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SYNTHESIS AND BIOLOGICAL PROPERTIES OF NEW 2-ARYL- AND 2-PYRIMIDINYLPROLINES (REVIEW)

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In this review presents the development of new accessible methods for the synthesis of substituted 2-aryl- and 2-pyrimidinylprolines, the study of biological properties and the establishment of a relationship between the chemical structure and biological activity.

Ref. 25, fig. 12, schem. 10.

When constructing the structures of the synthesized compounds, we proceeded from an approach associated with the synthesis of hybrid molecules containing structural elements of known natural antibiotics and other biologically active compounds. These molecules particularly were the antibacterial antibiotic ampicillin, the natural antitumor antibiotic sarkomycin and the HIV none-nucleoside reverse transcriptase inhibitor loviride (fig. 1).

The study of 2-phenylproline derivatives is limited due to the small number of available routes for the synthesis of this class of compounds. Methods described in the literature are laborious, rather sensitive to the reaction conditions, and do not provide high yields of target products [1-9].

Our proposed route for the preparation of these compounds includes the synthesis of the corresponding phenylglycine derivatives and intramolecular cyclization under phase transfer catalysis (PTC) conditions.

The most widely used phase-transfer catalysts are quaternary ammonium salts, in particular triethylbenzylammonium chloride (TEBA). According to our proposed method, the intramolecular cyclization reaction

is carried out under mild conditions, that is, under PTC conditions − in acetonitrile, in the presence of K_2CO_3 and the phase transfer catalyst TEBA.

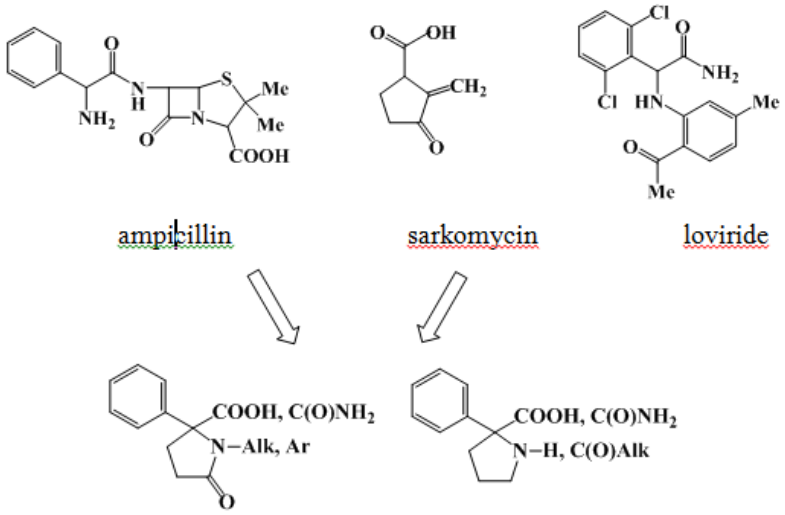


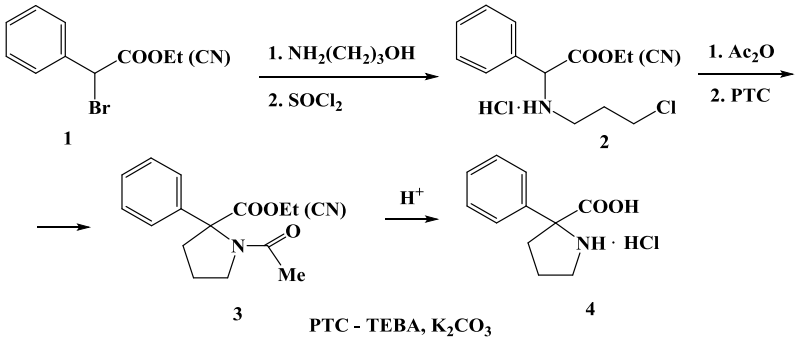
Fig. 1

2-phenylproline derivatives

Synthesis of 2-aryl- and 2-pyrimidinylprolines

Ethyl ester of 2-bromo-2-phenylacetic acid or 2-bromo-2-phenylacetonitrile used as starting materials **1**, which reacted with 1-amino-3-hydroxypropane to give the corresponding aminopropanols, which were further converted into chlorine derivatives **2** using thionyl chloride. Further acylation of these compounds with acetic anhydride to the corresponding acetamido derivatives, followed by intramolecular cyclization under PTC conditions, and acid hydrolysis resulted in prolines **4** in high yields (scheme 1) [10].

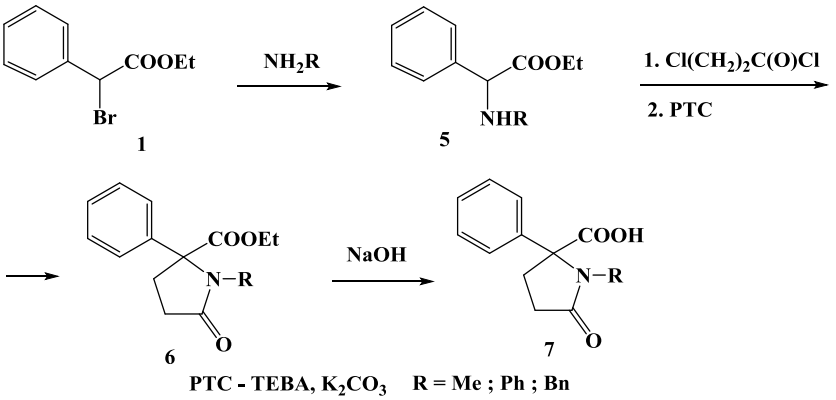
Scheme 1



In order to expand the possibility of using the PTC method, the synthesis of *N*-substituted 2-phenyl-5-oxoprolines was carried out. The ethyl ester of *α*-bromophenylacetic acid **1** is alkylated with diferent amines. Next,

the synthesized compounds **5** were acylated with 3-chloropropanoic acid chloride, followed by intramolecular cyclization under PTC conditions in the presence of the TEBA catalyst. As a result, ethyl esters of N-substituted 5-oxo-2-phenylpyrrolidine-2-carboxylic acids **6** were obtained, further hydrolysis of which with sodium hydroxide in methanol leads to the corresponding carboxylic acids **7** (scheme 2) [11].

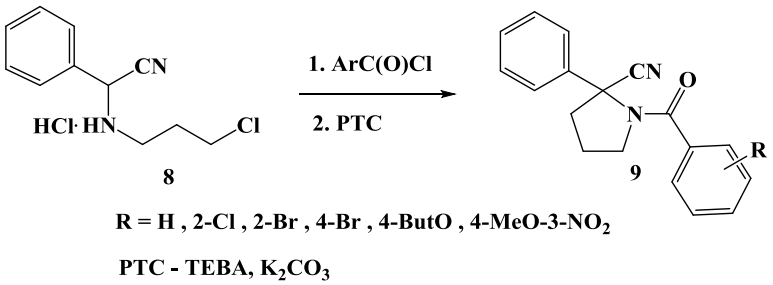
Scheme 2



In order to study biological properties in series of 2-phenylproline derivatives, as well as to reveal the relationship between the chemical structure and biological activity, methods for modifying the pyrrolidine ring were used and synthesis of new derivatives with different pharmacophore groups was carried out.

N-substituted 2-arylpyrrolidinecarbonitriles **9** were synthesized by acylation of 2-(3-chloropropylamino)-2-phenylacetonitrile **8** with substituted benzoic acid chlorides and further intramolecular cyclization under PTC conditions (scheme 3) [12].

Scheme 3

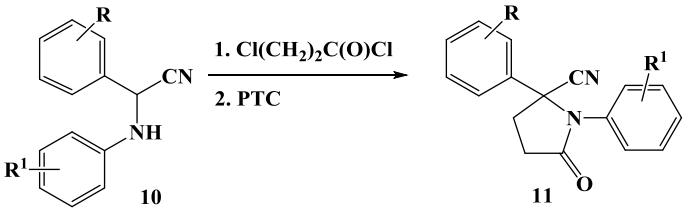


For the synthesis of the next series of 2-phenylproline derivatives, we choose *α*-aminonitriles as starting materials, which were synthesized by one of the main and widely used methods for the synthesis of aminonitriles by

the Strecker reaction − by the interaction of aldehydes with amines in the presence of various cyanide sources.

A number of substituted diferent benzaldehydes were introduced into interaction with aromatic amines in sodium cyanide - acetic acid system. Acylation of the obtained α-aminonitriles **10** with 3-chloropropanoic acid chloride and subsequent intramolecular cyclization under PTC conditions gave *N*-substituted 2-aryl-5-oxopyrrolidine-2-carbonitriles **11** (scheme 4) [12-15].

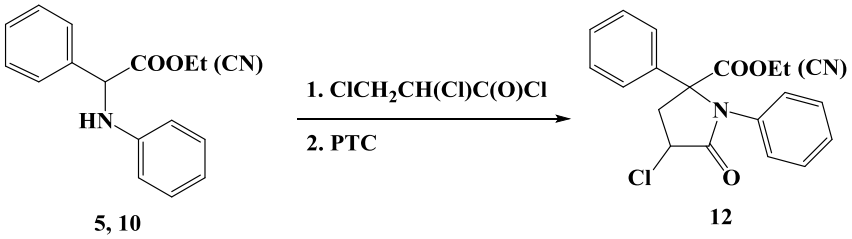
Scheme 4



R = H ; 4-Br ; 2,6-Cl_2 ; 4-MeO ; 3,4-$(MeO)_2$; 4-*iso*-PrO ; 2-OBn ; 4-OBn
R^1 = H ; 2-Me ; 4-Me ; 2-MeO ; 4-MeO ; 3,5-Me_2
PTC - TEBA, K_2CO_3

In the case of interaction of 2-anilino-2-phenylacetic acid ethyl ester **5** or nitrile **10** with α,β-dichloropropanoic acid chloride and subsequent intramolecular cyclization under PTC conditions gave chlorine-containing derivatives, 4-chloropyrrolidones **12** (scheme 5) [16,17].

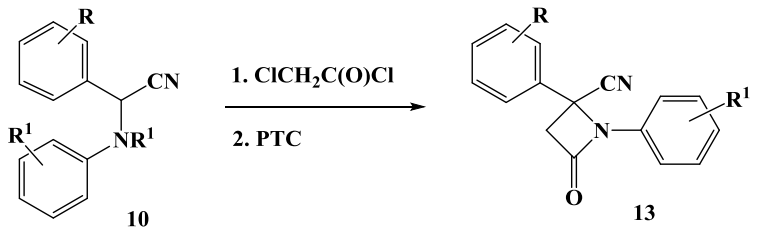
Scheme 5



PTC - TEBA, K_2CO_3

The next task was to study the effect of the size of the lactam cycle on biological activity. In order to reduce the ring size to four, we have carried out syntheses of the corresponding β-lactams – azetidines, with various substituents. The construction of the four-membered ring was realized by using monochloroacetic acid chloride instead of 3-chloropropanoic acid chloride as an acylating agent. Acylation of acetonitriles **10** with the indicated acid chloride and subsequent intramolecular cyclization under PTC conditions gave 2-aryl-4-oxoazetidine-2-carbonitriles **13** (scheme 6) [18].

Scheme 6

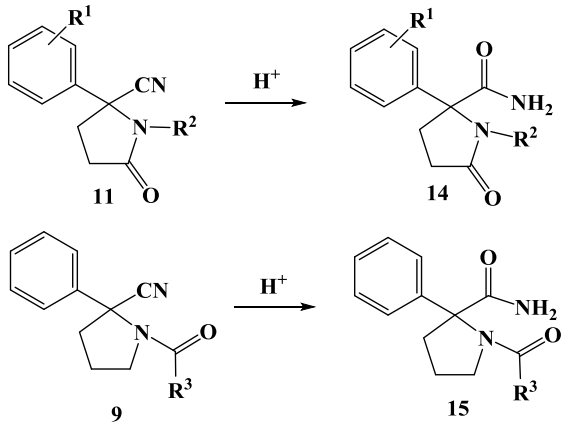


10 13

R = H ; 4-MeO ; 2-OBn ; 4-OBn ; R^1 = H ; 2-Me : 4-Me ; 2-MeO ; 4-MeO ; Bn
PTC - TEBA, K_2CO_3

We have also obtained carboxamide derivatives **14**,**15** of 2-arylpyrrolidines substituted at both phenyl groups. Hydrolysis of the nitrile group of pyrrolidinecarbonitriles without affecting the lactam ring was performed by treating corresponding nitriles **9**,**11** with concentrated sulfuric acid (scheme 7) [14].

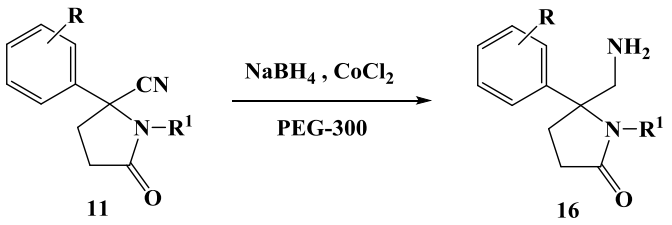
Scheme 7



R^1 = H : 4-Br ; 2,6-Cl_2 . R^2 = Ph ; Bn ; 4-MePh ; 4-MeOPh ; 3,5-Me_2Ph
R^3 = Me ; 2-ClPh ; 2-BrPh ; 4-BrPh ; 4-MeO-3-NO_2Ph

The next goal of our research was the synthesis of 2-aminomethylpyrrolidines **16** by reduction of the nitrile group in 2-arylpyrrolidinecarbonitrile **11** molecules. We have developed a new method for the selective reduction of nitrile group, in which a catalytic metal complex system was used. Advantages of this method are the reduction of only the nitrile group and the use of small amounts of metal complex salt and sodium borohydride. The optimal ratio of reagents are shown (scheme 8) [19,20].

Scheme 8



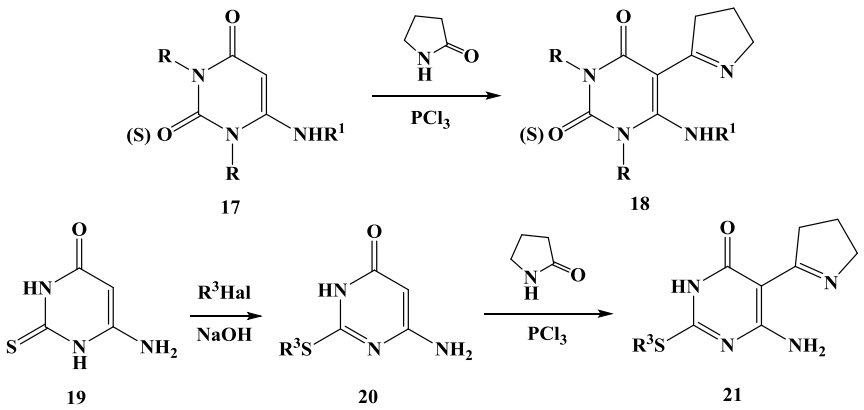
R = H ; 2,6-Cl_2 ; 3,4-$(MeO)_2$; 4-*iso*-PrO

R^1 = Ph ; Bn ; 4-MePh ; 3,5-Me_2Ph ; 2-OBn ; 4-OBn

pyrrolidinecarbonitrile : $CoCl_2$: PEG-300 : $NaBH_4$ - 1 : 0.2 : 1 : 5

Next, we synthesized proline pyrimidinyl derivatives by combining pyrimidine molecules with the pyrrolidinone pharmacophore cycle. A method has been developed for the condensation of pyrolidinones with 6-aminopyrimidine derivatives under Vilsmeier reaction conditions. The interaction of corresponding 6-aminopyrimidines **17** with pyrrolidinone in the presence of phosphorous threechloride synthesized 6-amino-5-(pyrrolyl) pyrimidinones **18**, which are pyrimidine analogs of *C*-azanucleosides. Similarly, 2-mercapto-substituted **17**,**19** pyrimidines were reacted with a pyrolidinone under conditions already described, leading to the formation of *C*-azanucleoside analogues **18**,**21** substituted at various positions of the pyrimidine ring (scheme 9) [21-23].

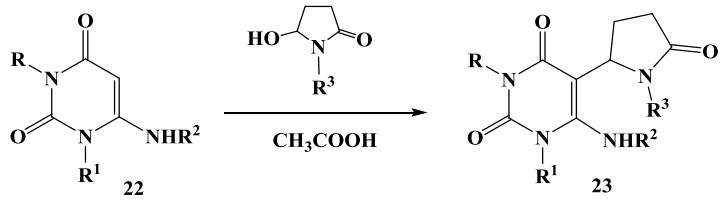
Scheme 9



R = H ; Me ; R^1 = H ; Me ; Bn ; $(CH_2)_3$Ph ; R^2 = H ; Ph ; 3,5-Me_2Ph ; R^3 = Pr ; Bn

Another method for the synthesis of pyrrolinylpyrimidine derivatives **23** is the reaction of *N*-substituted 5-hydroxypyrrolidinones with various pyrimidine derivatives **22** when heated in glacial acetic acid (scheme 10) [23].

Scheme 10



R = H ; Me ; R^1 = H ; Me ; Bn ; R^2 = H ; 3,5-$(MeO)_2$Ph ; R^3 = Bn ; 4-MeOPh

Thus, we have carried out the synthesis of new analogues and derivatives of pyrrolidines substituted at various positions of the ring (fig. 2).

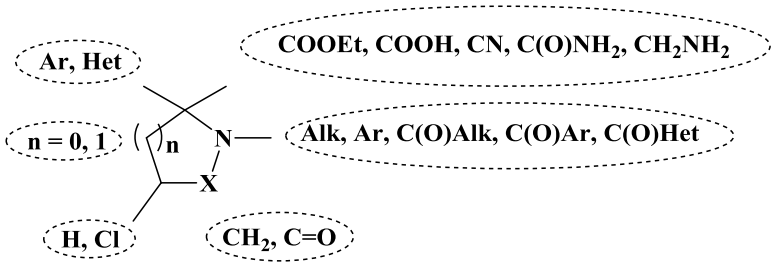


Fig. 2

Biological properties of synthesized compounds

The pyrrolidine ring is an important structural moiety of many biologically active compounds. In order to find antibacterial, antitumor and antiviral (anti-HIV) drugs among proline analogues, biological studies of synthesized 2-aryl- and 2-pyrimidinylproline derivatives were carried out, the structure-activity relationship was studied and the fragments responsible for the activity were identified.

Antibacterial activity

Antibacterial properties of the synthesized compounds were carried out at the "Laboratory of Chemotherapy and Toxicology" of the Institute of Fine Organic Chemistry of the Scientific and Tecnological Center of Organic and Pharmaceutical Chemistry NAS RA. In experiments were used follow microorganisms – *St. aureus* 209p, *St. aureus* 1, *Shigella dysenteriae Flexneri* 6858, and *Echerichia Coli 055*.

Among 2-arylpyrrolidines, 2-aminomethyl-1,2-diarylpyrrolidin-5-ones have a pronounced activity, some of which inhibit the growth of all used

microorganisms in a zone with a diameter of 20-25 *mm*, and the remaining 2-aminomethyl derivatives - of medium activity - with a diameter of 18-20 *mm*.

2-Phenylpyrrolidine-2-carboxylic acids showed average activity d = 17–19 *mm*. Derivatives containing 1,2-diaryl-5-oxo- and 1-aroyl-2-phenylpyrolidinecarbonitrile and carboxamide groups also possess weak antibacterial activity (d = 10-14 *mm*) (fig. 3) [11,13,24].

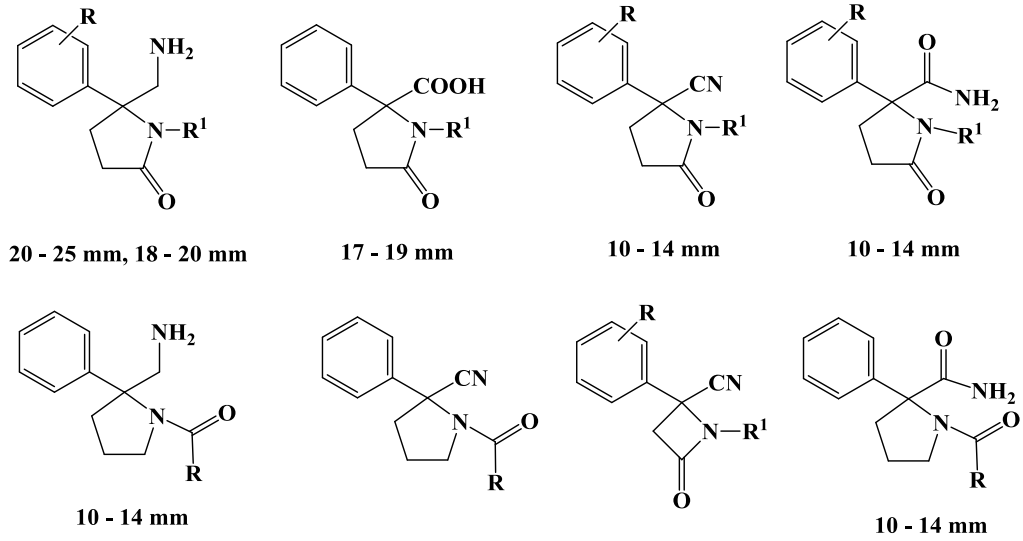


Fig. 3

Among 2-pyrimidinylprolines, one compound suppressed the growth of all used microorganisms in the 15-19 *mm* diameter zone, the rest did not show antibacterial activity (fig. 4).

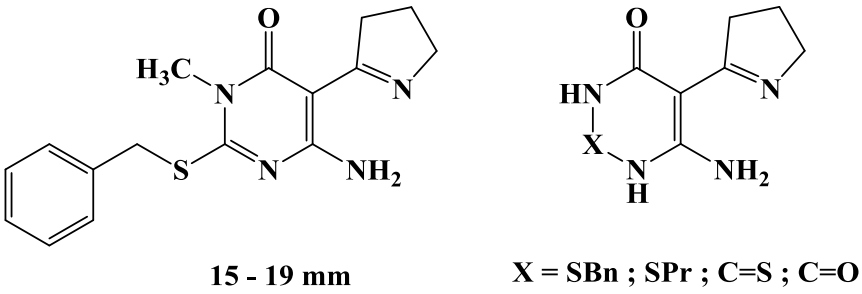


Fig. 4

Summarizing the results of studying the antibacterial properties of the studied compounds, we can highlight certain patterns of the relationship between the chemical structure and antibacterial activity:

- 1,2-Diaryl-5-oxopyrrolidines are relatively more active than 1-aroyl-2-phenylpyrolidines
- In contrast to 5-membered cyclic compounds − pyrrolidines, 4-membered cyclic derivatives − azetidines are little or no activity
- Me-, *iso*-PrO- and BnO- substituents in aryl fragments of 1-st and 2-nd positions of the pyrrolidine ring contribute to increased activity
- Among 2-arylpyrrolidines containing carboxamide-, nitrile-, carboxy- and aminomethyl- groups, an increase in antibacterial activity was observed in the following order of substituents:
- $C(O)NH_2 < CN < COOH < CH_2NH_2$
- Among pyrimidinylprolines containing oxo-, thiooxo-, propylthio- and benzylthio- groups, an increase in antibacterial activity was observed in the following arrangement of substituents:
- $C=O < C=S < PrS < BnS$.

Antitumor activity

Biological studies of antitumor properties of synthesized compounds were carried out at the "Laboratory of Chemotherapy and Toxicology" of the Institute of Fine Organic Chemistry of the Scientific and Tecnological Center of Organic and Pharmaceutical Chemistry NAS RA. Antitumor activity was studied in mice with transplanted tumors sarcoma − 37, sarcoma − 180 and Ehrlich's ascitic carcinoma. Some of more active compounds have been tested in rats with sarcoma − 45.

Studies have shown that 2-phenylpyrrolidinecarboxylic acids are practically non-toxic (LD_{100} 3000 and 4000 *mg/kg*) compounds and exhibit antitumor activity against sarcomas 45 and 37, suppressing their growth 42 – 49% (fig. 5) [13].

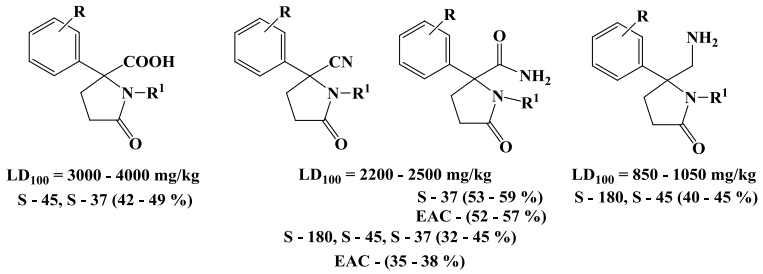


Fig. 5

Derivatives of 2-arylpyrrolidinecarbonitriles and 2-arylpyrrolidinecarboxamides have low toxicity (LD_{100} = 2200-2500 *mg/kg*). Carboxamide derivatives from this series suppress the growth of sarcoma 37 by 59 and 53% and extend the average lifespan of mice by 52-57%. The remaining compounds show a weak effect on the growth of all type sarcomas.

2-Aminomethyl-1,2-diarylpyrrolidines suppress tumor growth against sarcomas 45 and 180 by 40-45%, but are toxic (850-1050 *mg/kg*) compounds. 2-Pyrimidinylproline derivatives exhibit weak antitumor properties.

Summarizing results of the antitumor properties of studied compounds, some patterns of the relationship between the chemical structure and antitumor activity can be distinguished:

- Here too, 1,2-diaryl-5-oxopyrrolidines, as in antibacterial studies, are more active than 1-aroyl-2-phenylpyrrolidines
- Among compounds containing aminomethyl-, nitrile-, carboxamide- and acid- groups, an increase in antitumor activity was observed in the following sequence of agents:
- $CH_2NH_2 \leq CN < C(O)NH_2 < COOH$.

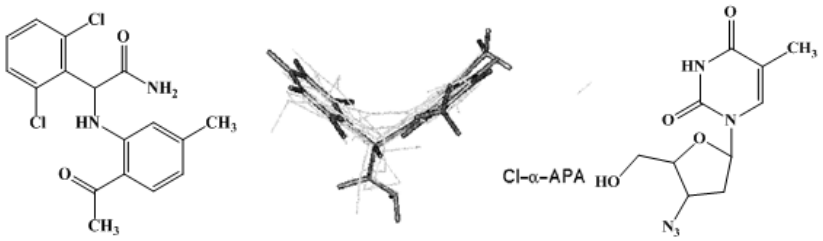
Anti-HIV studies

First, a little about current approaches to HIV drug discovery. The problem of drug therapy against the human immunodeficiency virus is to affect one or more stages of the life stages of virus reproduction with the help of chemical compounds with a certain structure. One prime target is the enzyme reverse transcriptase. Reverse transcriptase inhibitors interact with chemical groups of the active center of the enzyme, block its activity.

Loviride and its derivatives belong to the group of non-nucleoside reverse transcriptase inhibitors (NNRTIs). 2-Arylpyrrolidines synthesized by us are the cyclic derivatives of the latter. According to crystallographic studies, compounds of the NNRTIs class, whose structure is visibly similar to the "butterfly" conformation, show effective inhibition of reverse transcriptase enzyme (fig. 6).

X-ray structural studies of a number of synthesized 2-arylpyrrolidine derivatives were performed, in which structures of molecules are visibly similar to the "butterfly" conformation.

On the other hand, nucleoside reverse transcriptase inhibitors (NRTIs) - are known and widely used. One of drugs in this group was the 3'-azido-2',3'-dideoxythymidine (AZT), which is a derivative of the pyrimidine nucleoside thymidine (slide XXX). In this sense, 2-pyrimidinylprolines synthesized by us can be considered as C-azanucleosides (fig. 6).



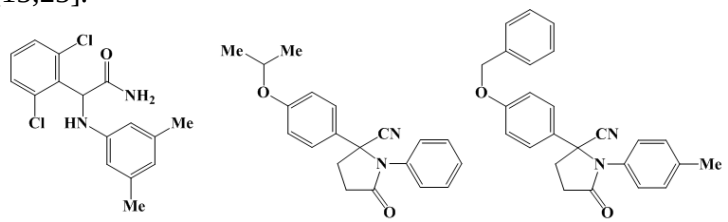
Loviride — "butterfly" conformation — AZT

NNRTIs inhibitor — NRTIs inhibitor

Fig. 6

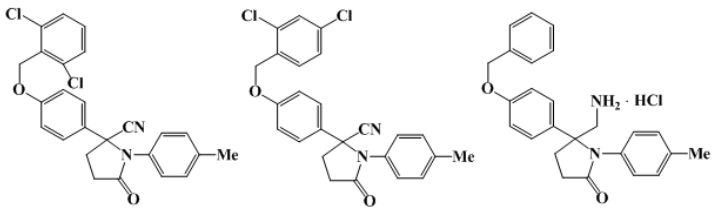
Biological studies on anti-HIV activity were carried out at laboratories of "Biochemical Pharmacology" of the Center for AIDS Research and Emory University School of Medicine (USA). Compounds were evaluated for their potential toxic effects on uninfected PHA-stimulated human PBM cells, in CEM (T-lymphoblastoid cell line) and Vero (African green monkey kidney) cells.

As a result of anti-HIV studies, it was found that 20 of the tested compounds show good activity and their effective concentration EC_{50} < 20 *μM*, but the aforementioned compounds are inferior in their activity to the control drug AZT. Some of the most active compounds are demonstrated in fig. 7-9 [15,25].



EC_{50} = 0.43 *μM* — EC_{50} = 5.2 *μM* — EC_{50} = 16.7 *μM*

Fig 7



EC_{50} = 2.0 *μM* — EC_{50} = 5.3 *μM* — EC_{50} = 10.8 *μM*

Fig 8

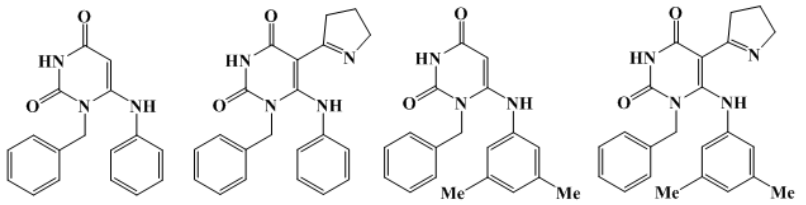


Fig 9

The NNRTIs inhibitor molecule must correspond to the spatial relief of the active site of the enzyme and the nature of the chemical groups. According to the molecular docking data, two examples of molecules of active compounds in the active center of the reverse transcriptase enzyme are shown (fig. 10,11).

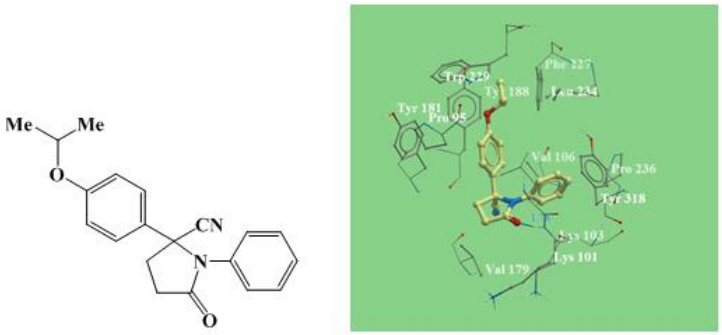


Fig. 10

Molecules in the active center of the enzyme

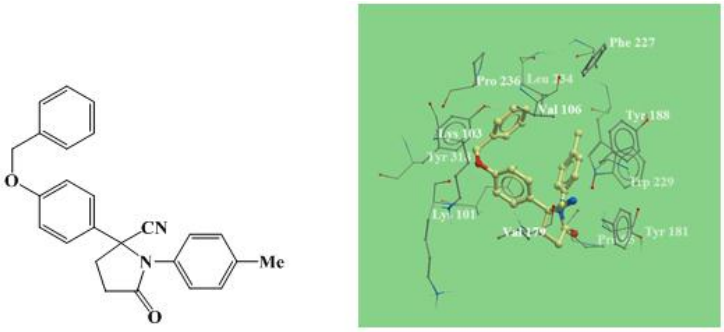
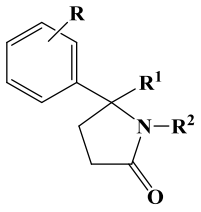


Fig. 11

Summarizing results of the investigation of antiviral properties of the studied compounds, some patterns of the relationship between the chemical structure and anti-HIV activity:

- Among derivatives of 2-arylpyrrolidines, the presence of methyl group in 4- or 3,5-positions of the aryl fragment of the 1-st position of the pyrrolidine ring, as well as the presence of benzyloxy- and isopropoxy- groups in the aryl fragment of the 2-nd position of the pyrolidine ring increase anti-HIV activity
- Among compounds containing nitrile-, aminomethyl- and carboxamide- groups, an increase in anti-HIV activity was observed in the following order of substituents:
- $C(O)NH_2 < CH_2NH_2 < CN$
- In series of 2-pyrimidinylpyrrolidines, the best results were demonstrated by derivatives, in whose structures the presence of a benzyl fragment in the 1-st position, an aniline fragment in the 6-th position, and a pyrrolidine fragment in the 5-th position of the pyrimidine ring play a huge role in the manifestation of anti-HIV activity, the latter modification leads to a sharp increase in the biological activity of compounds.

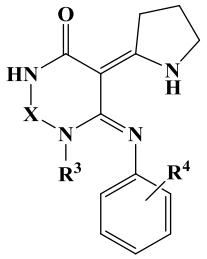
Summarizing results of all biological studies of synthesized 2-aryl- and 2-pyrimidinylprolines, we can state following (fig. 12).



antibacterial activity - R = *i*-PrO, BnO
$R^1 = CH_2NH_2$
R^2 = 4-MePh, 3,5-Me_2Ph

antitumor activity - $R^1 = COOH, C(O)NH_2$

anti-HIV activity - R = *i*-PrO, BnO
R^1 = CN
R^2 = 4-MePh, 3,5-Me_2Ph



anti-HIV activity - R^3 = Bn
R^4 = H; 3,5-Me_2
X - C=O

Fig. 12

ՆՈՐ 2-ԱՐԻԼ- ԵՎ 2-ՊԻՐԻՄԻԴԻՆԻԼՊՐՈԼԻՆՆԵՐԻ ՍԻՆԹԵԶԸ ԵՎ ԿԵՆՍԱԲԱՆԱԿԱՆ ՀԱՏԿՈՒԹՅՈՒՆՆԵՐԸ

Ս. Պ. ԳԱՍՊԱՐՅԱՆ, Մ. Վ. ԱԼԵՔՍԱՆՅԱՆ

Ակնարկը նվիրված է 2-արիլ- և 2-պիրիմիդինիլպրոլինների սինթեզի նոր մատչելի եղանակների մշակմանը, կենսաբանական հատկությունների ուսումնասիրությանը և քիմիական կառուցվածքի ու կենսաբանական ակտիվության միջև կապի բացահայտմանը:

СИНТЕЗ И БИОЛОГИЧЕСКИЕ СВОЙСТВА НОВЫХ 2-АРИЛ- И 2-ПИРИМИДИНИЛПРОЛИНОВ

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В обзоре представлены разработки новых доступных методов синтеза замещенных 2-арил- и 2-пиримидинилпролинов, исследование биологических свойств и установление связи между химическим строением и биологической активностью.

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