

Synthesis, chemical transformations and biological evaluation of aryl- and pyrimidinylpyrrolidine derivatives

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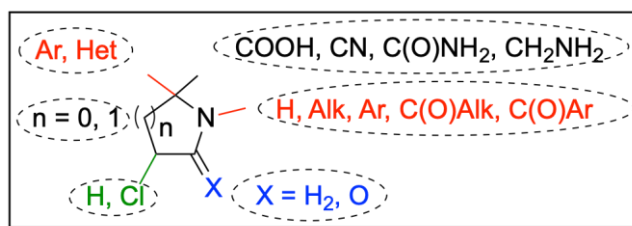
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Abstract

Taking into account the still insufficient knowledge of the chemistry and biology of arylpyrrolidine derivatives, this review reports the development of new and facile methods for the synthesis of 2-aryl- and 5-pyrimidinylpyrrolidines containing various pharmacophoric groups, the study of their antibacterial, antitumor and anti-HIV properties, as well as the identification of the relationship between chemical structure and biological activity and those structural fragments that play a major role in this context.



Keywords: Nitrogen heterocycles; pyrrolidines; azanucleosides; structure activity relationship investigations

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1. Introduction

Since cyclic derivatives of γ -aminobutyric acid – pyrrolidinones have a wide spectrum of biological activity, further research and synthesis of derivatives led to the production of pyrrolidone-2-acetamides (piracetams) – a representative of a new group of psychotropic drugs – “nootropics”.^{1,2} In the 1980s, two drugs came into use as antihypertensive (cardiovascular) agents: captopril and enalapril.³ Other known drugs in the series of pyrrolidine derivatives include lincomycin, isolated from the culture fluids of *S. lincolnensis*, and its semi-synthetic derivative, clindamycin. They are a modified amino acid condensed with a complex amino sugar and exhibit antibacterial activity, suppressing protein synthesis in gram-positive and anaerobic bacteria (Figure 1).⁴

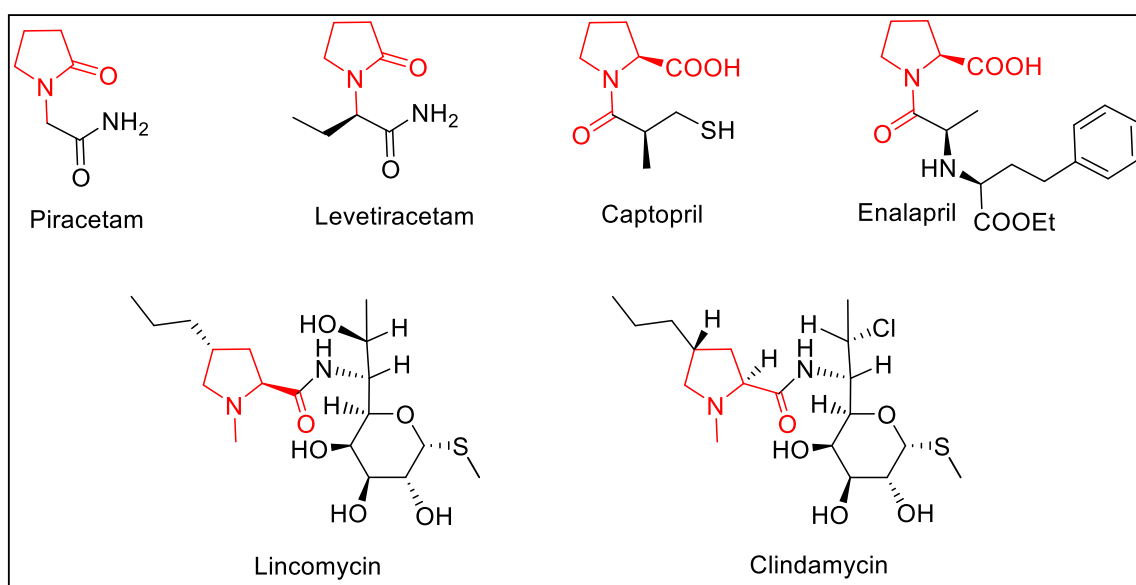


Figure 1. Cyclic derivatives of γ -aminobutyric acid.

Various natural and synthetic monocyclic γ -lactams are known, which, depending on the nature of the substituents of the pyrrolidine ring, exhibit potent analgesic,^{5,6} adrenolytic,⁷ antitumor^{8,9} and antituberculosis activity.¹⁰ The literature also contains reports on the identification and study in vitro of the inhibitory activity of substituted pyrrolidines in relation to dipeptidyl peptidase IV (DPP-IV)^{11,12} and prolyl oligopeptidase (POP).¹³ A number of analogues are anti-HIV-1 agents,¹⁴ and some exhibit inhibitory properties against the hepatitis C virus.¹⁵

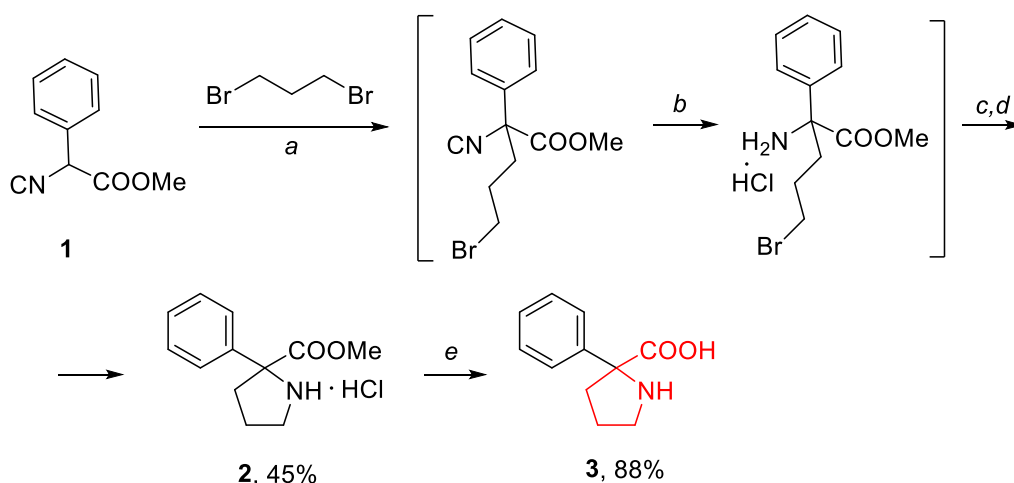
Taking into account the insufficient study of the chemistry and biology of 2-phenylproline analogues, in this work we present the developments of facile methods for the synthesis of 2-aryl- or 5-aryl- and 5-pyrimidinyl-pyrrolidines, the studies of their biological properties and the identification of the relationship between chemical structure and biological activity.

2. Synthesis of New 2-Arylpyrrolidine Derivatives via Intramolecular Cyclization and Their Biological Properties

2.1. Synthesis of new 2-phenylproline derivatives

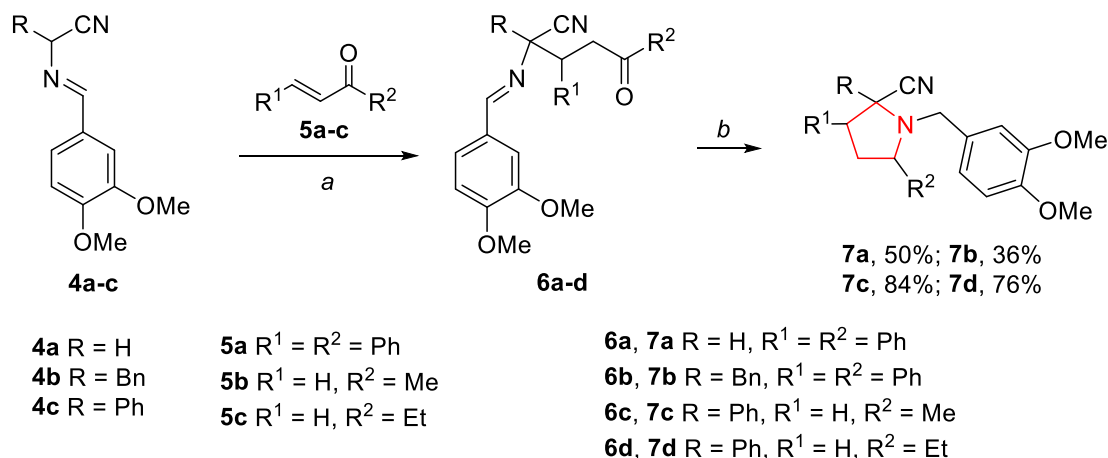
The study of 2-phenylproline derivatives is limited due to the small number of available routes for the synthesis of this class of compounds. The methods described in the literature are labor-intensive, rather sensitive to the reaction conditions, and do not provide high yields of the target products. Early and later strategies used intramolecular cyclization to create the pyrrolidine ring, so only approaches based on intramolecular cyclization will be discussed here.

In the work of Yasuo et al.,¹⁶ the synthesis of 2-phenylproline (**3**) was carried out by the reaction of methyl α -isocyanoacetate **1** with alkyl dibromide in the presence of sodium hydride (Scheme 1).



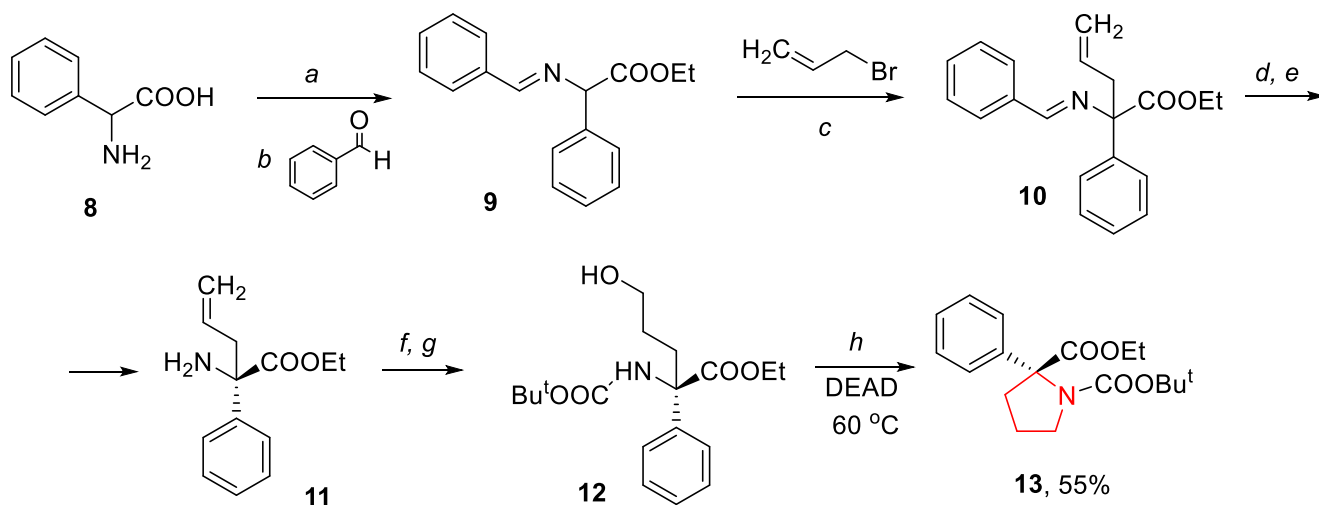
Scheme 1. Synthesis of 2-phenylproline (**1**). Reagents and conditions: *a* NaH/THF, 25 °C, 1 h; *b* MeOH/conc. HCl, 5–10 °C, 18 h; *c* Et₃N/THF, reflux, 1 h; *d* 10% HCl–MeOH; *e* 10% EtOH solution of NaOH, reflux, 30 min.

Meyer et al. synthesized polysubstituted pyrrolidines starting from α -aminonitriles **4a–c**, α -deprotonation of which with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) yielded stable carbanions. Further addition to α,β -unsaturated carbonyl compounds **5a–c** and reductive cyclization with sodium cyanoborohydride (NaBH₃CN) yielded polysubstituted pyrrolidines **7a–e** (Scheme 2).¹⁷



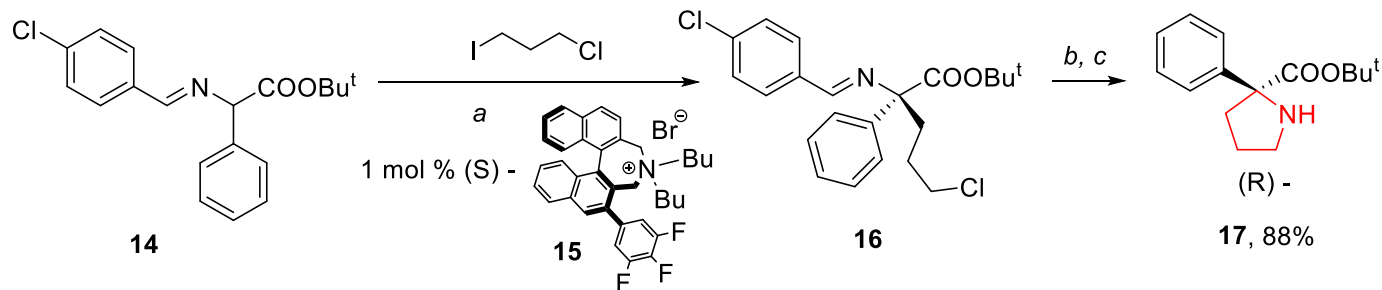
Scheme 2. Synthesis of polysubstituted pyrrolidines (**7a-d**). Reagents and conditions: *a* DBU/THF, under argon, r. t., monitored by TLC; *b* NaBH₃CN/EtOH/AcOH, under argon, 0 °C to reach r. t., overnight.

In the study by Betsbrugge et al., Boc-(*R*)- α -phenylproline ethyl ester **13** was synthesized using the Mitsunobu cyclization. Condensation of phenylglycine ethyl ester **8** with benzaldehyde, allylation under phase-transfer catalysis followed by acid hydrolysis and reaction with pig liver esterase (PLE) enzyme led to α -allylphenylglycine ethyl ester **10**. Further Boc protection, hydroboration and oxidation of the double bond, cyclization with triphenylphosphine and diethyl azodicarboxylate (DEAD) yielded the target product **13** in 55% yield (Scheme 3).¹⁸



Scheme 3. Synthesis of Boc-(*R*)- α -phenylproline ethyl ester (**13**). Reagents and conditions: *a* EtOH /gas. HCl, 0 °C, overnight, 1 h; *b* Na₂SO₄/Et₃N/CH₂Cl₂, warming up, 30 min; *c* Bu₄NHSO₄/10N NaOH/CH₂Cl₂, r. t., 4 h; *d* Et₂O/1N HCl, overnight; *e* 0.05M KH₂PO₄/PLE, 28 °C, monitored by TLC; *f* K₂CO₃/Boc₂O/dioxan-water:3:1, r. t., 4 h; *g* BH₃·Me₂S /NaOH/30% H₂O₂/THF, 0 °C to reach r. t., 1 h; *h* PPh₃/DEAD/THF, reflux, 2 h.

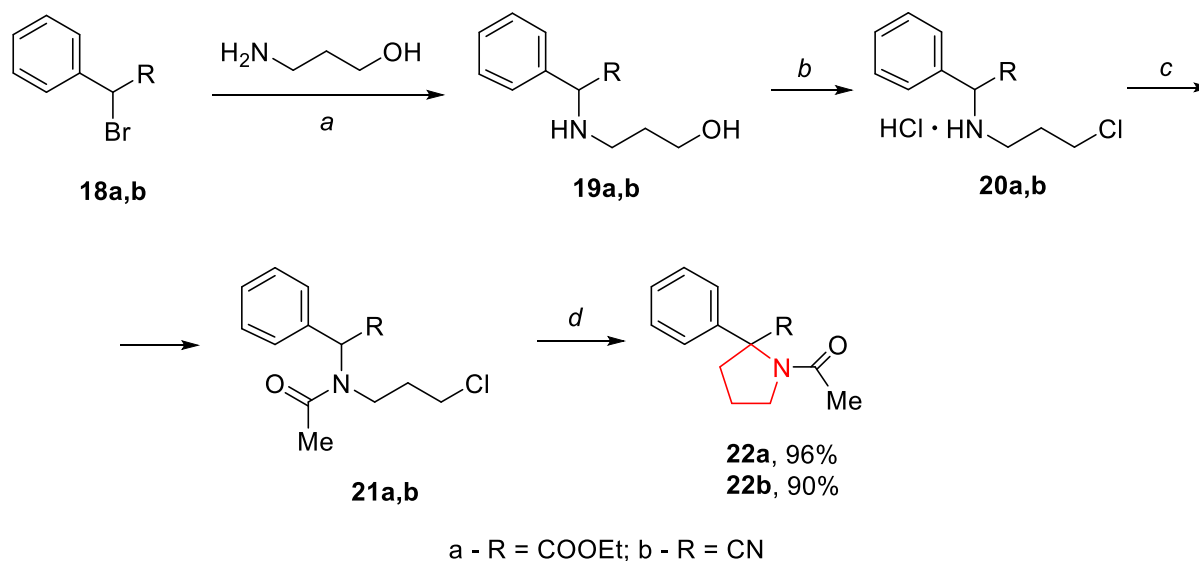
Kano et al., by asymmetric phase-interphase C-alkylation of an α -substituted amino acid derivative **14** using cesium hydroxide and a chiral phase-interphase catalyst **15** and subsequent intramolecular *N*-alkylation, carried out a catalytic asymmetric synthesis of 2-phenylproline **17** (Scheme 4).¹⁹



Scheme 4. Synthesis of 2-phenylproline (**17**). Reagents and conditions: *a* CsOH · H₂O/toluene, under argon, 0 °C, 8 h; *b* 1N HCl/EtOAc, r. t., 1 h; *c* Na₂CO₃/H₂O, r. t., 2 h.

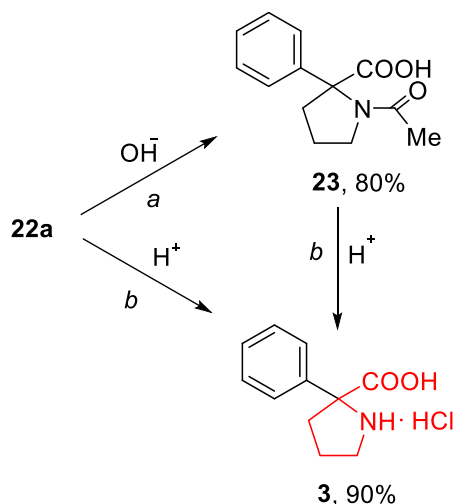
In 2000, we started research on the synthesis of various 2-phenylproline derivatives and studied their biological properties. We have developed and proposed another way of obtaining such compounds, which included the synthesis of the corresponding phenylglycine derivatives and intramolecular cyclization under phase-transfer catalysis (PTC) conditions. Given that quaternary ammonium salts, in particular triethylbenzylammonium chloride (TEBA), are the most widely used phase-transfer catalysts, the intramolecular cyclization reaction was carried out under mild conditions, in acetonitrile in the presence of K₂CO₃ and the TEBA phase-transfer catalyst.

Treatment of ethyl 2-bromo-2-phenylacetate (**18a**) or 2-bromo-2-phenylacetonitrile (**18b**) with 1-amino-3-hydroxypropane yielded aminopropanols **19a,b**, which were then converted into chloro derivatives **20a,b** using SOCl₂. Acylation of compounds **20a,b** to the corresponding acetamido derivatives **21a,b**, further intramolecular cyclization of which under PTC conditions led to prolines **22a, 22b** in high yields (Scheme 5).²⁰



Scheme 5. Synthesis of 2-phenylprolines (**22a,b**). Reagents and conditions: *a* K₂CO₃/CHCl₃, 40-45 °C, 2 h; *b* SOCl₂/CHCl₃, 50 °C, 3 h; *c* AcONa/Ac₂O, steam bath, 4 h; *d* CH₃CN/TEBA/K₂CO₃, 45-50 °C, 4 h.

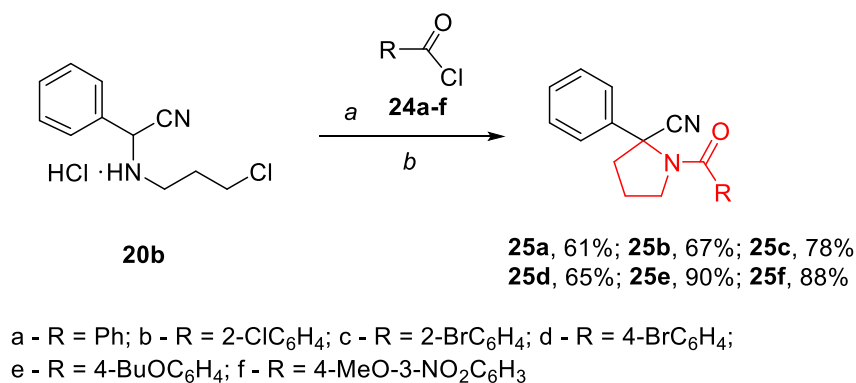
Subsequent alkaline or acidic hydrolysis and simultaneously occurring deacetylation of compound **30a** led to the synthesis of carboxylic acids **23** and **3** (Scheme 6).²⁰



Scheme 6. Synthesis of 2-phenylproline carboxylic acid (**3**). Reagents and conditions: *a* NaOH/MeOH, reflux, 4 h; *b* 5% HCl, reflux, 4 h.

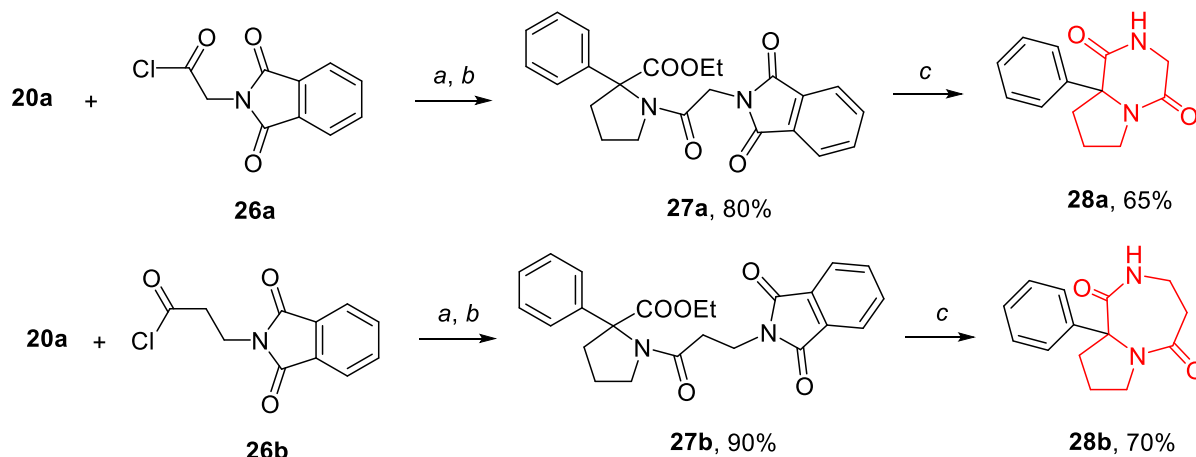
In order to study the biological properties of a series of 2-phenylproline derivatives, as well as to identify patterns of relationships between chemical structure and biological activity, further studies used methods of modifying the pyrrolidine ring and synthesized new derivatives with different pharmacophoric groups.

By acylation of 2-(3-chloropropylamino)-2-phenylacetonitrile hydrochloride (**20b**) with substituted benzoic acid chlorides **24a-f** and intramolecular cyclization using the method we developed in PTC with the presence of TEBA, new *N*-substituted 2-arylpyrrolidine-2-carbonitriles **25a-f** were synthesized in good yields (61-90%) (Scheme 7).^{21, 22}



Scheme 7. Synthesis of compounds (**25a-f**). Reagents and conditions: *a* K₂CO₃/1,2-dichloroethane, 10-15 °C to reach r. t., 30 min, then 40-45 °C, 2 h; *b* CH₃CN/TEBA/K₂CO₃, 45-50 °C, 4 h.

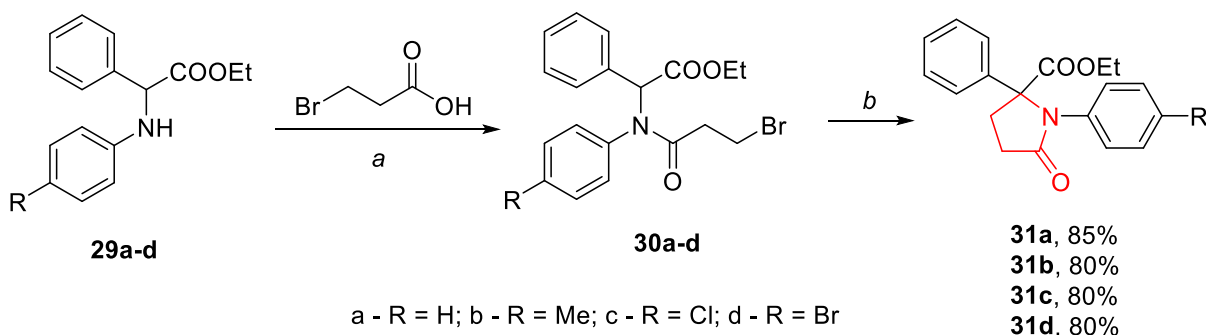
In continuation of the studies, the synthesis of phenyl-substituted derivatives of pyrazine **28a** and diazepine-1,5-diones **28b** was carried out. Acylation of ethyl ester of 2-(3-chloropropylamino)-2-phenylacetic acid (**20a**) with 2-(1,3-dioxoisindolin-2-yl)acetyl chloride (**26a**) and 3-(1,3-dioxoisindolin-2-yl)propanoyl chloride (**26b**) in the presence of K₂CO₃ and subsequent intramolecular cyclization in the presence of TEBA led to ethyl esters **27a,b**. Further interaction of esters **27a,b** with hydrazine hydrate proceeds with subsequent intramolecular cyclization to form 8*a*-phenylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**28a**) and 9*a*-phenylperhydropyrrolo[1,2-*a*][1,4]diazepine-1,5-dione (**28b**) in yields of 65% and 70%, respectively (Scheme 8).²³



Scheme 8. Synthesis of compounds (**28a**) and (**28b**). Reagents and conditions: *a* K_2CO_3 /1,2-dichloroethane, 10–15 °C to reach r. t., 30 min, then 40–45 °C, 2 h; *b* CH_3CN /TEBA/ K_2CO_3 , 45–50 °C, 4 h; *c* NH_2NH_2 /EtOH, steam bath, 2 h.

2.2. Synthesis of new 2-arylpyrrolidinone derivatives

The first mention of 2-aryl-5-oxopyrrolidines in the literature appeared in the late 1960s in the work of Chatterjee et al.,²⁴ where the synthesis was carried out starting from ethyl 2-phenyl-2-arylaminoacetates **29a–d**, the interaction of which with 2-bromopropanoic acid in the presence of PCl_3 and subsequent intramolecular cyclization in the presence of a 10% alcoholic solution of KOH led to the production of the corresponding ethyl esters of 5-oxo-2-phenyl-1-arylpyrrolidine-2-carboxylic acids **31a–d** (Scheme 9).



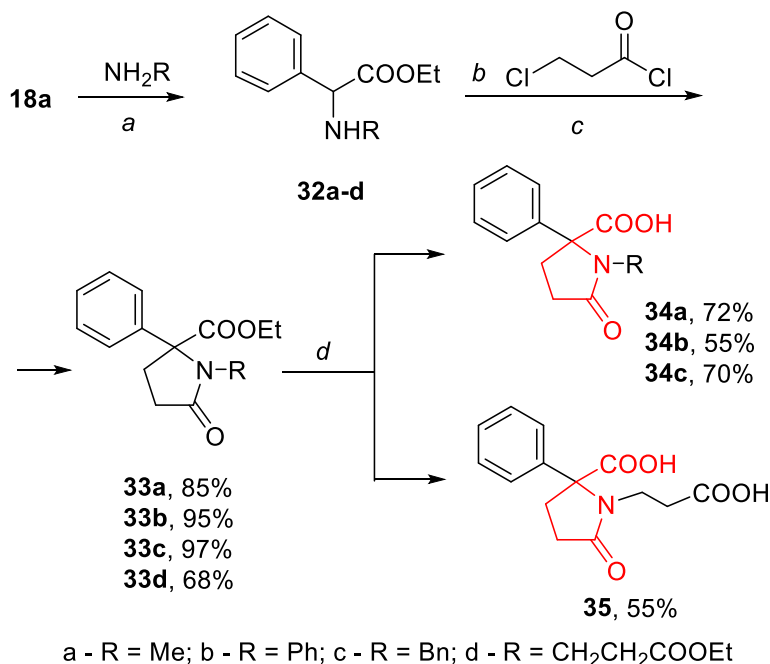
Scheme 9. Synthesis of compounds (**31a–d**). Reagents and conditions: *a* PCl_3 /benzene, reflux, 4 h; *b* 10% EtOH solution of KOH, r. t.

They also investigated the intramolecular cyclization reaction of aryl-substituted amino derivatives in the presence of another base – triethylamine. However, under the indicated conditions, only one compound was obtained – ethyl 5-oxo-2-(4-nitrophenyl)-1-phenylpyrrolidine-2-carboxylate with a 95% yield. The remaining β -bromopropanoyl amides underwent dehydrobromination with the formation of acrylyl amides.²⁵

Martin et al. carried out a similar cyclization using sodium alkoxide,²⁶ and Anderson et al. carried out the cyclization reaction using sodium hydride, but a mixture of 4-oxo-2-phenyl-2-azetidine- and 5-oxo-2-phenyl-2-pyrrolidinecarbonitriles was obtained in yields of 14% and 41%.²⁷

In order to expand the applicability of the PTC method, the synthesis of *N*-substituted 2-phenyl-5-oxoproline **33a–35** was carried out by us. The ethyl ester of α -bromophenylacetic acid (**18a**) was alkylated with methylamine, aniline, benzylamine, and the ethyl ester of β -alanine. Compounds **32a–d** were then acylated with

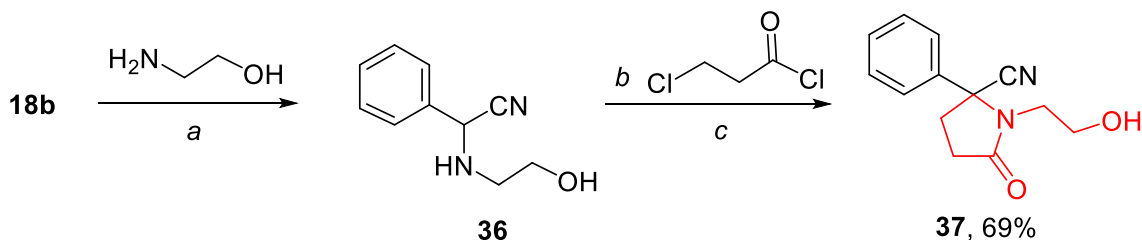
3-chloropropanoyl chloride, followed by intramolecular cyclization under PTC conditions in the presence of the TEBA catalyst. As a result, ethyl esters of *N*-substituted 5-oxo-2-phenylpyrrolidine-2-carboxylic acids **33a-d** were obtained, further hydrolysis of which with an alcoholic NaOH solution leads to carboxylic acids **34a-c**, **35** (Scheme 10).^{20, 28}



Scheme 10. Synthesis of carboxylic acids (**34a-c**, **35**). Reagents and conditions: *a* K₂CO₃/CHCl₃, 40-45 °C, 2 h; *b* K₂CO₃/acetone, 0-5 °C to reach r. t., 2 h; *c* CH₃CN/TEBA/K₂CO₃, 45-50 °C, 4 h; *d* NaOH/MeOH, reflux, 4 h.

It should be noted that the target ethyl esters of 5-oxo-2-phenylpyrrolidine-2-carboxylic acids **33a-c** are obtained in high yields (85-97%) and only in the case of compound **33d** the yield was only 68%. Thus, we have developed a straightforward and effective method for the synthesis of 2-phenylpyrrolidine derivatives under PTC conditions, which was successfully used in subsequent syntheses.

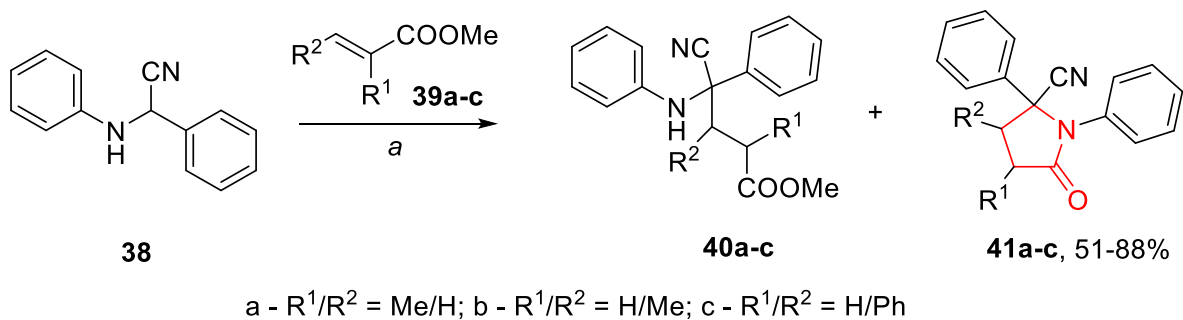
According to a similar synthetic scheme used in the synthesis of aminopropanol **19b**, the aminoethanol derivative **36** was obtained by aminolysis of α -bromophenylacetonitrile (**18b**) with 1-amino-2-hydroxyethane. Acylation of the intermediate 2-hydroxyethylamino derivative **36** with 3-chloropropanoyl chloride and subsequent intramolecular cyclization under the above-described conditions yielded 1-(2-hydroxyethyl)-5-oxo-2-phenylpyrrolidine-2-carbonitrile (**37**) in 69% yield (Scheme 11).²⁸



Scheme 11. Synthesis of compound (**37**). Reagents and conditions: *a* K₂CO₃/CHCl₃, 40-45 °C, 2 h; *b* K₂CO₃/acetone, 0-5 °C to reach r. t., 2 h; *c* CH₃CN/TEBA/K₂CO₃, 45-50 °C, 4 h.

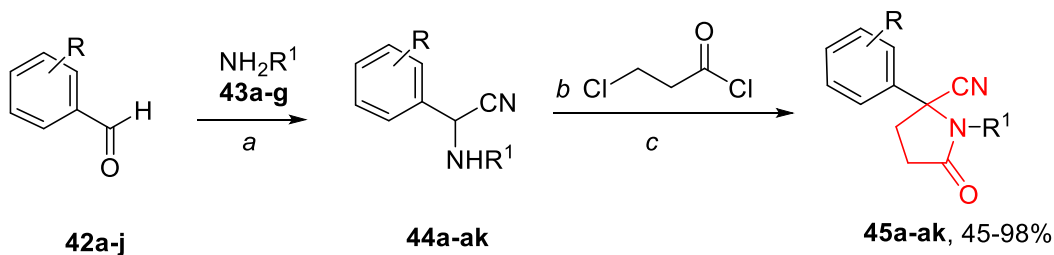
As starting materials in the synthesis of 2-arylpyrrolidinone derivatives α -aminonitriles were used, which are very useful precursors for the synthesis of various nitrogen-containing heterocycles. The Strecker reaction is one of the most efficient and straightforward methods for the synthesis of α -aminonitriles and it is generally carried out by the interaction of aldehydes or ketones with amines in the presence of various cyanide sources using different Lewis acid or Lewis base catalysts.^{29, 30}

N-Aryl-substituted pyrrolidine derivatives **41a-c** were synthesized by Z.-Y. He et al. via tributylphosphine (PBU₃) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed sequential Michael addition reaction of α -aminonitrile **38** and methyl acrylates **39a-c** as starting materials (Scheme 12).³¹



Scheme 12. Synthesis of *N*-aryl-substituted pyrrolidine derivatives (**41a-c**). Reagents and conditions: *a* PBU₃ (10 mol%) or DBU (20 mol%) /CH₃CN, under argon, 30-80 °C, 4-12 h.

To obtain phenylglycine derivatives – α -aminonitriles **44a-ak**, with substituents in different positions of the phenyl and amino groups, a series of benzaldehydes **42a-j** were introduced into interaction with aromatic amines **43a-g** in the NaCN/AcOH system at room temperature. By acylation of compounds **44a-ak** with 3-chloropropanoyl chloride and subsequent intramolecular cyclization under PTC conditions, *N*-substituted 2-aryl-5-oxopyrrolidine-2-carbonitriles **45a-ak** were synthesized (Scheme 13, Table 1, Table 2).^{21, 22, 32-34}



Scheme 13. Synthesis of 2-aryl-5-oxopyrrolidine-2-carbonitriles (**45a-ak**). Reagents and conditions: *a* NaCN/H⁺/EtOH/H₂O, r. t., 3 h; *b* K₂CO₃/1,2-dichloroethane, 10-15 °C to 40-45 °C, 3 h; *c* CH₃CN/TEBA/K₂CO₃, 45-50 °C, 4 h

Table 1. Molecular structures of compounds (**42a-j**, **43a-g**, **44a-ak** and **45a-ak**)

Comp.	<i>R</i> , <i>R</i> ¹	Comp.	<i>R</i> , <i>R</i> ¹	Comp.	<i>R</i> , <i>R</i> ¹
42a	H, –	44b,45b	H, Bn	44t,45t	4- <i>i</i> -PrO, 2-MeOC ₆ H ₄
42b	4-Br, –	44c,45c	H, 2-MeOC ₆ H ₄	44u,45u	4- <i>i</i> -PrO, 4-MeC ₆ H ₄
42c	2,6-Cl ₂ , –	44d,45d	H, 4-MeC ₆ H ₄	44v,45v	4- <i>i</i> -PrO, 4-MeOC ₆ H ₄
42d	4-MeO, –	44e,45e	H, 4-MeOC ₆ H ₄	44w,45w	2-OBn, Ph
42e	3,4-(MeO) ₂ , –	44f,45f	4-Br, Ph	44x,45x	2-OBn, Bn
42f	4- <i>i</i> -PrO, –	44g,45g	4-Br, 2-MeC ₆ H ₄	44y,45y	2-OBn, 2-MeC ₆ H ₄
42g	2-OBn, –	44h,45h	4-Br, 4-MeC ₆ H ₄	44z,45z	2-OBn, 2-MeOC ₆ H ₄
42h	4-OBn, –	44i,45i	4-Br, 2-MeOC ₆ H ₄	44aa,45aa	2-OBn, 4-MeC ₆ H ₄
42i	4-(2,4-Cl ₂ C ₆ H ₃ CH ₂ O), –	44j,45j	4-Br, 4-MeOC ₆ H ₄	44ab,45ab	2-OBn, 4-MeOC ₆ H ₄
42j	4-(2,6-Cl ₂ C ₆ H ₃ CH ₂ O), –	44k,45k	2,6-Cl ₂ , 4-MeC ₆ H ₄	44ac,45ac	4-OBn, Ph
43a	–, Ph	44l,45l	2,6-Cl ₂ , 3,5-Me ₂ C ₆ H ₃	44ad,45ad	4-OBn, Bn
43b	–, Bn	44m,45m	4-MeO, Ph	44ae,45ae	4-OBn, 2-MeC ₆ H ₄
43c	–, 2-MeC ₆ H ₄	44n,45n	4-MeO, 4-MeOC ₆ H ₄	44af,45af	4-OBn, 2-MeOC ₆ H ₄
43d	–, 2-MeOC ₆ H ₄	44o,45o	3,4-(MeO) ₂ , 4-MeC ₆ H ₄	44ag,45ag	4-OBn, 4-MeC ₆ H ₄
43e	–, 4-MeC ₆ H ₄	44p,45p	3,4-(MeO) ₂ , 3,5-Me ₂ C ₆ H ₃	44ah,45ah	4-OBn, 4-MeOC ₆ H ₄
43f	–, 4-MeOC ₆ H ₄	44q,45q	4- <i>i</i> -PrO, Ph	44ai,45ai	4-OBn, 3,5-Me ₂ C ₆ H
43g	–, 3,5-Me ₂ C ₆ H ₃	44r,45r	4- <i>i</i> -PrO, 3,5-Me ₂ C ₆ H ₃	44aj,45aj	4-(2,4-Cl ₂ C ₆ H ₃ CH ₂ O), 4-MeC ₆ H ₄
44a, 45a	H, Ph	44s, 45s	4- <i>i</i> -PrO, 2-MeC ₆ H ₄	44ak,45ak	4-(2,6-Cl ₂ C ₆ H ₃ CH ₂ O), 4-MeC ₆ H ₄

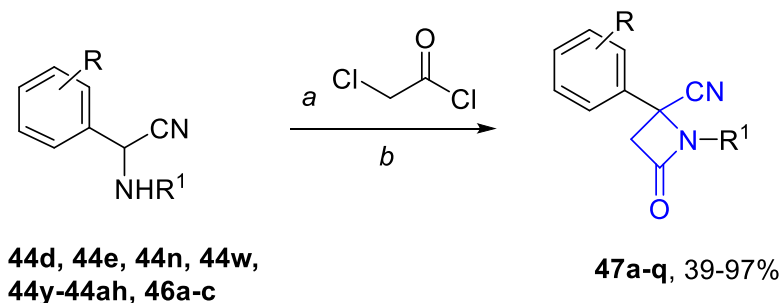
Table 2. Isolated yields of compounds (**45a-ak**)

Comp.	Yield (%)	Comp.	Yield (%)	Comp.	Yield (%)	Comp.	Yield (%)
45a	97	45k	65	45u	72	45ae	45
45b	98	45l	69	45v	92	45af	55
45c	98	45m	60	45w	58	45ag	61
45d	98	45n	65	45x	62	45ah	64
45e	95	45o	92	45y	57	45ai	81
45f	69	45p	95	45z	57	45aj	81
45g	63	45q	96	45aa	67	45ak	76
45h	70	45r	98	45ab	63		
45i	65	45s	70	45ac	55		
45j	74	45t	74	45ad	57		

2.3. Synthesis of new functionalized 2-arylpyrrolidine's derivatives

Next, we set the task of studying the effect of the size of the lactam ring on biological activity. In this regard, it is important to note that various natural and synthetic monocyclic β -lactams, depending on the nature of the ring substituents, exhibit high antibacterial, antifungal, antitumor, neuroprotective and other activities.³⁵⁻³⁷

In the context of the above, in order to reduce the ring size to four, we have synthesized the corresponding β -lactams – azetidines with various substituents. We have constructed a four-membered ring by using monochloroacetyl chloride instead of 3-chloropropanoyl chloride as an acylating agent. By acylating acetonitriles **44d**, **44e**, **44n**, **44w**, **44y-44ah**, **46a-c** with the indicated acid chloride and subsequent intramolecular cyclization under the above-described conditions, 2-aryl-4-oxoazetidine-2-carbonitriles **47a-q** were synthesized (Scheme 14, Table 3, Table 4).³⁸



Scheme 14. Synthesis of 2-aryl-4-oxoazetidine-2-carbonitriles (**47a-q**). Reagents and conditions: *a* K_2CO_3 /1,2-dichloroethane, 10-15 °C to 40-45 °C, 3 h; *b* CH_3CN /TEBA/ K_2CO_3 , 45-50 °C, 4 h.

Table 3. Molecular structures of α -aminonitriles (**44d**, **44e**, **44n**, **44w**, **44y-44ah**, **46a-c**) and azetidine-2-carbonitriles (**47a-q**)

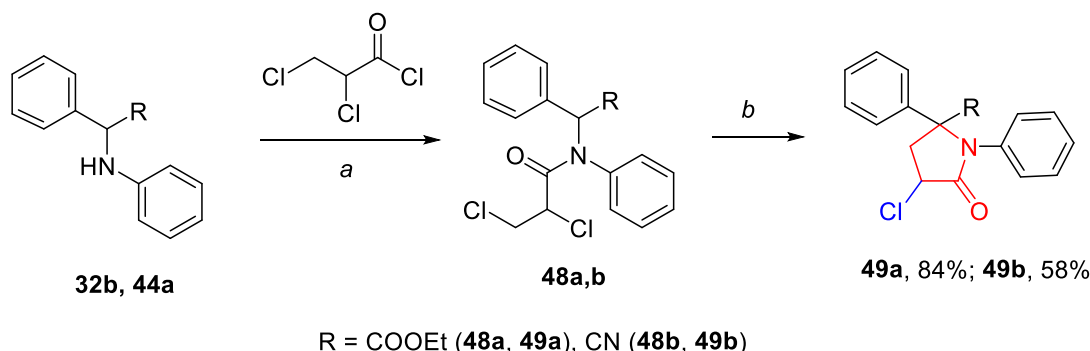
Comp.	<i>R</i> , <i>R</i> ¹	Comp.	<i>R</i> , <i>R</i> ¹	Comp.	<i>R</i> , <i>R</i> ¹
46a,47a	H, 2-MeC ₆ H ₄	44w,47g	2-OBn, Ph	44ad,47m	4-OBn, Bn
44d,47b	H, 4-MeC ₆ H ₄	44y,47h	2-OBn, 2-MeC ₆ H ₄	44ae,47n	4-OBn, 2-MeC ₆ H ₄
44e,47c	H, 4-MeOC ₆ H ₄	44z,47i	2-OBn, 2-MeOC ₆ H ₄	44af,47o	4-OBn, 2-MeOC ₆ H ₄
46b,47d	4-MeO, 2-MeC ₆ H ₄	44aa,47j	2-OBn, 4-MeC ₆ H ₄	44ag,47p	4-OBn, 4-MeC ₆ H ₄
46c,47e	4-MeO, 4-MeC ₆ H ₄	44ab,47k	2-OBn, 4-MeOC ₆ H ₄	44ah,47q	4-OBn, 4-MeOC ₆ H ₄
44n,47f	4-MeO, 4-MeOC ₆ H ₄	44ac,47l	4-OBn, Ph		

Table 4. Isolated yields of compounds (**47a-q**)

Comp.	Yield (%)	Comp.	Yield (%)	Comp.	Yield (%)
47a	39	47g	48	47m	45
47b	43	47h	45	47n	49
47c	60	47i	50	47o	52
47d	40	47j	44	47p	60
47e	92	47k	82	47q	45
47f	97	47l	55		

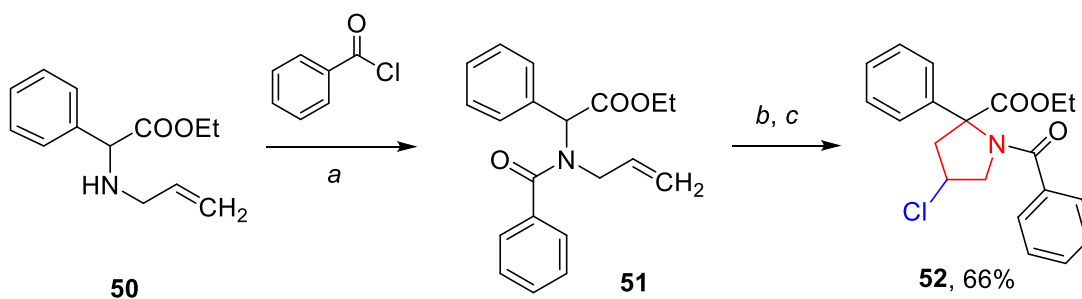
Summarizing the existing literature and our own studies, it should be noted that we have developed and used for the first time an effective method for the synthesis of γ -lactams based on the reactions of acylation of α -aminonitriles with 3-chloropropionic acid chloride and subsequent intramolecular cyclization under PTC conditions.

We have studied the possibilities of additional functionalization of the pyrrolidine ring, in particular, the introduction of a halogen atom into the five-membered cycle. We synthesized such derivatives by two approaches. The first approach is based on the interaction of ethyl ester **32b** or nitrile of 2-anilino-2-phenylacetic acid **44a** with the acid chloride of α,β -dichloropropanoic acid, which already contains a chlorine atom. The chlorine-containing derivatives **48a,b** obtained in this way were cyclized into 4-chloropyrrolidones **49a** and **49b** under the developed conditions of phase-transfer catalysis (Scheme 15).^{39, 40}



Scheme 15. Synthesis of 4-chloropyrrolidones (**49a,b**). Reagents and conditions: *a* Et₃N/acetone, 0-5 °C to reach r. t., 2 h; *b* CH₃CN/TEBA/K₂CO₃, 45-50 °C, 4 h.

We have also carried out some studies to implement the second approach, i.e. direct chlorination of the corresponding starting compounds with a double bond. Initially, ethyl 2-allylamino-2-phenylacetic acid (**50**) was synthesized by alkylation of ethyl 2-bromo-2-phenylacetic acid with allylamine, which was then acylated with benzoyl chloride in the presence of triethylamine. Subsequent chlorination and intramolecular cyclization under PTC conditions led to the target 4-chloro derivative **52** (Scheme 16).⁴⁰



Scheme 16. Synthesis of 4-chloro derivative (**52**). Reagents and conditions: *a* Et₃N/diethyl ether, 0-5 °C to reach r. t., 2 h; *b* pyridine/gas. Cl₂/1,2-dichloroethane, 0-5 °C; *c* CH₃CN/TEBA/K₂CO₃, 45-50 °C, 4 h.

Similarly, from acetonitriles **53a,b**, by successive reactions of benzoylation, chlorination and heterocyclization, similar to that described above, 4-chloro-substituted pyrrolidinecarbonitriles **54a** and **54b** were obtained (Figure 2).⁴⁰

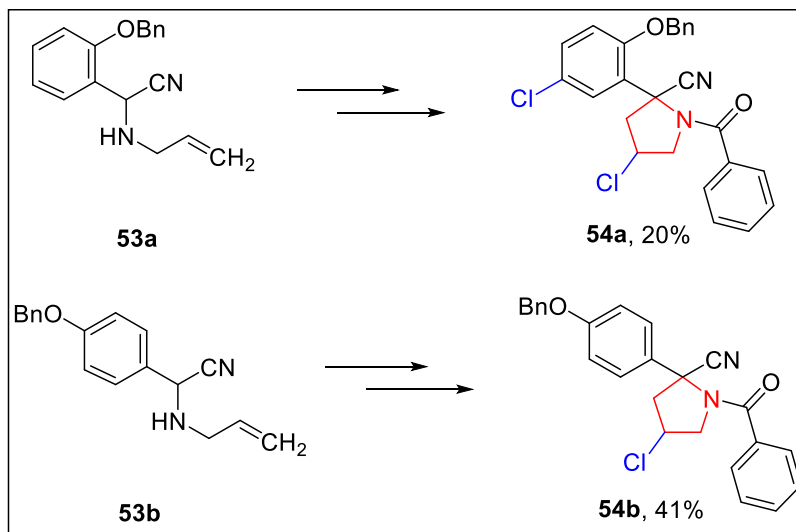


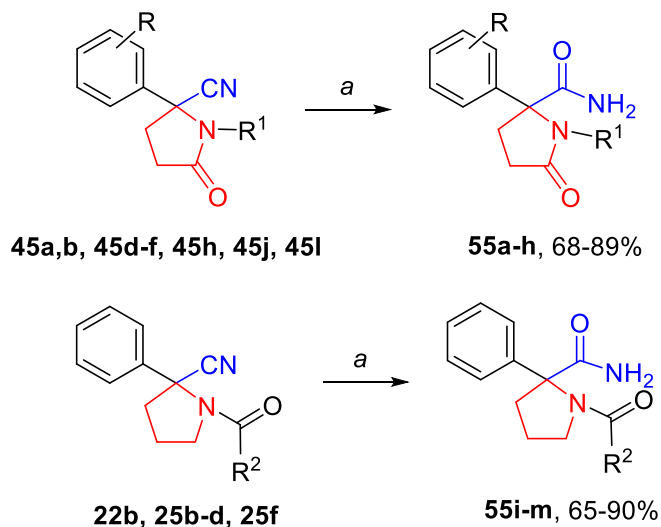
Figure 2. Synthesis of 4-chloro-substituted pyrrolidinecarbonitriles (**54a,b**).

It should be mentioned, that after chlorination and subsequent cyclization, we isolated pyrrolidine **54a** containing a chlorine atom in the aryl group, which was not noted during the synthesis of compounds **52** and **54b**. This course of the reaction can be explained by the presence of the electron-donating BnO group in the benzene ring, which promotes electrophilic substitution in the para position. Taking into account the equimolar amount of chlorine introduced into the reaction, it can be assumed that the reaction proceeds simultaneously in two directions – addition and substitution, with the latter being responsible for the low yield of the final product **54a** (Figure 2).

In the structures of chlorine-substituted pyrrolidine analogues **49a,b**, **52**, **54a,b** there are two asymmetric centers (atoms C1 and C4 of the pyrrolidine ring), which can result in the formation of four different possible stereoisomers: (2*R*,4*R*), (2*R*,4*S*), (2*S*,4*R*), (2*S*,4*S*), during the synthesis of each of these compounds. Therefore, the structures of the compounds of the grown crystals were studied by X-ray diffraction.

According to X-ray diffraction data, all four possible stereoisomers were revealed only in the structure of ethyl ester of 1-benzoyl-2-phenyl-4-chloropyrrolidine-2-carboxylic acid (**52**), in the crystal of which all 4 isomers (2*R*,4*R*), (2*R*,4*S*), (2*S*,4*R*), (2*S*,4*S*) are present in a ratio of ~7:3:5:5. Nitriles **49b**, **54a,b**, unlike compound **52**, were racemic mixtures of two stereoisomers – (2*R*,4*S*) and (2*S*,4*R*).⁴⁰⁻⁴²

In order to study the biological properties of new 2-arylpyrrolidines, we obtained their carboxamide derivatives substituted at both phenyl groups. Hydrolysis of the nitrile group of pyrrolidinecarbonitriles **45a,b**, **45d-f**, **45h**, **45j**, **45l**, **22b**, **25b-d**, **25f** without affecting the lactam cycle was carried out by us by treating the indicated nitriles with conc. H₂SO₄ in the cold with the formation of carboxamides **55a-m** (Scheme 17, Table 5).^{22, 33, 34}



Scheme 17. Synthesis of carboxamides (**55a-m**). Reagents and conditions: *a* conc. H₂SO₄, 0-5 °C, 3 h.

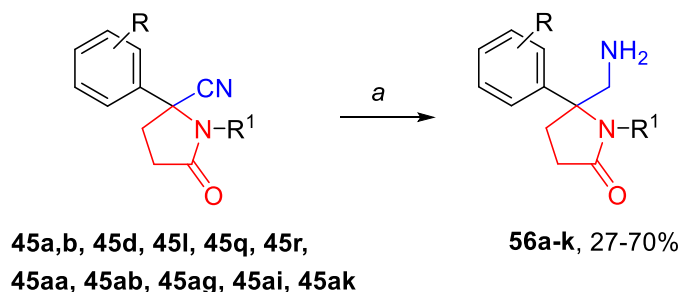
Table 5. Molecular structures and isolated yields of carboxamides (**55a-m**)

Comp.	<i>R, R¹, R²</i>	Yield (%)	Comp.	<i>R, R¹, R²</i>	Yield (%)
55a	H, Ph, –	87	55h	2,6-Cl ₂ , 3,5-Me ₂ C ₆ H ₃ , –	87
55b	H, Bn, –	89	55i	–, –, Me	80
55c	H, 4-MeC ₆ H ₄ , –	75	55j	–, –, 2-ClC ₆ H ₄	84
55d	H, 4-MeOC ₆ H ₄ , –	80	55k	–, –, 2-BrC ₆ H ₄	65
55e	4-Br, Ph, –	79	55l	–, –, 4-BrC ₆ H ₄	90
55f	4-Br, 4-MeC ₆ H ₄ , –	74	55m	–, –, 4-MeO-3-NO ₂ C ₆ H ₃	80
55g	4-Br, 4-MeOC ₆ H ₄ , –	68			

The next goal of our research was the synthesis of new amino derivatives of 2-arylpyrrolidines by reducing the nitrile group. It should be noted that there are various methods for reducing the nitrile group to an amine group using a wide range of reducing agents, in particular, metallic sodium in alcohols, complex metal hydrides (lithium aluminum hydride), as well as catalytic hydrogenation, etc.⁴³ However, the side reactions accompanying the reduction by these methods and associated with their low selectivity served as the reason for us to study the possibility of selectively reducing the nitrile group to an amine group using a significantly milder reducing agent – sodium borohydride. The expediency of using NaBH₄ is due to the fact that nitro and carbonyl groups, nitriles and acid amides, and multiple bonds are inert with respect to NaBH₄, but its reducing ability and selectivity increase in the presence of certain inorganic salts, in particular, CoCl₂,^{44, 45} ZrCl₄,⁴⁶ dialkylselenium dibromide,⁴⁷ I₂,⁴⁸ BF₃·Et₂O,⁴⁹ NiCl₂]^{50, 51}.

On the other hand, it is well known that cyclic and non-cyclic polyethers (crown ethers) increase the rate and ensure high selectivity of reduction reactions. Polyethers of this type form complexes with cations of alkali and alkaline earth metals and, therefore, are capable of solubilizing salts of these metals in a non-polar medium. In particular, polyethyleneglycols (PEG) and their dimethyl ethers are readily available, low-toxic, and highly soluble in organic solvents and water, making them excellent substitutes for crown ethers, for example, in reduction reactions in the NaBH₄ : PEG-400 : PdCl₂ system.⁵²

In order to further optimize the conditions for carrying out the reduction and taking into account the above, we have developed a method for the selective reduction of nitrile groups, in which a catalytic metal complex system with polyethyleneglycol was used. In the developed reduction system, the optimal ratio of reagents is pyrrolidinecarbonitrile : CoCl_2 : PEG-300 : NaBH_4 – 1 : 0.2 : 1 : 5, with the help of which the synthesis of the corresponding 2-aminomethylpyrrolidines **56a-k** was carried out from substituted pyrrolidinecarbonitriles (Scheme 18, Table 6).^{32, 34, 53}



Scheme 18. Synthesis of 2-aminomethylpyrrolidines (**56a-k**). Reagents and conditions: *a* $\text{NaBH}_4/\text{PEG-400}/\text{CoCl}_2/\text{CH}_2\text{Cl}_2$, $-5-0^\circ\text{C}$, 8 h.

Table 6. Molecular structures and isolated yields of 2-aminomethylpyrrolidines (**56a-k**)

Comp.	<i>R, R</i> ¹	Yield (%)	Comp.	<i>R, R</i> ¹	Yield (%)
56a	H, Ph	45	56g	2-OBn, 4-MeC ₆ H ₄	27
56b	H, Bn	40	56h	4-OBn, Bn	35
56c	H, 4-MeC ₆ H ₄	55	56i	4-OBn, 4-MeC ₆ H ₄	52
56d	2,6-Cl ₂ , 3,5-Me ₂ C ₆ H ₃	30	56j	4-OBn, 3,5-Me ₂ C ₆ H ₃	70
56e	4- <i>i</i> -PrO, Ph	35	56k	4-(2,6-Cl ₂ BnO), 4-MeC ₆ H ₄	28
56f	4- <i>i</i> -PrO, 3,5-Me ₂ C ₆ H ₃	62			

Thus, a new metal complex system for selective reduction of the nitrile group is proposed, the advantage of which is a significant reduction in the amounts of inorganic salt and sodium borohydride used.

2.4. Biological properties of synthesized 2-arylpyrrolidine derivatives

Antibacterial activity of the synthesized compounds was studied using gram-positive staphylococci (*Staphylococcus aureus* 209p, *Staphylococcus aureus* 1) and gram-negative rods (*Shigella flexneri* 6858, *Escherichia coli* 055) and the agar-diffusion method with bacterial load 20×10^6 microbes per millimeter of medium. Compounds were studied at 1:20 concentrations. Results were calculated from the diameter (d, mm) of the microorganism growth inhibition zone at the application site of the compounds after growth for 1 day at 37°C (thermostatted).⁵⁴

The study of antibacterial activity showed that almost all of the studied 2-aminomethyl-1,2-diarylpyrrolidin-5-ones **56a-k** exhibit moderate activity. Among them, compounds **56c-e** exhibited the most pronounced activity, suppressing the growth of all used microorganisms in inhibition zones with diameters of 20-25 mm, 2-aminomethyl-1,2-diarylpyrrolidin-5-ones **56a** and **56b** are moderately active. 2-Phenylpyrrolidine-2-carboxylic acids **23**, **34b**, **35** also exhibit antibacterial activity, but somewhat weaker. In the series of 2-arylpyrrolidines, the

weakest antibacterial activity is exhibited by pyrrolidinecarbonitriles **45a-ak** and pyrrolidinecarboxamides **55a-m**, with the latter compounds showing activity only against gram-positive strains (Table 7).^{22, 28, 55}

Table 7. Antibacterial activity of most active 2-arylpyrrolidines

Comp.	Inhibition zone diameter (mm)			
	<i>Staphylococcus aureus</i> 209p	<i>Staphylococcus aureus</i> 1	<i>Shigella flexneri</i> 6858	<i>Echerichia coli</i> 055
23	17	17	19	17
34b	18	18	18	0
35	17	17	17	17
56a	18	17	20	20
56b	15	15	17	13
56c	25	25	22	20
56d	20	18	16	18
56e	25	20	21	18

Toxicity and antitumor activity of synthesized compounds were tested by the usual methods,^{56, 57} on white laboratory mice with transplanted tumors *sarcoma* 37 (S-37), *sarcoma* 180 (S-180) and *Ehrlich ascites carcinoma* (EAC). Some of the most active compounds were tested on rats with *sarcoma* 45 (S-45). Acute toxicity was studied in white mice with a single i.p. injection. The lethal (LD₁₀₀) and maximum tolerated (MTD) doses were determined for each compound. Antitumor activity was studied in mice with grafted *sarcoma* 37 and *Ehrlich ascites carcinoma* (EAC) tumors. Compounds were administered to the animals as suspensions in carboxymethylcellulose solution (0.5%) daily by i.p. injection for six days at doses from 1/10 to 1/15 of LD₁₀₀, because of their poor solubility. The criteria for the therapeutic effect were the percentage of tumor growth inhibition (T, %) for sarcomas 37, 45, and 180 and an increase in the average life expectancy of animals (ALE, %) in the case of EAC (relative to the control).

The study of the antitumor activity of the synthesized compounds established that in the series of synthesized 2-arylpyrrolidines, pyrrolidine-2-carboxylic acids **34a**, **34c** are low-toxic compounds and exhibit reliable antitumor activity against sarcomas 45 and 37 (Table 8).²²

Table 8. Antitumor activity of most active 2-arylpyrrolidines

Comp.	Acute toxicity, LD ₁₀₀ / MTD (mg/kg)	Inhibition of tumor growth, %			ALE, % EAC
		S - 180	S - 45	S - 37	
34a	3000 / 1250	-	49	46	-
34c	4000 / 1750	-	46	42	-
46o	2500 / 1250	-	-	45	39
57a	2500 / 1200	42.5	-	59	57
57b	2200 / 1050	40	34.8	40	38
57c	2500 / 1200	-	-	53	52
57d	2500 / 1200	38.4	39.4	50	45
57l	2200 / 1050	-	40	32	0
57m	2200 / 1000	43.3	42.4	43	0

Derivatives of 2-arylpyrrolidine-2-carbonitriles **45a-ak** and 2-arylpyrrolidine-2-carboxamides **55a-m** have low toxicity ($LD_{100} = 2200\text{--}2500$ mg/kg). In this series, only carboxamide derivatives **55a** and **55c** stand out. 2-Aminomethyl-1,2-diarylpyrrolidines **56a-k** are capable of inhibiting the growth of *sarcomas* 45 and 180 by 40–45 %, while being relatively toxic compounds ($LD_{100} = 850\text{--}1050$ mg/kg) (Table 8).

Anti-HIV-1 test of the synthesized compounds was carried out on primary human peripheral blood mononuclear cells (PBM) and HIV-1/LAI was used as a standard reference virus. The antiviral 50% effective concentration (EC_{50}) and 90% effective concentration (EC_{90}) were determined from the concentration-response curve using the median effect method.⁵⁸ The cytotoxicity of the compounds was determined by potential toxic effects on uninfected PHA-stimulated human PBM cells, CEM (*T-lymphoblastoid cell line*, obtained from the American Type Culture Collection, Rockville, MD) and Vero (African green monkey kidney) cells.⁵⁹

During the study of the anti-HIV-1 activity of the synthesized compounds, it was established that four compounds exhibited antiviral activity that was < 20 μM while also exhibiting no apparent toxicity ($IC_{50} \geq 30$ μM) in all three cell lines. Compounds **45aj**, **45ak** were the most active, but they were very toxic in all cell lines used. Compound **45q** showed the best activity, without pronounced cytotoxicity against all cell lines. However, the above-mentioned compounds were inferior in activity to the drug AZT, which was used as a positive control (Table 9).^{34, 60}

Table 9. Anti-HIV activity of most active 2-arylpyrrolidines

Comp.	Anti-HIV-1 activity in human		Cytotoxicity (IC_{50} , μM)		
	PBM cells (μM)		PBM	CEM	VERO
	EC_{50}	EC_{90}			
45q	5.2	29.8	95.8	> 100	> 100
45aa	17.3	> 100	22.8	16.1	77.9
45ad	9.8	30.7	5.9	7.0	3.0
45ag	16.7	> 100	> 100	30.3	53.9
45aj	5.3	24.4	9.7	6.6	21.8
45ak	2.0	51.9	14.1	16.6	52.9
47p	8.9	> 100	> 100	70.1	38.3
49b	14.4	51.7	8.4	31.2	50.0
56g	11.5	> 100	45.2	47.9	> 100
56i	10.8	41.5	15.9	33.7	12.3
AZT	0.0018	0.015	> 100	14.3	50.6

The conducted studies have established that in the series of 2-arylpyrrolidines, compounds containing BnOC_6H_4 - and *i*-PrO- groups, as well as Me- groups in the 4 or 3/5 positions of the 1-aryl fragment, exhibit high activity (Table 9).

3. Synthesis of Pyrimidinyl Derivatives of Pyrrolidine and Their Biological Properties

3.1. Synthesis of new 5-pyrimidinylproline derivatives

Nucleosides have been of great and continuing interest in recent decades due to their important role as antitumor and antiviral agents, and chemical modification of nucleosides has long been recognized as an

important way to enhance such activities.⁶¹⁻⁶³ In contrast to the more studied analogues of natural *N*-nucleosides, interest in modified *C*-nucleosides of natural bases has only recently emerged. In this regard, an important modification of nucleosides, including *C*-nucleosides, is the replacement of the cyclic furanose or pyranose oxygen atom by a nitrogen atom. Such a significant change in the chemical structure in the form of an aza analogue can cause an inhibitory effect on the glycohydrolase enzyme, which is responsible for the cleavage of glycosidic bonds.⁶⁴⁻⁶⁶ In this regard, a logical continuation of our studies was the synthesis of heteroarylpyrrolidines, which we consider as pyrimidine-based analogues of *C*-nucleosides.

The interest in pyrimidine derivatives has increased significantly after the appearance in the clinic of drugs with antitumor, antiviral, and especially anti-HIV activity based on substituted uracils. Among the active compounds with an effective effect against HIV, one can note 1-(2-hydroxyethoxy)methyl-6-(phenylsulfanyl)thymine (HEPT),⁶⁷⁻⁷⁰ 6-benzyl-5-isopropyl-1-(ethoxymethyl)uracil,^{71, 72} 2-alkoxy-6-benzyl-3,4-dihydropyrimidin-4(1*H*)-ones (DABOs) and thio-DABOs (*S*-DABOs),⁷³ and 3'-azido-2',3'-dideoxythymidine (AZT)⁷⁴ (Figure 3).

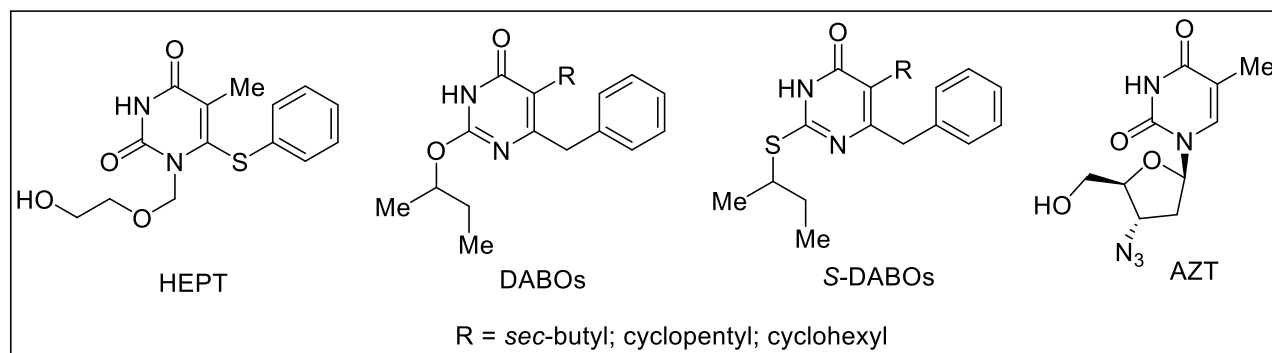
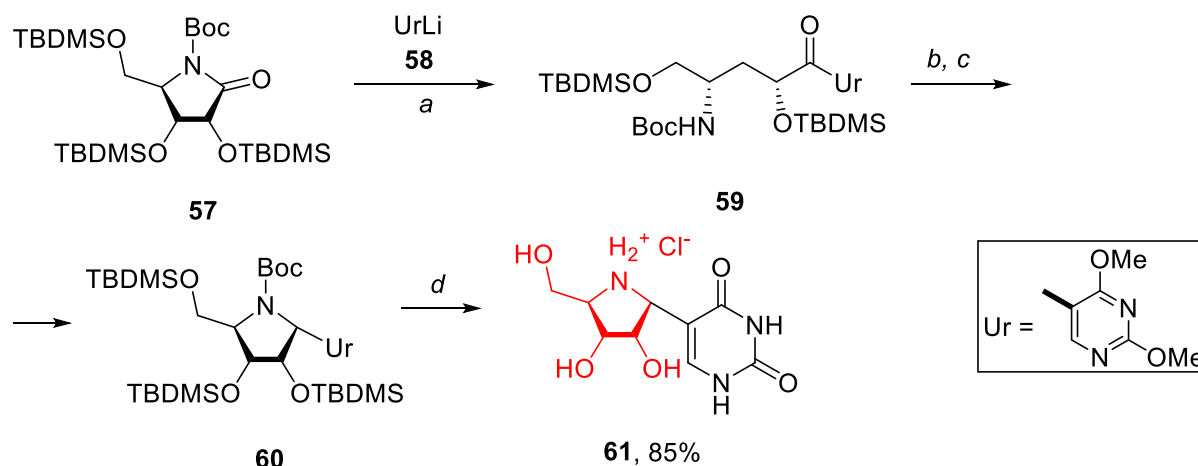


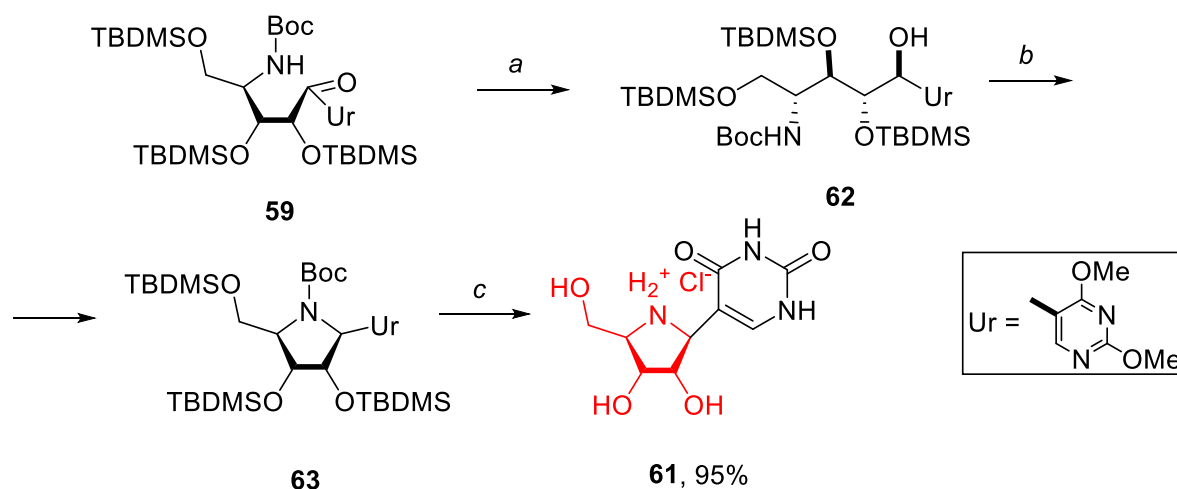
Figure 3. HEPT, DABOs, *S*-DABOs and AZT structures.

Various methods for synthesizing *C*-azanucleosides have been described in the literature, in particular, Yokoyama et al. synthesized *C*-4'-aminouracil from *L*-glutamic acid, in the sugar ring of which the oxygen was replaced by a nitrogen atom. Initially, *N*-Boc-*L*-pyroglutamate **57**, protected with *tert*-butyldimethylsilyl (TBDMS) groups, was synthesized from *L*-glutamic acid in several stages, by using the lithium reagent of 2,4-dimethoxypyrimidine (UrLi) **58**, which was prepared *via* halogen–metal exchange between 5-bromo-2,4-dimethoxypyrimidine and *n*-BuLi below -78°C . The interaction of the latter **59** with trifluoroacetic acid (TFA), subsequent intramolecular cyclization, reduction with NaBH_3CN and boiling with HCl/MeOH lead to the α -anomer of *C*-aminouridine **61** in 85% yield (Scheme 19).^{75, 76}



Scheme 19. Synthesis of α-anomer of C-aminouridine (**61**). Reagents and conditions: *a* THF, $-78\text{ }^{\circ}\text{C}$, 2 h; *b* TFA/ CH_2Cl_2 , r. t., 3 h; *c* NaBH_3CN /EtOH, r. t., 2.5 h; *d* conc. HCl/MeOH, reflux, 3 h.

For the synthesis of β-C-aminouridine, the keto derivative **59** was reduced with NaBH_4 to the oxy derivative **62**, stirring it with MsCl and Et_3N led to the cyclic compound **63**. Further removal of the protecting groups with HCl/MeOH gave the β-anomer of C-aminouridine **61** in 95% yield (Scheme 20).⁷⁶



Scheme 20. Synthesis of β-anomer of C-aminouridine (**61**). Reagents and conditions: *a* NaBH_4 /EtOH, r. t., 10 h; *b* MsCl / Et_3N / CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 1 h; *c* conc. HCl/MeOH, reflux, 3 h.

The same authors carried out similar reactions by replacing the 3,4-OTBDMS group with a 3,4-isopropylidene methylenedioxy group, with the formation of 80% α- and 11% β-anomers of C-aminouridine **66** in 95% yield (Figure 4).^{76, 77}

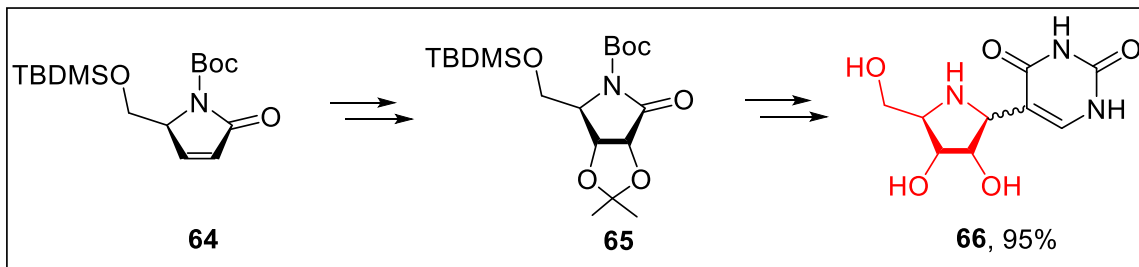
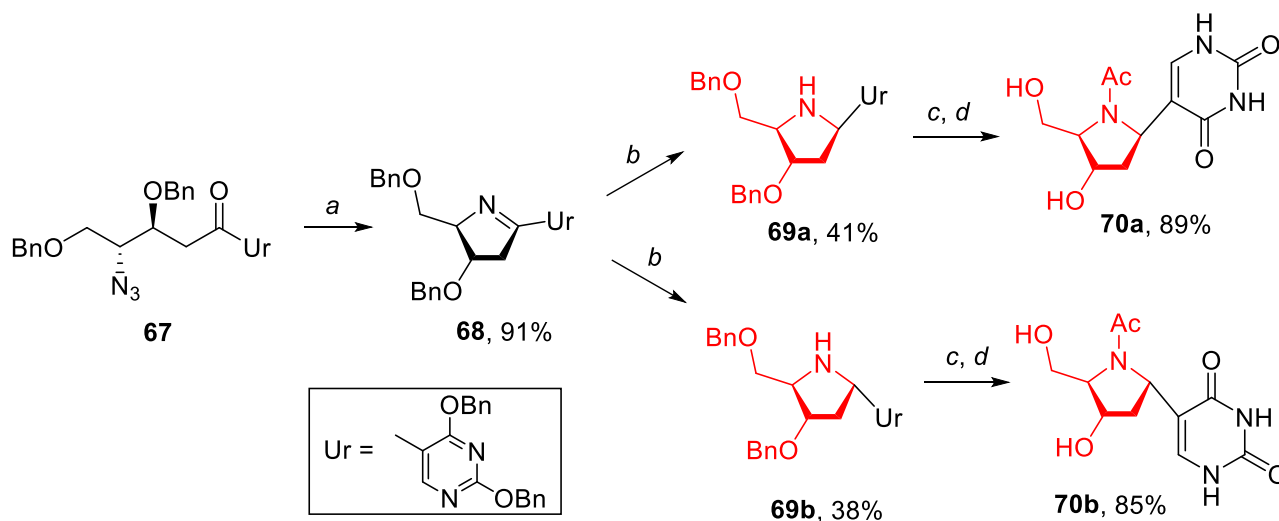


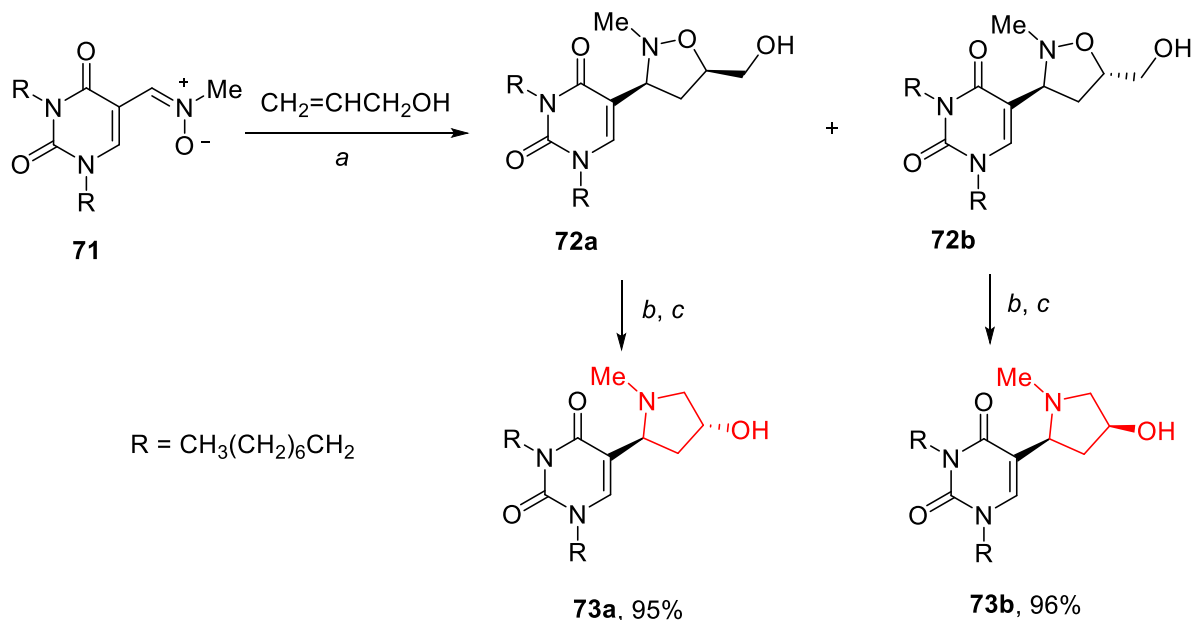
Figure 4. Synthesis of α- and β-anomers of C-aminouridine (**66**).

Kim et al. developed another method for the synthesis of new pyrrolidine C-nucleosides starting from a γ-azidoketone **67**, which is converted by Staudinger-aza-Wittig cyclization into a cyclized imine **68** using triphenylphosphine in THF. Reduction of the imine group with NaBH₃CN to afford a *ca.* 1:1 mixture of β- and α-anomers **69a** and **69b**, which could be separated by preparative TLC in 41% and 38% isolated yields. Acylation of **69a** and **69b** followed by hydrogenation over 10% Pd/C provided corresponding *N*-acetyl-C-aza-2-deoxy-*D*-ribonucleosides **70a** and **70b** in 89% and 85% yield (Scheme 21).⁷⁸



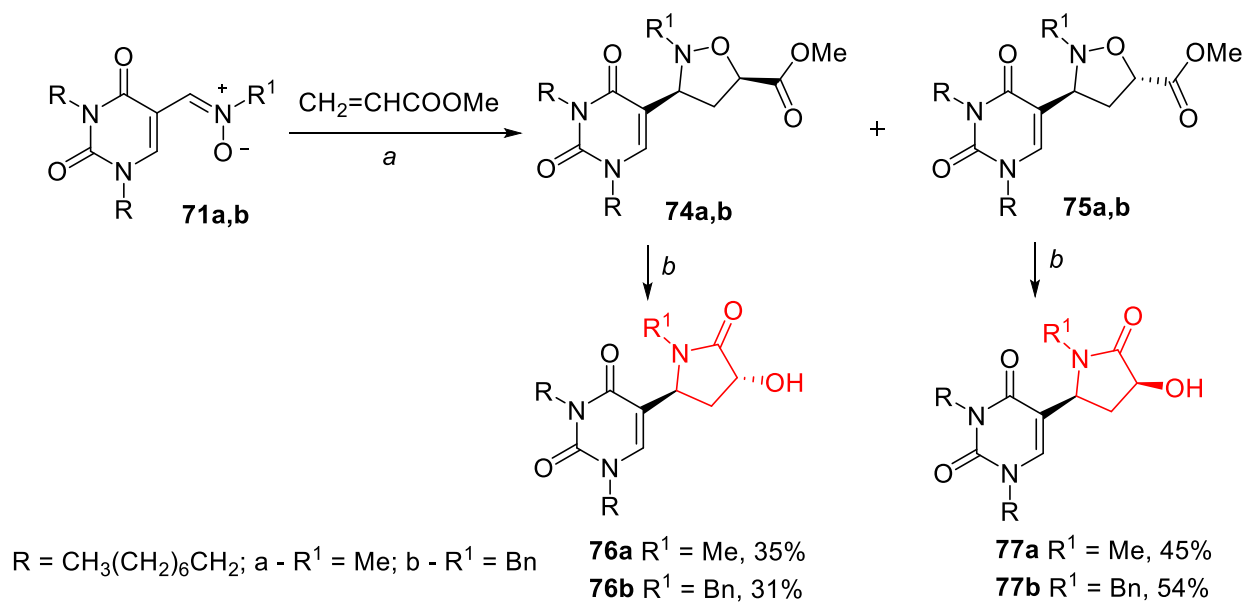
Scheme 21. Synthesis of β- and α-anomers of *N*-acetyl-C-aminouridine (**70a,b**). Reagents and conditions: *a* Ph₃P/THF, r. t., 18 h; *b* 2 h NaBH₃CN/MeOH/cat. AcOH, r. t., 10 h; *c* Ac₂O/pyridine/cat. DMAP; *d* 10% Pd/C/H₂/MeOH.

In the work of Coutouli-Argyropoulou et al.,⁷⁹ pyrrolidine analogues of C-nucleosides were synthesized by 1,3-dipolar cycloaddition reactions of uracil-5- and 2,4-dimethoxypyrimidine-5-nitrones with allyl alcohol and methyl acrylate, followed by reductive cleavage of the isoxazolidine cycloadducts. In the first case, stereoisomeric isoxazolidines were obtained from uracil-nitrone **71** and allyl alcohol, which were then converted into mesyl derivatives **72a,b** and hydrogenated over Pd/C leading to the corresponding uracil-5-hydroxypyrrolidines **73a,b** (Scheme 22).



Scheme 22. Synthesis of uracil-5-hydroxypyrrolidines (**73a,b**). Reagents and conditions: *a* reflux, 48 h; *b* mesylchloride/pyridine, r. t., 1-2 h; *c* Pd/C/H₂/MeOH, r. t., 48 h.

The reaction of the nitrones **71a,b** with methyl acrylate led to a mixture of two 5-substituted carboxymethyl isoxazolidines **74a,b** and **75a,b**, upon catalytic hydrogenation of which over Ra/Ni uracil-5-pyrrolidones were isolated **76a,b** and **77a,b** (Scheme 23).⁷⁹



Scheme 23. Synthesis of uracil-5-pyrrolidones (**76a,b**) and (**77a,b**). Reagents and conditions: *a* toluene, 80 °C, 48 h; *b* Ra/Ni/H₂/MeOH, r. t., 24 h.

Similar reactions were carried out with dimethoxypyrimidine nitrones **78a-c**, resulting in the corresponding C-azanucleosides **79a-c** and **80a-c** were synthesized (Figure 5).⁷⁹

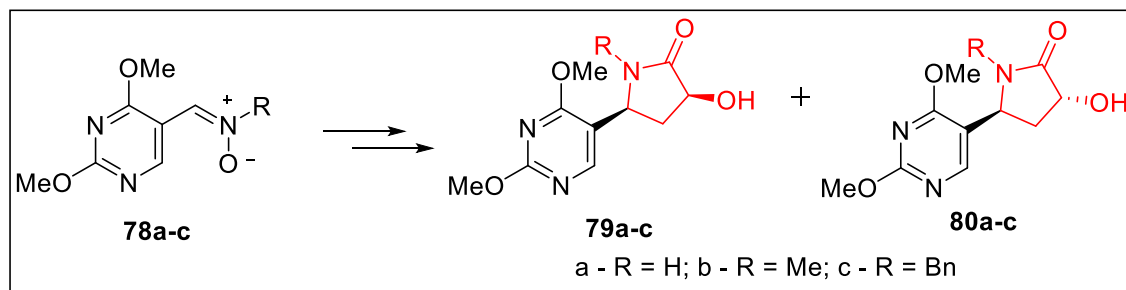
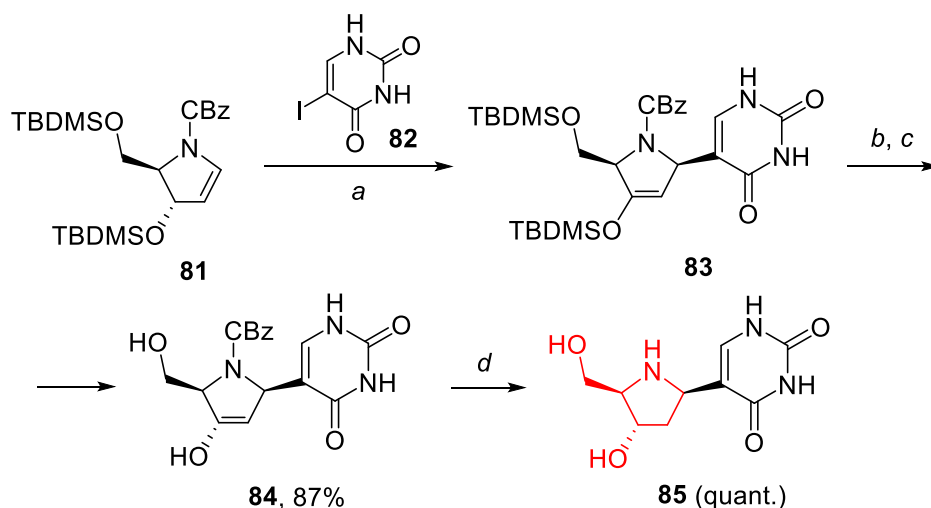


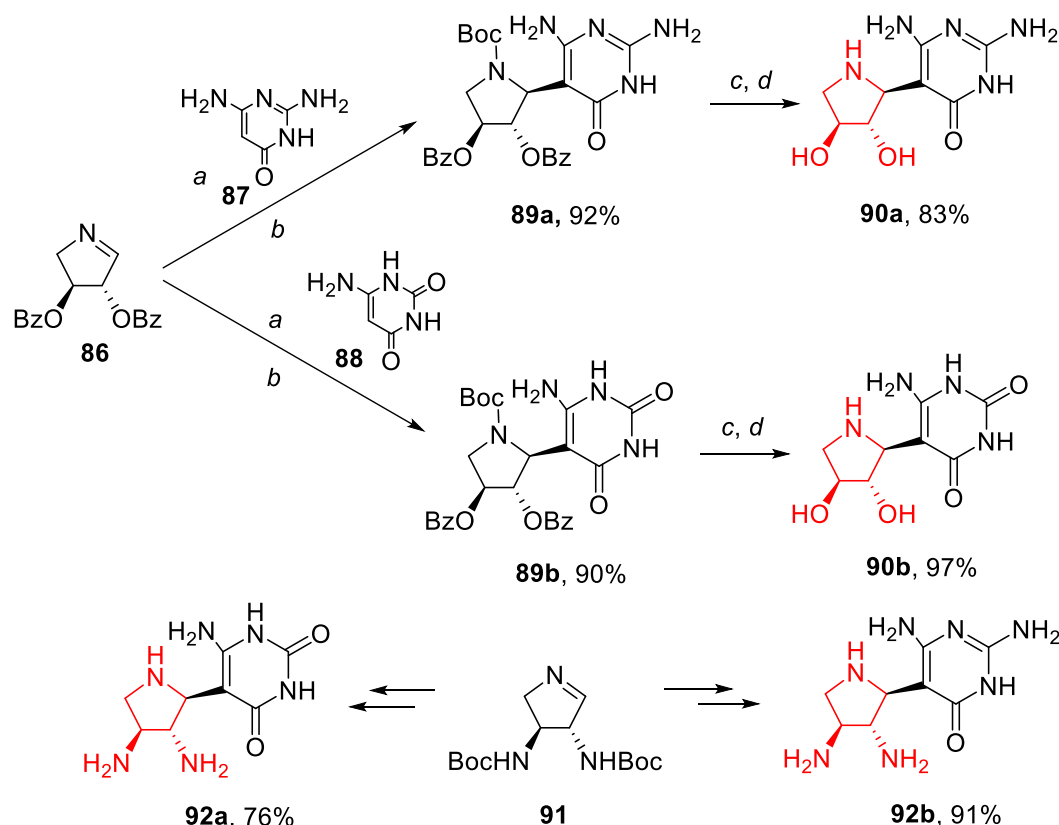
Figure 5. Synthesis of C-azanucleosides (**79a-c**) and (**80a-c**).

A new method for the synthesis of C-nucleosides of pyrrolidine was developed by Leumann et al. The key step of the synthesis is the addition of disubstituted *N*-protected 2-pyrroline **81** to 5-iodouracil **82** via the Heck reaction using the ligand AsPh_3 , $\text{Pd}(\text{OAc})_2$ as a catalyst and NBu_3 . Then the silyl ethers **83** are cleaved using tetrabutylammonium fluoride (TBAF), the keto group is reduced with $\text{NaB}(\text{OAc})_3\text{H}$. In the final step, the *C*-benzoyl group of **84** is removed by hydrogenation with Pd and the C-nucleoside derivative **85** is obtained (Scheme 24).^{80, 81}



Scheme 24. Synthesis of C-nucleoside derivative (**85**). Reagents and conditions: *a* $\text{AsPh}_3/\text{Bu}_3\text{N}/\text{Pd}(\text{OAc})_2/\text{DMF}$, 65 °C, 2 days; *b* $\text{AcOH}/\text{TBAF}/\text{THF}$, -15 °C to reach r. t., 37 h; *c* $\text{NaB}(\text{OAc})_3\text{H}/\text{AcOH}/\text{CH}_3\text{CN}$, -15 °C to reach r. t., 20 min; *d* $\text{Pd}/\text{C}/\text{H}_2/\text{MeOH}$, r. t., 4 h.

By acid-catalyzed C-nucleosidation of 2,3-di-*O*-benzoylpyrroline **86** with the corresponding pyrimidines **87**, **88** and subsequent reaction with Boc_2O , pyrimidine C(5)-azanucleosides **89a,b** were synthesized by Eschenmoser et al. in high yields (> 90%) as a pure α -anomer. Further debenzoylation of the latter with methanolic ammonia solution and the action of dry HCl in diethyl ether gave the corresponding C-azanucleoside hydrochlorides **90a,b**. Under similar conditions, the C-nucleosidation reaction of 2,6-disubstituted 4-aminopyrimidines was carried out with 2,3-di-*N*-Boc-pyrroline **91** as a substrate. As a result, pyrimidine C(5)-azanucleosides were isolated as α/β -anomers in a ratio of > 9:1. Further removal of the Boc-protecting groups led to the corresponding C-azanucleosides **92a,b**, without loss of stereochemical integrity at the anomeric center (Scheme 25).⁸²

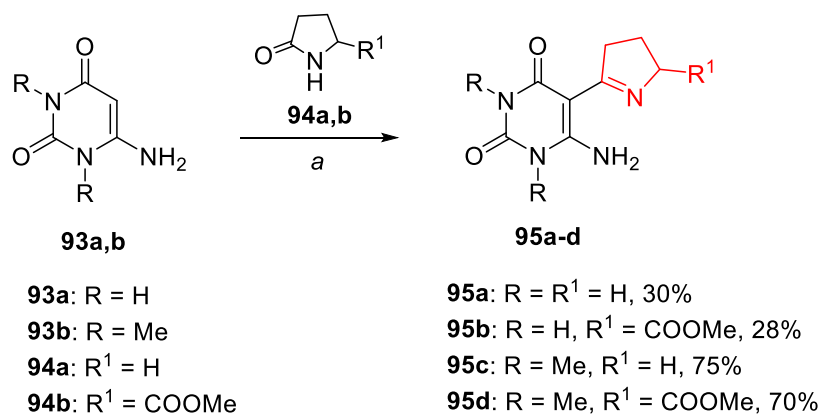


Scheme 25. Synthesis of C-azanucleoside hydrochlorides (**90a,b**) and (**92a,b**). Reagents and conditions: *a* TsOH·H₂O/DMF, 50 °C, 5 h; *b* Boc₂O/Et₃N/DMF, r. t., 30 min to 2 h; *c* sat. NH₃ in MeOH, r. t., 24–48 h; *d* 2 M to sat. HCl in Et₂O, r. t., 1.5–2 h.

These various methods for synthesizing C-azanucleosides described in the literature are labor-intensive, multi-stage, and require the use of expensive reagents, so the development of new, more accessible methods for synthesizing these compounds is relevant.

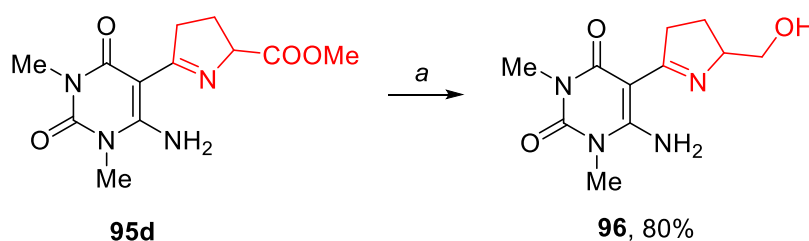
In this regard, it seems appropriate to combine the pyrimidine molecule with the pharmacophoric cycle of pyrrolidin-2-one and study their biological properties. To implement the task, a method for the condensation of pyrrolidin-2-ones with 6-aminopyrimidine derivatives under Vilsmeier reaction conditions has been developed.⁸³ By reacting 6-aminopyrimidines **93a,b** with pyrrolidin-2-one **94a** or methyl ester of pyroglutamic acid **94b** in the presence of PCl₃, 6-amino-5-(3,4-dihydro-2H-pyrrol-5-yl)-pyrimidine-2,4(1H,3H)-diones **95a**, **95c** and methyl esters of 5-(6-aminopyrimidin-5-yl)-3,4-dihydro-2H-pyrrole-2-carboxylic acids **95b**, **95d** were synthesized (Scheme 26).⁸⁴

It should be noted that carrying out the condensation reaction in a pyrrolidin-2-one as a reagent and a solvent leads to a slight increase in the yield of compounds **95a-d**. Low yields of compounds **95a,b** are probably due to the poor solubility of the starting 6-amino-1,2,3,4-tetrahydro-2,4-pyrimidinedione (**93a**) in the reaction medium, while *N,N*-dimethyl derivatives **95c,d** were synthesized with good yields. As a result of the studies, we synthesized new pyrimidine analogs of C-nucleosides of a fundamentally new design.



Scheme 26. Synthesis of 6-amino-5-pyrrolylpyrimidines (**95a-d**). Reagents and conditions: *a* PCl₃/1,4-dioxane, 0-5 °C to reach r. t., 10 min, then 90-95 °C, 5 h.

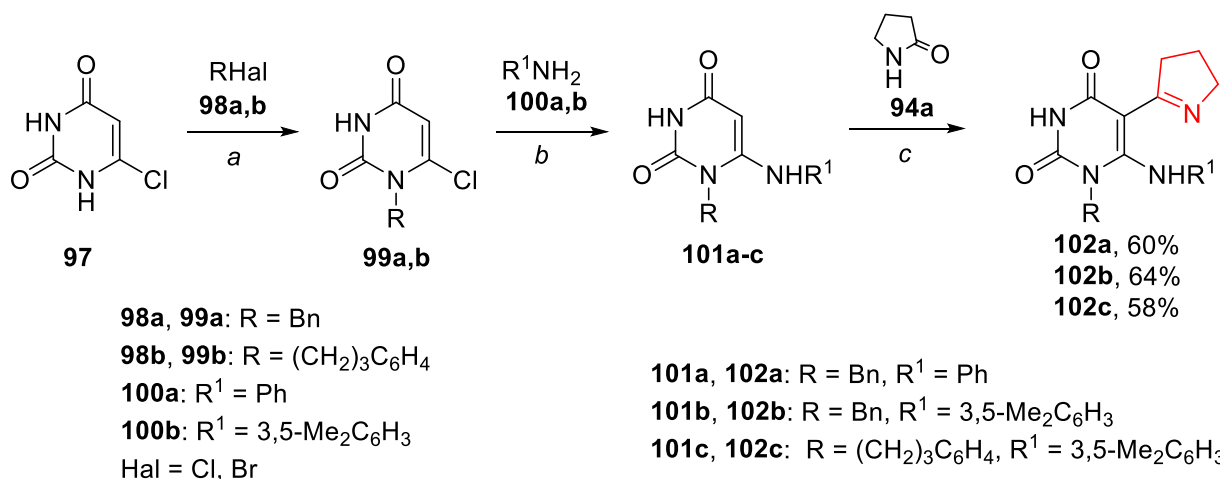
To reduce the double bond of the pyrrole ring in compound **95d**, the NaBH₄/1,4-dioxane/CoCl₂/PEG-400 reducing system was used. The reaction resulted in the reduction of the ester group to a hydroxymethyl group while the double bond remained intact, which led to the formation of 6-amino-5-(2-(hydroxymethyl)-3,4-dihydro-2H-pyrrol-5-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**96**) in high yield (Scheme 27).⁸⁴



Scheme 27. Synthesis of compound (**96**). Reagents and conditions: *a* NaBH₄/CoCl₂·6H₂O/PEG-400/1,4-dioxane, reflux, 2 h.

There are reports in the literature that some substituted 6-anilinouracils are potential and selective inhibitors of the enzyme IIIC DNA polymerase of gram-positive bacteria^{85, 86} and 1-arylmethyl and 6-(arylthio) derivatives of uracil exhibit antiviral activity against HIV-1^{87, 88}. It is also known that the presence of pyrrolidine at the end of the C-6 chain and benzyl groups in the *N*-1, *N*-3 positions of the pyrimidine ring increases the antitumor activity of these molecules.⁸⁹

Taking into account the above, we synthesized new pyrimidine analogs substituted at positions 1 and 6 of the pyrimidine ring using a similar synthetic route. The starting compound was chosen 6-chloropyrimidine-2,4(1H,3H)-dione (**97**),⁹⁰ which was alkylated with benzyl chloride **98a** or phenylpropyl bromide **98b** in DMF in the presence of K₂CO₃, yielding the corresponding *N*-1-derivatives **99a**⁹¹ and **99b** (Scheme 28).



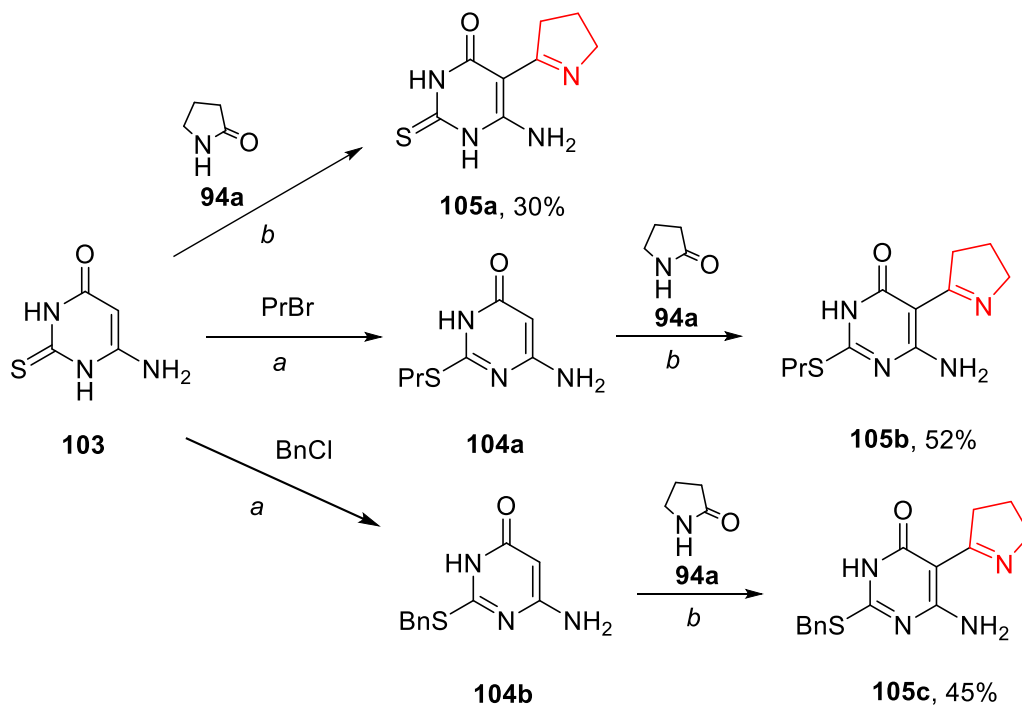
Scheme 28. Synthesis of 5-pyrrolyl-6-arylaminopyrimidines (**102a-c**). Reagents and conditions: *a* K₂CO₃/DMF, 65 °C, 8 h; *b* reflux, monitored by TLC; *c* PCl₃/1,4-dioxane, 0–5 °C to reach r. t., 10 min, then 90–95 °C, 5 h.

The chlorine atom at position 6 of the ring of compounds **99a,b** reacts smoothly with aniline **100a** and 3,5-dimethylaniline **100b**, resulting in 6-anilino-substituted pyrimidines **101a-c**. The latter, according to the already developed one-step synthesis, were converted by condensation with pyrrolidin-2-one **94a** in the presence of PCl_3 into the target 1-benzyl-5-(3,4-dihydro-2*H*-pyrrol-5-yl)-6-(phenylamino)-, 1-benzyl-5-(3,4-dihydro-2*H*-pyrrol-5-yl)-6-(3,5-dimethylphenylamino)- and 5-(3,4-dihydro-2*H*-pyrrol-5-yl)-6-(3,5-dimethylphenylamino)-1-(3-phenylpropyl)pyrimidine-2,4-(1*H*,3*H*)-diones **102a-c** (Scheme 28).⁹²

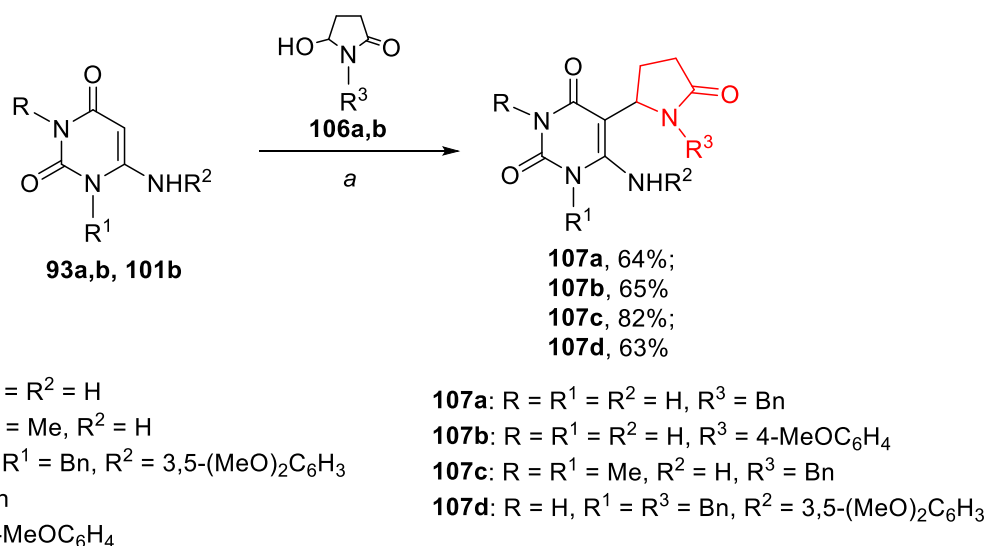
In order to further study the influence of functional groups on biological activity, it became necessary to expand the range of synthesized 2-pyrimidinylpyrrolidines, in connection with which we obtained 2-mercapto-substituted derivatives **105a-c**. Preliminarily, by the interaction of equimolar amounts of 6-amino-2-sulfanylidene-2,3-dihydropyrimidin-4(1*H*)-one (**103**), NaOH, and 1-bromopropane or benzyl chloride,⁹³ the corresponding sulfanyl derivatives **104a,b** were synthesized. Next, the starting thione **103** and *S*-alkylated pyrimidines **104a,b** were introduced into a reaction with pyrrolidin-2-one **94a** under the conditions already described, leading to the formation of *C*-azanucleoside analogues **105a-c** substituted at various positions of the pyrimidine ring (Scheme 29).⁹²

Another very promising method for the synthesis of pyrrolinylpyrimidine derivatives is the interaction of *N*-substituted 5-hydroxypyrrolidin-2-ones with various pyrimidine derivatives with an unsubstituted position 5- of the ring, which we have developed. Of the numerous methods for obtaining 5-hydroxypyrrolidin-2-ones substituted at the nitrogen atom by borohydride reduction of *N*-substituted succinimides, the pH-controlled reduction method turned out to be the most optimal.⁹⁴ Despite the rather wide permissible temperature range (-20 - 0 °C) recommended by various authors, only reduction at -30 °C allowed us to obtain compounds **110a,b**.

By heating pyrimidine derivatives **93a,b**, **101b** with *N*-substituted 5-hydroxypyrrolidin-2-ones **106a**⁹⁵ and **106b**⁹⁶ in glacial acetic acid, by analogy with the described method,⁹⁷ 5-pyrrolidone-substituted pyrimidine-2,4(1*H*,3*H*)-diones **107a-d** were obtained (Scheme 30).⁹²



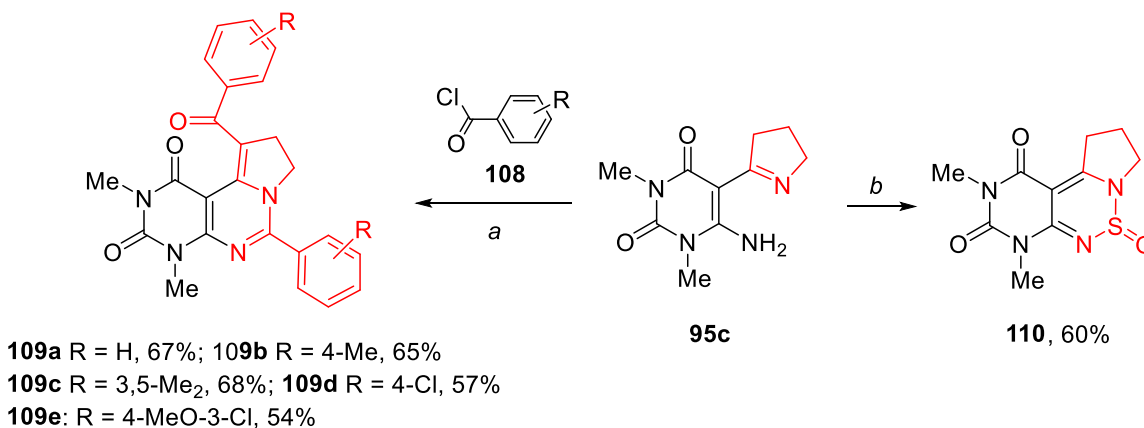
Scheme 29. Synthesis of C-azanucleoside analogues (**105a-c**). Reagents and conditions: *a* NaOH/H₂O/PrOH, reflux, 16 h; *b* PCl₃/1,4-dioxane, 0-5 °C to reach r. t., 10 min, then 90-95 °C, 5 h.



Scheme 30. Synthesis of 5-pyrrolidone-substituted pyrimidines (**107a-d**). Reagents and conditions: *a* glacial AcOH, 115-130 °C, 2 h.

According to the data available in the literature, it is known that a large number of pyrimidopyrimidine derivatives exhibit a wide spectrum of pharmacological activities, in particular, antitumor, antiviral, antioxidant, antifungal, hepatoprotective, and antidepressant.⁹⁸⁻¹⁰⁰ This is the reason for our study of the reaction of 6-amino-5-(3,4-dihydro-2H-pyrrol-5-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**95c**) with substituted benzoic acid chlorides and SOCl₂ in the presence of triethylamine. When studying the reaction products, it was found

that the reaction results in double inclusion of the benzoyl fragment, i.e., acylation of the enamine is accompanied by condensation with the formation of 6-aryl-10-aryl-2,4-dimethyl-1,2,3,4,8,9-hexahydropyrimido[5,4-*e*]pyrrolo[1,2-*c*]pyrimidine-1,3-diones **109a-e**. The reaction of compound **95c** with SOCl_2 in the presence of triethylamine proceeds via binucleophilic substitution with ring closure and the formation of 2,4-dimethyl-9,10-dihydro-2*H*-pyrimido[5,4-*d*]pyrrolo[1,2-*b*][1,2,6]thiadiazine-1,3(4*H*,8*H*)-dione-6-oxide (**110**) (Scheme 31).^{84, 101}



Scheme 31. Synthesis of compounds (**109a-e**) and (**110**). Reagents and conditions: *a* $\text{Et}_3\text{N}/\text{CHCl}_3$, reflux, 2 h; *b* $\text{SOCl}_2/\text{Et}_3\text{N}/\text{CHCl}_3$, reflux, 2 h.

Thus, a fundamentally new method for the synthesis of previously inaccessible 5,6-substituted pyrimidine-2,4(1*H*,3*H*)-diones by the interaction of 6-aminopyrimidine derivatives with various 5-hydroxypyrrolidin-2-ones has been developed.

3.2. Biological properties of 5-pyrimidinylproline derivatives

Antibacterial activity of the synthesized compounds was studied using the method given above, in the section 1.4.⁵⁴ Based on the results of biological studies, compounds **105c** and **110**, in which structures the aryl fragment in position 5- of the pyrrolidine ring is replaced by a pyrimidine fragment, are moderately active, inhibiting the growth of all used microorganisms. In a study of the antibacterial activity of 2-substituted (6-amino-2*H*-pyrrolo-5-yl)pyrimidinones **95a**, **105a-c**, it was found that replacing the 2-oxo group with a 2-thioxo group and alkylation at the sulfur atom leads to a noticeable increase in activity. Thus, the 2-oxo derivative **95a** has virtually no antibacterial activity, while the 2-thioxo derivative **105a** already exhibits weak activity. A further increase in activity is observed for the *S*-Pr derivative **105b** and even more so for the *S*-Bn derivative **105c**. The latter compound exhibits pronounced antibacterial activity on all strains used (Table 10).^{22, 28, 55}

Table 10. Antibacterial activity of most active 5-pyrimidinylpyrrolidines

Comp.	Inhibition zone diameter (mm)			
	<i>Staphylococcus aureus</i> 209p	<i>Staphylococcus aureus</i> 1	<i>Shigella flexneri</i> 6858	<i>Echerichia coli</i> 055
105c	19	15	18	17
109b	15	12	13	18
110	18	18	18	18

Toxicity and antitumor activity of 5-pyrimidinylpyrrolidines were tested by the usual methods, given in the section 1.4.^{56, 57} Derivatives from the 5-pyrimidinylpyrrolidine series differed in toxicity, among them compounds **95a**, **110** turned out to be the most toxic, and the toxicity of the remaining compounds was significantly lower ($LD_{100} = 1800\text{--}2500$ mg/kg). In the treatment of mice with *sarcoma* 180, compounds **95a**, **109c,d**, **110** exhibited antitumor activity, and derivatives **95a**, **109a** were active against mice with *sarcoma* 37 and rats with *sarcoma* 45. Thus, in the 5-pyrimidinylpyrrolidine series, only compound **109a** can be distinguished, which exhibits comparatively high antitumor activity and low toxicity (Table 11).²²

Table 11. Antitumor activity of most active 2-pyrimidinylpyrrolidines

Comp.	Acute toxicity, LD_{100} / <i>MTD</i> (mg/kg)	Inhibition of tumor growth, %		
		<i>S</i> - 180	<i>S</i> - 45	<i>S</i> - 37
95a	250 / 110	45.5	45.5	47.8
109a	2200 / 1000	-	41.2	37.3
109c	1800 / 750	48	-	-
109d	1800 / 750	46	-	-
110	250 / 110	44	-	-

Anti-HIV-1 test of the synthesized compounds was carried out by the methods, given in the section 1.4.^{58, 59} During the study of the anti-HIV-1 activity of the synthesized compounds, it was established that four compounds exhibited antiviral activity that was < 20 μM while also exhibiting no apparent toxicity ($IC_{50} \geq 30$ μM) in all three cell lines. Compound **102b** was the most active, but it was very toxic in all cell lines used. Compounds **101b** and **109a** showed the best activity, without pronounced cytotoxicity against all cell lines.^{34, 60} However, the above-mentioned compounds were inferior in activity to the drug AZT, which was used as a positive control (Table 12).

Table 12. Anti-HIV-1 activity of most active 2-pyrimidinylpyrrolidines

Comp.	Anti-HIV-1 activity in human PBM cells (μM)		Cytotoxicity (IC_{50} , μM)		
	EC_{50}	EC_{90}	PBM	CEM	VERO
101b	4.7	13.9	> 100	50.0	32.8
102a	8.9	45.6	15.5	27.8	35.3
102b	0.48	2.8	20.4	18.5	8.0
109a	4.5	> 100	11.4	> 100	> 100
AZT	0.0018	0.015	> 100	14.3	50.6

The conducted studies have established that in the series of 5-pyrimidinylpyrrolidines, the best results were demonstrated by compounds in the structures of which the presence of a Bn- fragment in position 1, an aniline fragment in position 6 and a pyrrolidine fragment in position 5 of the pyrimidine ring plays a huge role in the manifestation of anti-HIV activity, the last mentioned modification leading to a sharp increase in the biological activity of the compounds (Table 12).^{34, 60}

4. The Study of Structure-Activity Relationship in the Row 2-Aryl- and 5-Pyrimidinylpyrrolidines

We have developed and carried out syntheses of new pyrrolidine analogs substituted at various positions of the ring. In order to find antibacterial, antitumor and antiviral (anti-HIV) drugs among proline analogues, biological studies of the synthesized derivatives of 2-aryl- and 5-pyrimidinylpyrrolidines were conducted. Due to the fact that the synthesis of the compounds and biological studies were carried out in parallel, and also taking into account the literature data, the expediency of introducing certain substituents into the target molecules was determined in accordance with the tendency to enhance biological activity. It is the latter factor that explains the different number of derivatives in the synthesized series of compounds. The structure-activity relationship was studied and the fragments responsible for the activity were identified:

• **Antibacterial activity**

- 2-aminomethyl-1,2-diarylpyrrolidin-5-ones have a fairly high antibacterial activity,
- four-membered 1,2-diarylazetidines are inferior in antibacterial activity to the corresponding five-membered pyrrolidinecarbonitriles, while derivatives of 1,2-diarylpyrrolidinecarbonitriles were more active than 1-aryl-2-phenylpyrrolidines,
- the presence of Me, *i*-PrO, BnO substituents in the aryl fragments in the 1st and 2nd positions of the pyrrolidine ring in the series of 1,2-diarylpyrrolidines leads to an increase in antibacterial activity,
- among 2-arylpyrrolidines containing carboxamide, nitrile, carboxyl and aminomethyl groups, antibacterial activity increases in the following order: C(O)NH₂ < CN < COOH < CH₂NH₂,
- in the series of 5-pyrimidinylpyrrolidines with substituents in the 2-position of the pyrimidine ring, activity increases in the series C=O < C=S < PrS < BnS.

• **Antitumor activity**

- 2-phenylpyrrolidine-2-carboxylic acids and 2-arylpyrrolidine-2-carboxamides, having relatively low toxicity, exhibit moderate antitumor activity,
- derivatives of substituted 1-aryl-2-phenylpyrrolidines are inferior to analogs of 1,2-diaryl-5-oxopyrrolidines in terms of toxicity and antitumor activity,
- among the synthesized compounds containing aminomethyl, nitrile, carboxamide and carboxyl groups, an increase in antitumor activity was observed in the following order: CH₂NH₂ ≤ CN < C(O)NH₂ < COOH.

• **Anti-HIV activity**

- in the series of 2-arylpyrrolidines, pyrrolidinecarbonitriles substituted at various positions of the pyrrolidine ring: in position 1 – 3,5-Me₂C₆H₃- and 4-MeC₆H₄- groups, and in position 2 – 2-BnO-, 4-BnO- and 4-*i*-PrO groups, contribute to the enhancement of anti-HIV activity,
- in 1,2-diarylpyrrolidines containing carboxamide, aminomethyl and nitrile groups in the second position of the pyrrolidine ring, an increase in activity is observed in the following series: C(O)NH₂ < CH₂NH₂ < CN,
- in the series of 5-pyrimidinylpyrrolidines, the best results were demonstrated by compounds carrying a Bn fragment in position 1, a pyrrolidine fragment in position 5, and an aniline fragment in position 6 of the pyrimidine ring.

The structures of more active compounds are presented in the general formula (Figure 6).

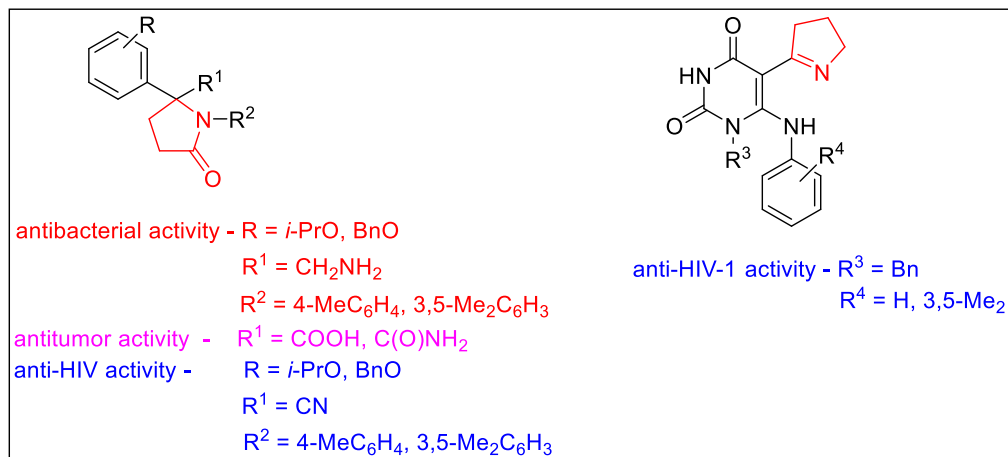


Figure 6. General structure of active 2-aryl- and 5-pyrimidinylpyrrolidine derivatives.

Conclusions

A new efficient method for the synthesis of 2-arylpyrrolidines and 2-arylazetidines by intramolecular cyclization of arylglycine derivatives under PTC conditions has been developed. A new method for the selective reduction of nitrile groups of pyrrolidinecarbonitriles using a catalytic metal complex system based on sodium borohydride and polyethyleneglycol has been proposed. Alternative methods for the synthesis of 6-substituted pyrimidinediones containing a pyrrole fragment in position 5 of the pyrimidine ring have been developed. In order to find antibacterial, antitumor and antiviral (anti-HIV) drugs among proline analogues, biological studies were conducted, the structure-activity relationship was studied and the fragments responsible for the activity were identified.

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