgetic Promedol was of great importance in the field of synthesis of dimethylsubstituted piperidine ketones. The technology of this production has a number of significant disadvantages: mercury salts used as catalyst in this process are higly toxic, and the raw materials are characterized as highly flammable and explosive. Development of new more accessible and safe methods of synthesis of 2,5- dimethyl and N-substituted 2,5-dimethylpiperidine-4-ones and searching for new medicines on their basis is the purpose of these investigations. Creation of modern synthesis technologies of new compounds on the basis of available raw materials requires, first of all, the solution of fundamental problems of organic chemistry, such as conformation of molecule and its reactivity, stereochemical and conformational regularities of the reaction procedure, and the use of quantum-chemical calculations for determination of the energy parameters of the molecule for purposeful synthesis.

The set target contained the solution of such problems, as the development of new methods of synthesis of 2,5-dimerhyl – and N-substituted 2,5-dimethylpiperidine-4-ones from acetoacetic ether with studying of general mechanisms of selective reduction of olefine bond of intermediate enaminoethers, catalytic nucleophylic addition of amines to multiple bonds of sterically hindered ethers α,β-unsaturated carbonic acids, cyclization of aminodiethers into 2,5-dimethyl- and N-substituted 2,5- dimethylpiperidine-4-ones; experimental basis of the main processes parameters.

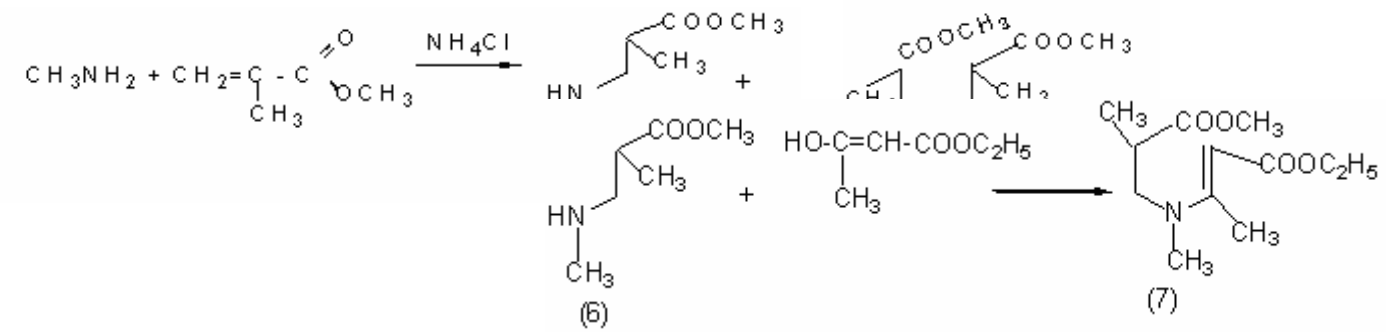
On the basis of the obtained results we have developed new methods of synthesis of 2,5- dimethyl- and N-substituted 2,5-dimethylpiperidine-4-ones from acetoacetic ester:

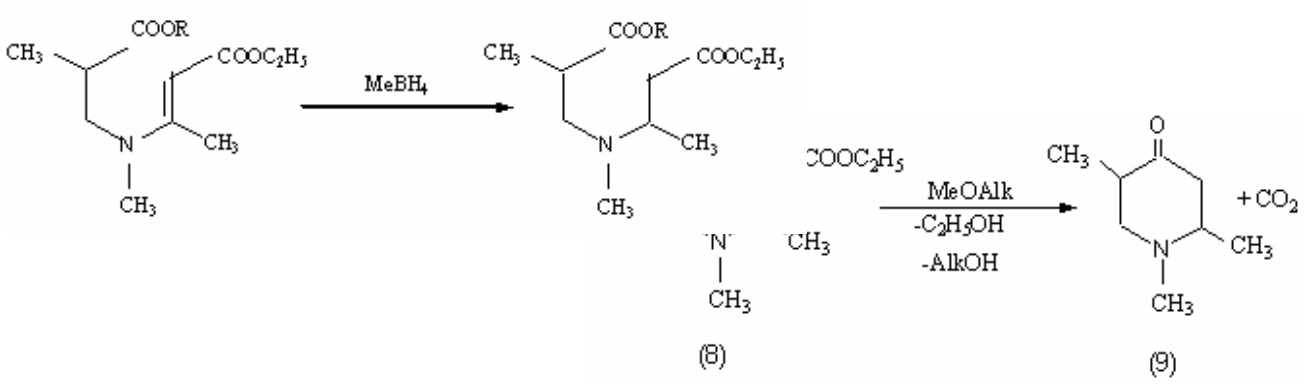


Analysis of existing literary and obtained by us experimental data let us prove a new approach to ethers synthesis of β-amino acids, which is concluded in purposeful enamine conformation change for consistent selective catalytic and hydride reduction of olefinic bond.

Quantum-chemical estimation of cis-S-cis, trans-S-cis and trans-S-trans conformers of esters of 3-amino-2-butene acid were carried out. On the base of received results we developed a new industrial method of synthesis of ethyl ester of β -aminooil acid by selective hydrogenation of ethyl ester of β -aminocrotonic acid on Ni-Re and Ph/C. Tran-s-trans conformer should be hydrogenated easily and with high level of selectivity, which has increased electron density >C=C< and the largest shift of electron density on oxygen atom of carbonic function , due to the presence of unshared electrons pair coupling of nitrogen atom with multiple bonds system >C=C–C=O. Cis-s-cis conformer, having carbon function connected with NH-group of intra-molecular hydrogen bond, can't adsorb on the catalyst surface, and therefore, it is obvious that it shouldn't be hydrogenated. For the hydrogenation velocity increasment of α,β-unsaturated carbon acids ethers it is usual to protect catalyst from unshared electrons couple of oxygen atoms of carbonyl group or OR-function by addition of substances, having nucleophilic properties towards metals. It should be expected that ethyl ether of β-aminobutyric acid (3), produced during the hydrogenation process, as more strong nucleophil in comparison with initial enaminoether (2), will be adsorbed on the catalyst surface by unshared electrons couple of nitrogen atom, forcing out oxygen electrons couple of OR-function. And it will also increase activity and selectivity of hydrogenation catalysts of enaminoether olefinic bond.

By condensation of acetoacetic ester with secondary amines we have synthesized tertiary enaminoesters in trans-S-cis conformation, the following reduction of which by sodium borhydride allowed us to develop industrially available methods of obtaining the esters of tertiary β -aminoacids.





Also we have developed an alternative method of synthesis of differently substituted esters of secondary and tertiary β -aminoacids by catalytic nucleophilic addition of amines to multiple bonds of esters of a, β - saturated carbonic acids. We have suggested a mechanism of catalysis.

Developed for the first time industrial available methods of ethers β –aminoacids, optically active form of the esters of ß-hydroxibutyric acid is a perspective monomer for manufacture of biodegradabled polymers. They can find application for reception of plasticizers.

There was developed the method of production of the new hydrogel on the basis of ethyl ester of ß-aminocrotonic and acrylic acids (it founds an application in biotechnology – in purification and separation of proteins, immobilization and stabilization of enzymes, fermentative catalysis, in pharmaceutics – as an auxiliary material for prolongation of medical products, in petrochemistry – as an inhibitor of corrosion of metals at an oil recovery, antidepressant).

Fundamental researches on synthesis, search of the structure and physiological activity of Piperidine derivatives allowed us to develop some original highly-effective preparations: local anesthetics, antibacterial, dermatoprotector, immunocorrector and anti-cancer medicines. Pre-clinical researches of the preparations were carried out at laboratories of Cuban Medical Academy (Russia) by professor Galenko-Jaroshevskiy P.A. and other. In modern medicine one of the most actual problems remains to be the struggle with pain which includes the development and improvement of anaesthetics

The original highly-effective drug Richlocaine (benzoic ester of a-isomer of 1-allyl-2,5-dimethylpiperidol-4) has the most successful combination of anaesthetic activity and low toxicity, it causes quick, deep and durable anaesthesia, has an analgesic effect, is active in citatricial tissues, does not exert a local irritating effect, does not cause toxic and allergic reactions, side effects and is very tolerable (especially in case of children). It also has a well-pronounced antiarrhythmic, antispasmodic, dermatoprotective and antimicrobe effects. It possesses bacteriostatic action against a wide range of pathogenic and relatively pathogenic bacteria, both gram-negative and gram-positive ones. It has been shown that Richlocaine is an immunocorrector and activator of anticancer preparations and is recommended for treatment of ovaries cancer. The drug forms of Richlocaine such as gels, ointment, films for treatment of suppurotive wonds have been proposed for using in surgery and stomatology. We have carried out the transformation of functional group of piperidine series. The effect of quarternizing agents is being studied, immobilization of Richlocaine and its derivatives on synthetic and natural polymer matrixes is being carried out. Pharmacological investigations showed that composition preparations possess a prolonged effect with high activity and low toxicity.

Pharmacological and clinical investigations were carried out in the leading scientific and medical centers of Russia and Kazakhstan (Moscow, St-Peterburg, Novosibirsk, Novokuznetsk, Kharkov and Almaty). Richlocaine, permitted for medical application and industrial production in Russia and Kazakhstan. Organization of the Richlocain production is planned in Kazakhstan on 2006- 2007 years (substances and ready- made medicinal forms).

The second perspective for application in medicine drug (АН-89- Я) is the derivative of 2,5-dimethyl 4-benzoiloxipiperidine, is 4.8 times more effective for terminal anaesthesia than lidocaine and trimecain , respectively, its range of therapeutic effect is 5.2 times wider than the above preparations.

In case of *infiltration* anaesthesia it is comparable with bupivocaine (marcaine) by the rate of anaesthesia, it causes anaesthesia 1.7 times quicker than lidocaine, trimecain and by the time of total anaesthesia and its duration it does not differ from bupivocaine (marcaine).

In case of *block* anaesthesia the preparation has the same effect as marcaine as for the rate of anaesthesia, its depth and duration.

In *epidural* anaesthesia the preparation is slightly less effective than marcaine but more effective than other anaesthetics. It does not reveal irritant action in concentrations 0.25, 0.5 и 0.75%, it is compatible with adrenaline and in this case its local anaesthetic activity increases 5.5 times.

Irritable action of АН- 98- Я was investigated by its conjuctive injection to rabbits. In the studied concentrations it didn't cause irritable action on eyes conjuctives.

The compound АН- 98- Я was investigated on membrane activity, which significantly blockade the transportation of sodium ions, potassium and calcium in corresponding ion canals. The compound produces maximum effect in concentration 10^{-4} mol/ liters. The compound АН- 98- Я exceeds lidocain in 2 times on ability to blockade rapid incoming sodium current. It was stated that the compound produces properties of local anesthetic of calcium blockator and what is more impotent, of potassium keeping substance.

Antiarrythmic properties were investigated on aconitine (cupiration) and adrenaline (prevention) models of arrhythmia in narcotic rats (sodium ethaminal 40 mg/ kg intraperitonitiesly), where the first model is specific for blockators of rapid sodium canals, the second- of slow calcium canals. In the conditions of aconitine arrhythmia АН- 98- Я exceeds in activity novocainamid, hinidine, kordaron, aimaline, lidocain respectively in 23, 6, 9, 3, 2, 4, 2, 0, and 4, 6 times.

In the conditions of adrenaline arrhythmia АН- 98- Я exceeds in activity drugs of comparison in some time. It can be supposed, that there is an ability to blockade rapid sodium and, in greater degree slow calcium canals of heart miocitos in the basis of antiarrhythmic effect of АН- 98- Я.

АН-89- Я has a dermatoprotective action, i.e. the capacity to rise the survival of skin shred. The amount estimate of influence of compound АН-89- Я the viability of tissues in the conditions of reduced blood-circulation showed, that it exceeds standards drugs (sodium and lithium oxybuthirates) in the 490,0 and 220,0 times. With the increasing dose of compound АН-89- Я dermatoprotecting action increases.

Anticonvulsive action was investigated on mice by intravenous injection. In the conditions of maximum electroshock it exceeds the standard Phenobarbital in 9,2 times, in corazol spasms it will be confronted with it.

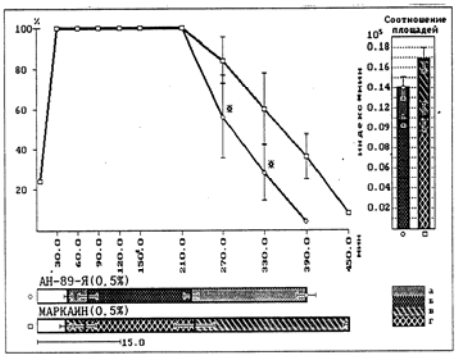
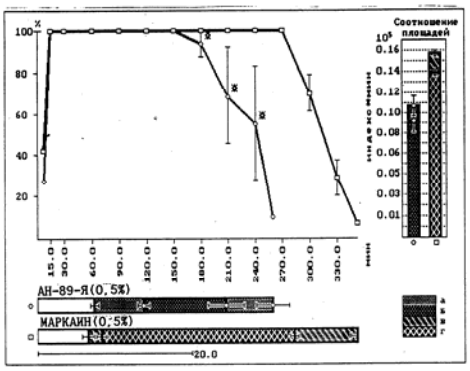


Fig.1

Local anaesthetic activity of preparations for infiltration anaesthesia at rabbits



Fig,2

Local anaesthetic activity of preparations for block anaesthesia at rats

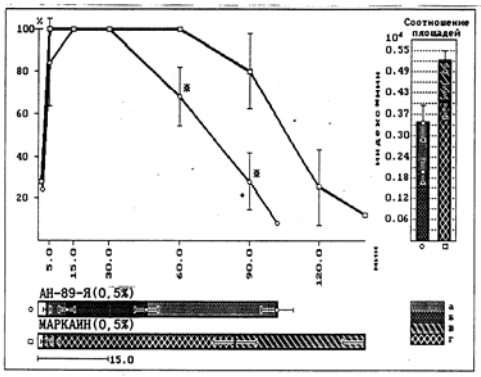


Fig.3

Local anaesthetic activity of preparations for Epidural anaesthesia at rabbits

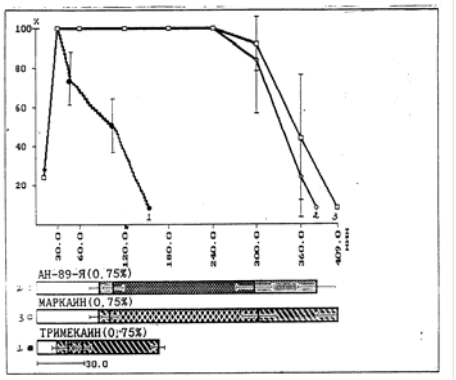


Fig.4

Local anaesthetic activity of preparations for block anaesthesia at rabbits

Depth of anaesthesia and duration of action, a, c – general anaesthesia, b, d – total anaesthesia

АН-89-Я is recommended for further preclinical trial. Medical products on dimethylpiperidine-4-ones basis are noted by higher stability because of having particular spatial structure, the lowered toxicity and more valuable therapeutic properties in contrast to piperidone-4, which does not have alkyl radicals in a cycle. Synthesis and search of new derivations on its basis, in particular, for treatment of the AIDS-INFECTION has good prospects.

Company " Romat" conducts this direction of the researches in common with the department of organic chemistry and chemistry of natural compounds of Kazakh National University named by Al- Farabi, Almaty. Fore predclinical researches of new medicinal forms (specific types of activities, toxicology) are conducted by specialists from pharmacologic department of Kuban Medical Academy, Krasnodar (Russian Federation) under the leadership of corresponding member of Russian Medical Science Academy , professor Galenko- Yaroshevskii P.A . Methods of testing of new drugs are corresponded to international standards.

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Identification of mycobacteria with the use of gas and high performance liquid chromatography. The study of pecularities of composition and type of fatty and mycolic acids of drug-resistant of mycobacteria tuberculosis

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During last decade tuberculosis again become an enemy in the world. Global annual expenses on tuberculosis problems are $ 12, 000,000 US. Every year 8.4 million cases of tuberculosis are detected. Mortality percentage of tuberculosis in the world is 23% of all deaths, caused by illnesses and different calamities. In countries with a wide –spread HIV-infection the death-rate runs up to 50%. According to suppositions of experts of the

World Health Organization one third of the earth population is infected with tuberculosis mycobacteria (about 2 billions people) and 5-10% of them will fall ill with some tuberculosis forms of tuberculosis during their life. The growth of tuberculosis is brought out by multi-drug resistance. Spreading HIV- infection brought about sharp growth of tuberculosis.

Kazakhstan according to the World Health Organization has one of the highest rates of newly diagnosed tuberculosis in the world and has one of the highest tuberculosis mortality percentage. According to official data, given in the report of academician Aliev M.A. at the First Congress of Kazakhstan specialists on tuberculosis, Almaty, 2004, the incidence of newly diagnosed patients with tuberculosis was 438,2 per 100 thousand population. In the agricultural population the rate was 150,2/100000, and in children it was up to 47,2 per 100 thousand. Although these are the official government data, recent improvements in the national TB surveillance system should allow more accurate determination of these rates in the near future. According to the National centre of tuberculosis problems of Kazakhstan Ministry of Health, initial multiresistant forms of tuberculosis in Kazakhstan are increasing, in 2001 have made 9,9 % and grow with each year. Frequency of the acquired drug resistance in 2001 has made 65,4 %, including MDR accordingly 18,3 % and 22,5 %. The next years these figures steadily grow.

In Kazakhstan, the situation is further complicated by the fact that patients, especially in prisons, are not isolated from each other. HIV infection is also a common confounding factor. In Kazakhstan more than 45 thousand HIV-infected people were registered on December, 2004, and according to estimated data the real number of HIV-infected people in Kazakhstan makes about 100-130 thousand. Disease of tuberculosis at patients with the HIV-infection makes 2,5-15% per year, that is 50 times more than that at the whole population. More over, HIV-infected patients have the special strain of *M. tuberculosis*, highly resistant to drugs. 10 % patients with AIDS are sick a tuberculosis, the death rate achieves 43-89 %. One of the most often and dangerous diseases accompanying the HIV-INFECTION, is also a chronic hepatites C. Some part of patients have all three infections simultaneously. It means that in the nearest some years doctors will meet with a problem of large-scale treatment of the patients suffering simultaneously by three hardest diseases: tuberculosis, chronic hepatites C and the HIV-infection.

Patients may be infected not only with multiple strains of *M. tuberculosis* but also with other species of mycobacteria. Atypical mycobacteriosis caused by potentially pathogenic nontubercular Mycobacterium avium complex (MAC), concerns to the most widespread superinfection associated with AIDS and practically not be diagnosed in Kazakhstan. Various infringements of immune system at tubercular patients result in increase in tens times disease a fungoid infection. According to the data of the National centre of tuberculosis problems of Kazakhstan Ministry of Health in 2004 the hard forms of lung-bronchial, vulvo-vaginal and gastro-esophagal forms of visceral candidosis were revealed at 27,7 % of patients. At treatment of a tuberculosis by reserve preparations the risk of candidosis defeats makes more than 54 %, the risk of respiratory fungoid defeats is increased in 14 times.

Activators - conditionally-pathogenic yeastoid fungies such as Candida of the Criptococcaceae Candida albicans group makes 22-24 % among all fungies of this sort. The part of activators of candidosis, C. Pseudotropicalis, C. Krusei, C. stellatodea, C. glabrata, C. Usentaniae etc. is increasing. Besides candidosis such microorganizms as mould mycosises, Zigomycetes, Ascomycetes, Fungi imperfecti, Aspergillus, Penicillium, Micor etc. are widely distributed.Aspergillosis - a fungoid infection of lungs, has the tendency to 1,5-time growth. Activators – fungies of Aspergillus type from Trichomaceae group.Aspergillosic pneumonia, aspergilloma of lungs, penicilliosis, zigomycosis.

One of the reasons of tuberculosis spreading is the absence of new effective drugs. In connection with the duration, complication and the high prices of testing new drugs, for the last years there wasn't developed any new drug, applied drugs were developed more than 50 years ago.

The peculiarity of tuberculosis mycobacteria is the slow growth, there acquired some weeks only for growing a colony of tuberculosis mycobacteria for researches. In order to get the result about the drug efficiency or its medical susceptibility there acquired 90 days. It is one of the reasons, retarding the elaboration of new antituberculosis drugs, as the opportunities of variation of formula, composition, and technological methods of creating medicinal forms are limited due to the test duration in vitro, bad reproduction of high financial cost.

The data on infections with mycobacteria other than tuberculosis (MOTT) is lacking in part because of the lack of tools to identify species of *Mycobacterium*, although some work is being done with conventional biochemical tests and polymerase chain reaction (PCR)-based methods. The basic laboratory method for the diagnosis of tuberculosis in Kazakhstan is bacterioscopy. The method is directed at detecting patients with advanced disease – those who have a cavity of disintegration in their lungs. Treatment of such patients is difficult, expensive, and long. In Kazakhstan, the criterion for success of a patient's treatment is a negative result of bacterial culture tests, rather than X-ray data demonstrating closing of a cavity of disintegration. Drug-resistance of *M. tuberculosis* isolates is also defined by culture-based tests. . Before receipt of drug-susceptibility results, the patient is usually treated with a standard regimen which may include antituberculosis preparations to which the bacteria has developed resistance.

During the last 10-15 years, new methods to accelerate the identification of M*ycobacterium tuberculosis* and other pathogenic *Mycobacterium* species from cultures have been developed and evaluated in the USA, Europe and elsewhere. New tests for rapidly determining drug susceptibilities of mycobacteria have also been developed. One of the identification methods for mycobacteria is the analysis of methyl esters of mycolic acids with the help of HPLC. The important advantages of this method are that it is a relatively-low cost method and that a single test can identify most pathogenic *Mycobacterium* species. The expenses on material and laboratorial devices are : 10,94$ for one test (chromatography), 26,58$ (PCR) *и* 42,31$ for traditional biochemical identification. Many hospitals and public health laboratories in the United States have begun using HPLC as a primary identification method because of these advantages and because of the development and publication of standard methods and protocols for the test (Standardized Method for HPLC Identification of Mycobacteria, US Department of Health and Human services, 1996

A recent improvement in the HPLC method was the introduction of a protocol for labeling mycolic acids with fluorescent probes and detection using a fluorescence detector. This greatly increased the sensitivity of the method and allows the detection of *M. tuberculosis* directly in sputum specimens. Other researchers have also explored the use of HPLC to measure the amount of mycolic acids as a way to determine the drug susceptibility of mycobacterial isolates to currently used and experimental drugs. A related technique, gas chromatography (GC), has also been used to detect mycobacterial products such as fatty acids, 2-eicosonol, and tuberculostearic acid for the rapid diagnosis of tuberculosis.

In the CIS-countries, such rapid diagnostic tests are not routinely used yet. Although PCR-based detection tests are used in a number of scientific research institutes and large institutes of tuberculosis, there are no standardized methods, approaches, or

recommendations for the use of PCR. These tests have been used primarily for research applications and not for clinical diagnosis.

Purpose investigations**:** development of standardized methods for the identification of mycobacteria by the methods of gas chromatography and high-performance liquid chromatography (HPLC) in Kazakhstan and their harmonization with the internationally accepted methods. Studying the quantitative and qualitative features of the fatty and mycolic acids composition of mycobacteria exposed to antituberculosis drugs to identify changes that may be indicative of susceptibility or resistance to the drugs. Studying the features of fat-acidic character and mycolic acids of mycobacteria with medicinal stability to antitubercular preparations. The aimed selection of new compounds, preventing the growth of mycolic acids and foundation on its bases new preparations, effective for treatment of drug resistant tuberculosis forms..

The Kazakh National Medical University collect clinical isolates from patients with tuberculosis and infections with MOTT from various regions of Kazakhstan. There held identification of collected isolates grown on solid and liquid media by standard phenotypic and molecular biological methods, and preparation of mycobacterial extracts for GC and HPLC tests to be done in the participating laboratories. Chromatographic analysis (GC and HPLC) of methyl esters of fatty acids and mycolic acids and other mycobacterial components of the collected clinical isolates are carried out in the Kazakh National Medical University, Laboratory of Monitoring of Stepnogorsk, Microbiological Laboratory of Romat.

studied the quantitative and qualitative features of the fatty and mycolic acids composition of mycobacteria exposed to antitubercululosis preparations to identify changes that may be indicative of susceptibility or resistance to the drugs. There studied the features of fat-acidic character and mycolic acids of mycobacteria with medicinal stability to antitubercular preparations.

There created the library of chromatograms for fatty acids and mycolic acids of *M. tuberculosis* (reference and clinical isolates grown on solid and liquid media including BACTEC 960) and other well-characterized *Mycobacterium* species including *M. avium*, *M. intracellulare*, *M. gordonae*, *M. kansasii*, *M. fortuitum*, etc. (there are more than 40 pathogenic *Mycobacterium* species) and there held comparisons with existing libraries such as the one of the U.S. HPLC Users group.

Development and evaluation of the accelerated high-sensitive automated method of identification of mycobacteria by the HPLC method with fluorescence detection from smear-positive sputum specimens which will be used for testing of new drugs.

Expected results

1. A collection of well-characterized clinical isolates of *M. tuberculosis* and other pathogenic species of *Mycobacterium* collected from patients in various regions of Kazakhstan will be created.
2. A library of chromatograms of methyl esters of fatty acids and mycolic acids of identified clinical isolates and *Mycobacterium* species will be created. The library will be a critically needed resource for laboratories who uses the new methods to identify *Mycobacterium* species. The library generated in Kazakhstan will be harmonized with existing libraries of international colleagues.
3. A standardized method for the identification of mycobacteria by GC and HPLC will be developed for use in diagnostic laboratories in Kazakhstan. The method will be compatible with existing protocols used in other countries.

4. Criteria to determine resistance of *M. tuberculosis* to antituberculosis preparations on a basis of fatty acid composition or the content of mycolic acids will be developed.

5. Features of fatty acidic character and the structure of mycolic acids at mycobacteria isolates with various sensitivity to medical products will be established.

6. A rapid, highly sensitive, automated method of identification of mycobacteria by the HPLC method with fluorescent detection from smear-positive sputum specimens will be developed.

7. New compounds preventing the growth of mycolic acids for drug resistant tuberculosis mycobacteria will be brought out. There will be created new drugs on its basis effective for treatment drug resistant tuberculosis.

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Information about Romat pharmaceutica company

ROMAT is the largest pharmaceutical company in Central Asia.

- ROMAT is focused on creating a transparent, efficient and resilient production, wholesale and retail systems
  - №2 local producer with 4 out of 7 pharmaceutical plants in Kazakhstan
  - Two plants were build in accordance with international GMP standards
  - Romat plans to receive of the GMP certificate in 2007 year.
  - Romat owns the «Pharmstandard»- quality testing laboratory with microbiological department, which has the nursery of animals (mice, rabbits).
  - №1 wholesale branch network in Kazakhstan
  - Among top 5 wholesale traders by sales in Kazakhstan
  - №2 largest retail network in Kazakhstan

International standards

- promotion of international standards, such as GMP (Good Manufacturing Practice)
- IAS audit
- foreign consultants with broad experience
  - Kate McCormick, GB, (World Health Organization)
  - Robert Stevenson, USA (VP,Pharmacia Upjohn)
  - Christo Angelov, USA, (member of Nobel prize committee on biochemistry)

The Pavlodar plant was build by Swedish firm "Pharmadul"

- Built in accordance with GMP standards
- Has a capacity to produce 1.2 bln tablet packages per year

- Antituberculosis (isoniazid, ethambutol, rifampicin, pyrazinamide, new combinations of tuberculosis drugs)
- Analgesis(aspirin, paracetamol, analgin,acetylsalicyl acid, diclofenac)
- Cardiovascular medicines (enalapril, captopril, atenolol, riboxin)
- Vitamins (ascorbic acid, ascorutin,hexavit, undevit)
- No seasonality risks

The top products that Romat produces:

- Haematogen
- Pancreatin, the ferment drug
- Peptone for bacteriological research
- VNIIMS, used in cheese production

The only plant in Kazakhstan that produces disposable syringes:

- Original investments over USD 10mln
- Built in accordance with GMP standards

Produces the following syringes:

- 2 milliliters
- 5 milliliters
- 10 milliliters

The largest branch network – 17 branches with own warehouses:

- Proven reputation among foreign pharmaceutical companies, including:
  - GlaxoSmithKline
  - Elly Lilly
  - Pfizer
- 4 regional centers:
  - South – Almaty
  - North – Karaganda
  - West – Aktobe
  - East - Semipalatinsk
  - Nestle
  - Shearing
  - Others

Clients include:

- Other wholesale companies
- Pharmacies
- State tenders
- Hospitals

One of the largest retail networks:

- 31 own pharmacies
- Including 3 franchisees
- Largest pharmacies have own phitobars and laboratories

Wholesale business

Customers:

- Other wholesale companies
- Retail pharmacies
- Hospitals

- State tenders

Network
- 17 branches
- 4 regional centers

Retail business
- 28 own pharmacies
- 3 franchise pharmacies & plans to increase up to 100
- Plans to computerise all pharmacies to control stocks on-line
- Medicines inquiry bureau

International Standards
- International consultants
- Annual audit by PWC
- Plans to install SAP software

History of success

- Triple winner of the national competition " The choice of the year 2001 – 2004" in the nomination "The best pharmaceutical company in Kazakhstan"
- Four times winner of the Republican competition "The best goods of Kazakhstan" in the nomination of "the guarantee of safety" on ready medicines
- Euromarket Award (EMRC) 2002
- Universal pharmaceutical holding strongly positioned to be a top player in Central Asia
- Provides a unique diversified exposure to the growing economy of Kazakhstan
- Clear cut strategy implemented by focused and professional management, including foreign consultants
- ROMAT has a successful experience of working with foreign investors by working with EBRD (shareholder and a long term investor)
- 12 years of successful cooperation with the world known companies Elli Lilly (USA), GlaxoSmithKline (Great Britain), Nestle (Switzerland), Novonordix (Denmark), Ancell (France), Pfizer (USA) etc.
- Complies with international standards and is transparent to foreign investors
- ROMAT has an extensive production experience by manufacturing more than 150 medicine types
- The Company has created nationwide wholesale and retail medicine sales that sells more than 3000 types

Romat is willing to consider mutually beneficial proposals for joint venture opportunities