ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

Հայաստանի քիմիական հանդես
Химический журнал Армении **71, №4, 2018** Chemical Journal of Armenia

UDC 547.854

# SYNTHESES AND BIOLOGICAL PROPERTIES OF BENZO[4',5']IMIDAZO[2',1': 6,1]PYRIDO[2,3-d]PYRIMIDINES: MINI-REVIEW

**A. A. HARUTYUNYAN**[1,2]

[1]Russian-Armenian (Slavonic) University, Yerevan
[2] The Scientific Technological Centre
of Organic and Pharmaceutical Chemistry of NAS RA
26, Azatutyan Ave., Yerevan, 0014, Armenia
E-mail: harutyunyan.arthur@yahoo.com

The known methods for the synthesis of benzo[4',5']imidazo[2',1': 6,1]pyrido[2,3-d]pyrimidine heterocyclic derivatives based on heterocyclic reactions of substituted benzimidazoles and alternative approaches using substituted pyrimidinyl-5-propanoic acids have been considered. It was shown that the developed synthetic strategy based on the heterocyclization of substituted pyrimidinyl-5-propanoic acids is a successful addition to the previously described methods, since it allows to bypass the significant limitations associated with the use of substituted benzimidazoles and introduce various types of functional substituents in the target heterocyclic system and at different positions of the ring. The available data on the biological properties of synthesized compounds are summarized.

Figs. 2, references 18.

## 1. Introduction

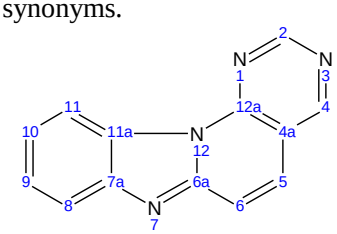
Polycyclic heteroaromatic compounds based on annelated azaheterocycles, the most important structural feature of which is the planar structure, exhibit high biological activity, including antitumor, antibacterial, antiviral and others [1,2]. The biological activity of this class of compounds is due to their ability to interact with DNA, being associated with small and large grooves or intercalation between adjacent bases in a double helix, the interaction mechanism of the latter being considered as the main one. In both cases, the secondary structure of DNA is distorted and its functioning is disrupted, and therefore the connections with this mechanism of action are considered as the most promising in developing new-generation drugs for the treatment of tumor diseases and viral and bacterial infections [3]. It should be noted that bi-and tricyclic compounds are best known as

intercalating heterocycles, while tetra- and higher-annealed compounds are less well studied, although the possibility of intercalation and the associated pharmacological activity are shown for them [4].

Among the tetracyclic heteroaromatic compounds, we have drawn attention to the syntheses and biological properties of the derivatives of the benzo[4′,5′]imidazo[2',1': 6,1]pyrido[2,3-d]pyrimidine (1) condensed on the basis of three nitrogen-containing heterocycles, and of which there are a limited number of publications in the literature. Therefore, in view of the growing interest in the synthesis and biological properties of polycyclic azaheterocycles and limited information on benzo[4′,5′]imidazo-[2',1': 6,1]pyrido[2,3-d]pyrimidines, this review summarizes all available works in this area, including own research, especially since the latter constitute an essential part of the available data.

## 2. Synthesis of benzo[4′,5′] imidazo[2',1': 6,1]pyrido[2,3-d]pyrimidine derivatives

Before proceeding to the discussion of works in this area, it is appropriate to dwell briefly on the name of the heterocyclic system 1, which can be compiled in accordance with the nomenclature rules and recommendations of the IUPAC and CAS rules using computer programs based on the above nomenclature rules. Thus, compound 1 can be named pyrimido[5',4': 5,6]pyrido[1,2-a]benzimidazole (ACD / ChemSketch package, version ACD / Labs 6.0) and benzo[4,5]imidazo[2 ',1': 6,1]pyrido[2,3-d]pyrimidin (package ACD / Name, version 1.0), therefore, in the further presentation of the work the names of the derivatives are given in author's versions and are treated as synonyms.

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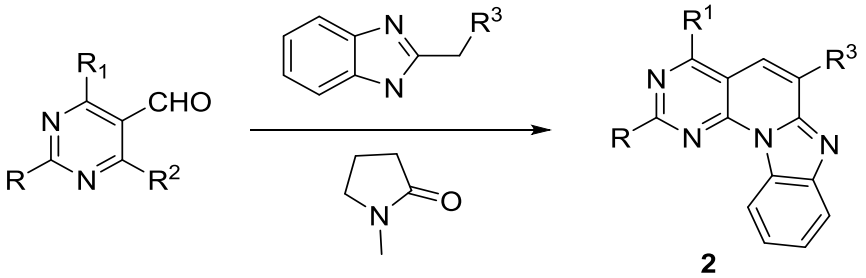
In order to systematize the presentation, the known syntheses of the derivatives of the heterocyclic system under discussion are conventionally divided into two groups according to two alternative synthetic strategies that are based on the annealating of functionalized benzimidazoles or on the heterocyclization of substituted pyrimidinyl-5-propanoic acids.

### 2.1. Synthesis based on substituted benzimidazoles

For the first time, the pyrimido[5',4': 5,6]pyrido[1,2-a]benzimidazole derivatives 2 were obtained in good yields by heating 5-carbaldehydebarbituric acid or 2,4,6-trichloropyrimidinyl-5-carbaldehyde with 2-substituted benzimidazoles in

N-methylpyrrolidone according to Scheme 1 and patented as photographic materials and fluorescent dyes [5-7].

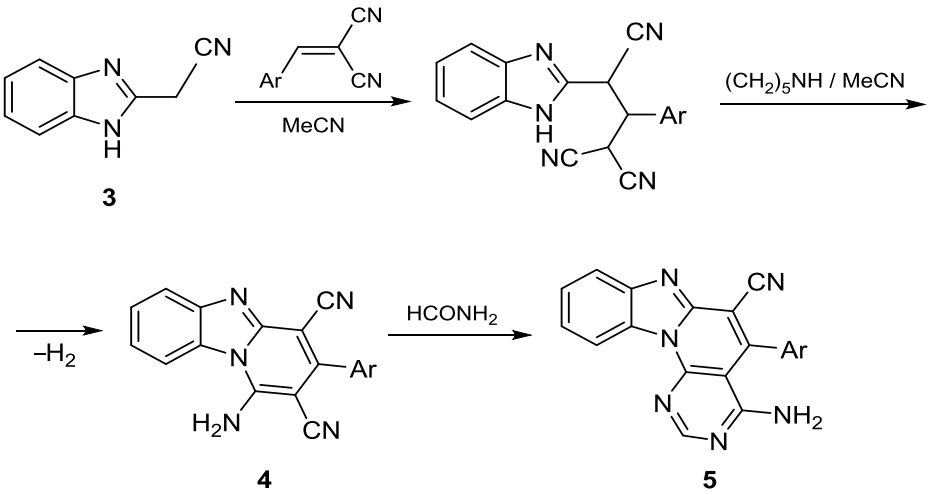
Scheme 1




2. R, $R^1$, $R^2$ = Hal, OH, $N(Et)_2$, NHPh; $R^3$ = benzimidazol-2-yl, benzoxazol-2-yl, benzothiazol-2-yl, 4-$NO_2C_6H_4$, CN, COOH.

According to the method proposed by the Polish authors, 1H-benzimidazole-2-acetonitrile (3) is condensed with arylidene malononitriles under the Michael reaction conditions, after which the adduct formed is boiled in MeCN in the presence of piperidine in a six-membered cycle with simultaneous aromatization. The thus formed 1-amino-3-arylpyrido[1,2-a]benzimidazole-2,4-dicarbonitriles 4 are converted by boiling with formamide to the desired 5-aryl-4-methylpyrimido[5',4': 5,6 ]pyrido[1,2-a]- benzimidazole-6-carbonitrile 5, according to Scheme 2 [8]:

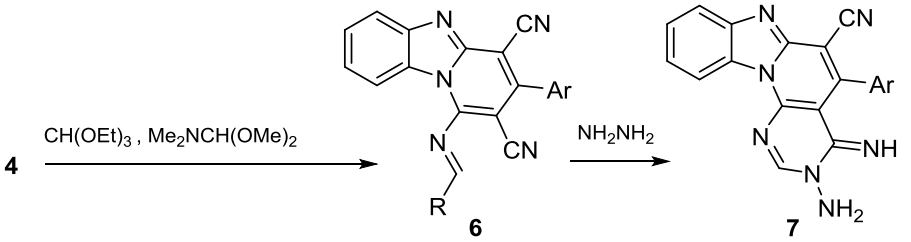
Scheme 2




4.5: Ar = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$ClC_6H_4$, 3-$NO_2C_6H_4$, 4-$NMe_2C_6H_4$.

Dicarbonitriles 4 were the starting compounds also in the synthesis of the 3-amino-4-imino derivatives of the heterocyclic system under discussion according to scheme 3 [9]:

Scheme 3

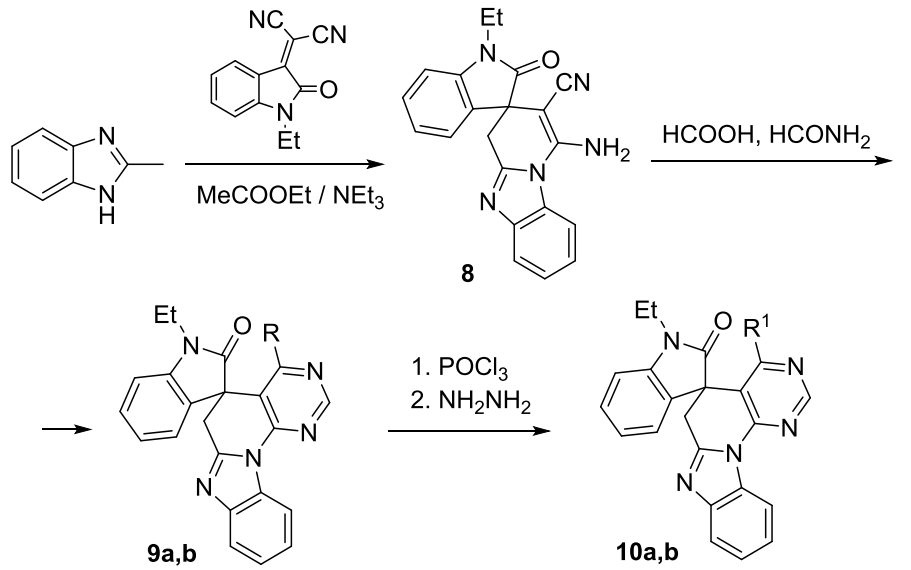



6.7: R = OEt, $NMe_2$; Ar = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$ClC_6H_4$.

The interaction of 1-amino-3-arylpyrido[1,2-a]benzimidazole-2,4-dicarbonitriles 4 with triethyl orthoformate or dimethylformamidedimethylacetal gives imines 6 which with hydrazine hydrate form 3-amino-5-aryl-4-iminopyrimido[5',4': 5,6]pyrido[1,2-a]benzimidazole-6-carbonitrile.

In the synthesis of spirocondensed pyrimido[5',4': 5,6]pyrido[1,2-a]benzimidazole derivatives, by reacting 2-methylbenzimidazole with 3-dicyanomethylidene-1-ethyl-2-oxoindoline, cyano-3,4-dihydro-1'-ethylspiro {benzimidazo[1,2-a]pyridine-3,3'-indolin}-2'-one (8) were synthesized, which are cyclized by the action of formamide or formic acid thus forming 4-amino-5,6-dihydro-1'-ethylspiro-{benzimidazo[1',2': 1,6]pyrido[2,3-d]pyrimidine-5,3'-indoline}-2'-one (9a) and 3,5,6-trihydro-1'-ethylspiro{benzimidazo[1',2': 1,6]pyrido [2,3-d]pyrimidine-5,3'-indoline}-2',4-dione (9b). The latter was subsequently converted to 4-chloro- and 4-hydrazino derivatives 10a, b by the subsequent chlorination with $POCl_3$ and hydrazinolysis according to Scheme 4 [10]:

Scheme 4




9a, b: R = $MH_2$ (a), OH (b); 10a, b: $R^1$ = Cl (a), $NHNH_2$ (b).

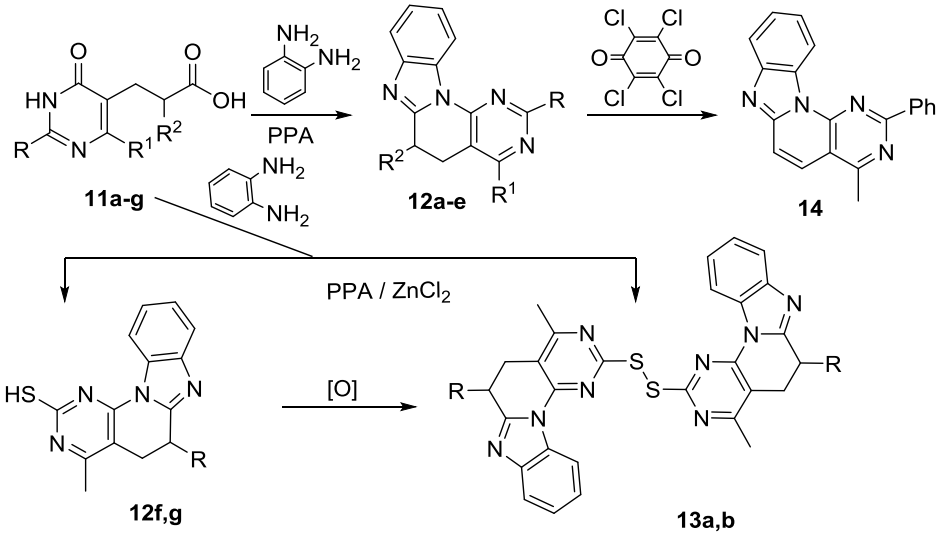
### 2.2. Syntheses based on substituted pyrimidinyl-5-propanoic acids

As follows from the above syntheses, in all the developed approaches as one of the initial synthons, 2-substituted benzimidazole necessarily appears and the substituents in the resulting compounds are limited to benzazoles, nitrile- and amino groups and aryl groups.

Interestingly, the number of synthesized pyrimido[5',4':5,6]pyrido[1,2-a]benzimidazole derivatives according to the indexes of Subject Index CAS and RZhChimia was only 28 compounds and their biological activity data was absent. The limitations of the described approaches are related to the fundamental impossibility to introduce into the molecules, in particular, methylene and methyl groups at different positions of the ring, aryl and sulfanyl groups into the pyrimidine fragment. Meanwhile, the presence of methylene and methyl groups in π-deficient heterocyclic systems can substantially increase the possibilities of obtaining new types of derivatives by condensation of these groups with aromatic aldehydes to produce heteroaromatic compounds with extended π-conjugation chains, as well as a sulfanyl group possessing wide functionality.

In this regard, in recent years, a fundamentally new method for constructing the heterocyclic system under discussion has been developed based on readily available synthons – 2-substituted pyrimidinyl-5-propanoic acids, allowing methylene, methyl and sulfanyl groups to be introduced into the molecule according to Scheme 5:

Scheme 5

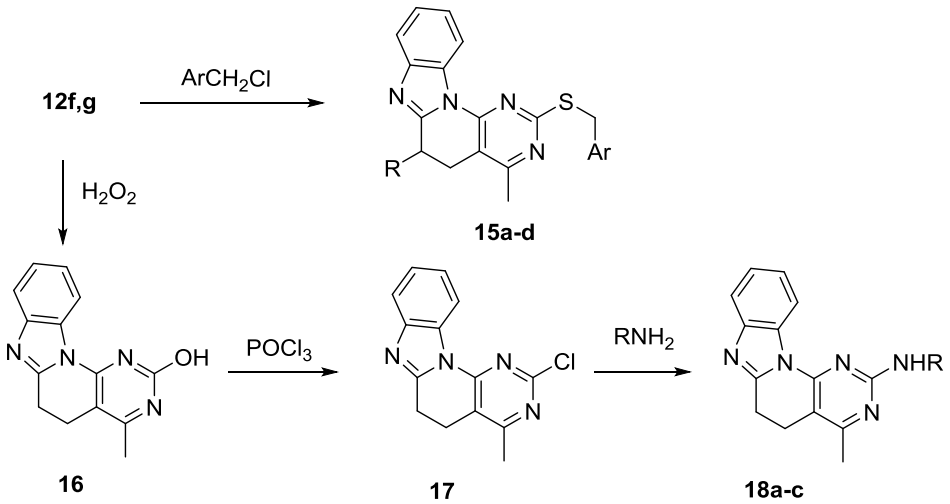



11a-g: R, $R^1$, $R^2$ = Ph, Me, H (a), 4-Me$C_6H_4$, Me, H (b), Ph, Me, Me (c), Ph, OH, H (d), Ph, OH, Me (e), SH, Me, H (f), SH, Me, Me (g); 12a-e: R, $R^1$, $R^2$ = Ph, Me, H (a), 4-Me$C_6H_4$, Me, H (b), Ph, Me, Me (c), Ph, OH, H (d), Ph, OH, Me (e); 12f,g: R = H (f), Me (g).

It was found that the reaction of the corresponding 2-aryl-6-methyl(hydroxy)-3,4-dihydro-4-oxopyrimidine-5-ylpropanoic and 2-methylpropanoic acids 11a-e with 1,2-diaminobenzene in polyphosphoric acid (PPA), of acids 11f, g ‾ in a mixture of PPA-$ZnCl_2$ proceeded by a cascade mechanism and led in a single step to a 4-methyl-, 4,6-dimethyl-4-hydroxy-6-methyl derivative of 2-aryl-5,6-dihydro-benzo[4',5']imidazo[2',1': 6,1]pyrido[2,3-d]pyrimidines 12a-e and the corresponding thiols 12f,g, and two disulfides 13a,b. Disulfides are formed in the form of an impurity with a yield of about 15% directly as a result of condensation, and also in the oxidation of 2-thioxoderivatives 12f,g with air oxygen. Oxidative aromatization of 5,6-dihydropyrrolidene 12a with chloranyl was carried out to form a substituted benzo[4',5']imidazo[2',1': 6,1]pyrido[2,3d]pyrimidine 14 with a 16π electron circuit [ 11-15].

The presence of the thiol group in the molecule substantially increased the possibilities of chemical transformation of the starting compounds 12f,g into new derivatives, as shown in Scheme 6:

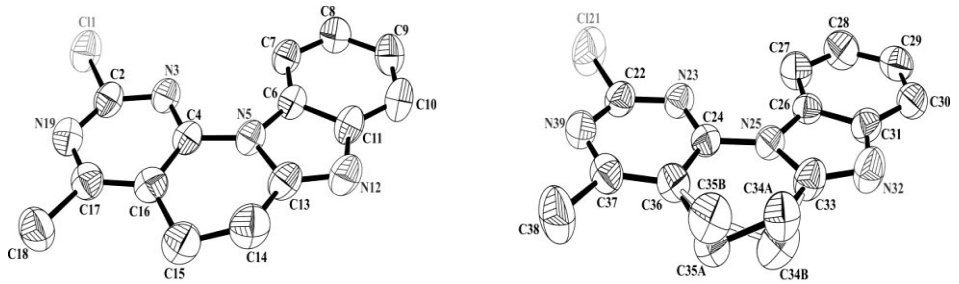
Scheme 6




15a-d: R, Ar = H, 3-$NO_2$-4-$MeOC_6H_3$ (a); H, 2-$ClC_6H_4$ (b); Me, 2-$ClC_6H_4$ (c); Me, 4-$FC_6H_4$ (d); 18a-c: R = H (a), Me (b), Ph (c).

Alkylation of thiols 12f,g with substituted benzyl chlorides produced S-benzyl derivatives 15a-d, by oxidation of $H_2O_2$ in an alkaline medium ‾ 2-hydroxy derivative 16. Chlorination of the latter yielded 2-chloro derivative 17, aminolysis of which synthesized 2-amino derivatives 18a-c.

The spatial structure of the 2-chloro-4-methyl-5,6 dihydrobenzo[4',5']imidazo [2',1': 6,1]pyrido[2,3-d]pyrimidine (17) and that of its tetramer are shown in Fig. 1 and 2 (the numbering of atoms is arbitrary).




a b

Fig. 1. Structures of symmetrically nonequivalent molecules of compound 17 with ordered structure (a) and with disordered structure (b). Ellipsoids are depicted with 50% probability.

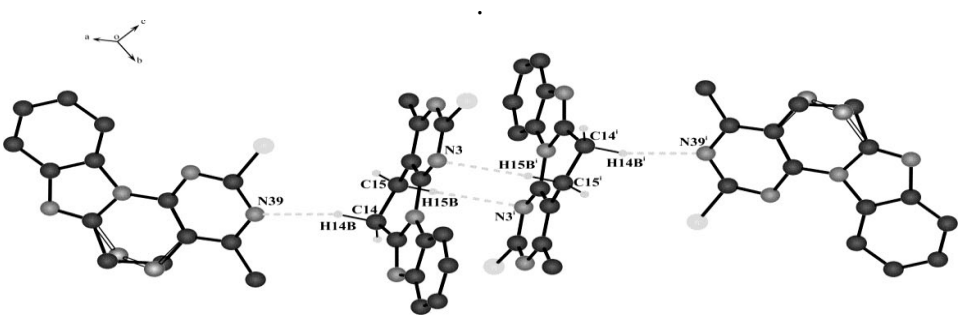
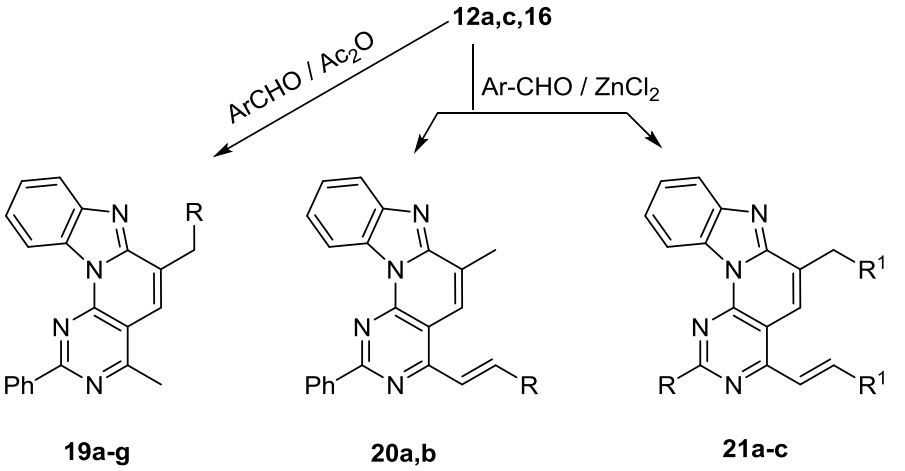



Fig. 2. A tetramer of the molecules of compound 17, formed by non-classical hydrogen bonds.

X-ray diffraction analysis of the tetracycle 17 crystal showed that the phenyl, imidazole and pyrimidine rings had an almost flat conformation, the molecules forming a tetramer (Fig. 2) by binding non-classical hydrogen bonds (C14-H14B ... ..N39 and C15H15B ... ..N3i).

Based on the new method for the synthesis of benzo[4',5']imidazo[2',1': 6,1] pyrido[2,3-d]pyrimidine derivatives, an additional possibility of functionalization of the starting compounds by condensation of 4-methyl-, (RS)-4,6-dimethyl-2-phenyl-5,6-dihydrobenzo[4',5']imidazo[2',1': 6,1]pyrido[2,3-d]pyrimi-dines 12a,c and 4-methyl-5,6-dihydrobenzo[4',5']imidazo[2',1': 6,1]pyrido[2,3-d]pyrimidin-2-ol (16) with aromatic and heterocyclic aldehydes under various experimental conditions was realized, according to the following Scheme 7 [16]:

Scheme 7




19a-g: R = Ph (a), 2-AcO-naphthalen-1-yl (b), 2,4-$Cl_2C_6H_3$ (c), 4-$MeOC_6H_4$ (d), CH = $CHC_6H_4$ (e), thiophene-2-yl (f), 4-$C_6H_5CH_2OC_6H_4$ (g); 20a, b: R = 4-$NO_2$ (a), Cl (b). 21a-c: R, $R^1$ = Ph, 4-$NO_2C_6H_4$ (a), OH, 4-$NO_2C_6H_4$ (b), OH, 4-$ClC_6H_4$ (d).

It was shown that the reactive 4-methyl- and 6-methylene groups in the substituted 5,6-dihydro-benzo[4',5']imidazo[2',1':6,1]pyrido[2,3-d]pyrimidines reacted with aromatic aldehydes under various conditions: boiling in acetic anhydride to form 6-aryl (heteryl)methyl-4-methyl derivatives 19a-g, and by co-heating in the presence of $ZnCl_2$ – 4-substituted derivatives 20a,b and bis-derivatives 21a-c.

Thus, the available methods for the synthesis of substituted benzo[4',5'] imidazo[2',1',6,1]pyrido-[2,3-d]pyrimidines provide efficient preparation of a variety of heterocycle derivatives for subsequent biological and technical studies.

### 3. Biological properties of benzo[4,5] imidazo[2',1':6,1]pyrido[2,3-d]pyrimidines derivatives

In the literature, only the antibacterial and antimonoaminoxidase properties of benzo[4′,5′]imidazo[2',1':6,1]pyrido[2,3-d]pyrimidine derivatives are described, exclusively in the works of domestic authors.

Antibacterial properties of some derivatives of benzo[4′,5′]imidazo[2',1': 6,1]pyrido[2,3-d]pyrimidi-nes have been studied for strains of gram-positive bacteria (*Staphylococcus aureus* 209p and *S. aureus* 1) and gram-negative rods (*Shigella flexneri* 6858, *Escherichia coli* 0-55) by the methods of "diffusion in agar" and "two-fold serial dilutions", the control drug is furazolidone. It has been shown that benzo[4′,5′]imidazo[2',1': 6,1]pyrido[2,3-d]pyrimidines 12b,i, 13a, 15a, 16 show weak antibacterial activity on all four strains, and the compounds 12a, 13b, 15b-d, 19a-f, 20a,b, 21a,c are completely devoid of activity.

At the same time, as a result of the modification of completely inactive heterocycle 12a, the derivatives 12d, 14 were obtained, exhibiting moderate antimicrobial properties, somewhat higher for gram-positive bacteria [17].

The antimonoaminoxidase properties of compounds were studied by their effect on the deamination of serotonin (5-OT) by the brain monoamine oxidase (MAO) *in vitro*, the control ‑ drug indopan. It has been found that tetracycles 19d, 20b, 21a show pronounced anti-MAO activity, inhibiting enzyme activity by 60-63%, while derivatives 12a, c, e, 19b are much weaker [18].

## ԲԵՆԶՕ[4',5']ԻՄԻԴԱԶՕ[2',1':6,1]ՊԻՐԻԴՕ[2,3-d]ՊԻՐԻՄԻԴԻՆՆԵՐԻ ՍԻՆԹԵԶՆԵՐԸ ԵՎ ԿԵՆՍԱԲԱՆԱԿԱՆ ՀԱՏԿՈՒԹՅՈՒՆՆԵՐԸ: ՀԱԿԻՐՃ ԱՄՓՈՓԱԳԻՐ

**Ա. Ա. ՀԱՐՈՒԹՅՈՒՆՅԱՆ**

*Դիտարկվել են հետերոցիկլիկ համակարգի՝ բենզո[4',5']իմիդազո[2',1':6,1]պիրիդո-[2,3-d]պիրիմիդինի սինթեզի հայտնի մեթոդներ, հիմնված տեղակալված բենզիմիդազոլի հետերոցիկլման և այլընտրանքային մոտեցումներ տեղակալված պիրիմիդինիլ-5-պրոպա-նաթթվի կիրառման վրա: Ցույց է տրվել, որ մշակված սինթետիկ ռազմավարությունը՝ հիմնված տեղակալված պիրիմիդինիլ-5-պրոպանաթթվի հետերոցիկլման վրա, համար-վում է հաջողված լրացում նախկինում նկարագրված մեթոդներին, քանի որ թույլ է տա-լիս շրջանցել էական սահմանափակումները՝ կապված տեղակալված բենզիմիդազոլի կի-րառման հետ, և ներմուծել ամբողջական հետերոցիկլիկ համակարգ տարբեր տիպի ֆունկցիոնալ տեղակալիչներ՝ տարբեր դիրքերում: Ընդհանրացվել են սինթեզված միա-ցությունների կենսաբանական հատկությունների վերաբերյալ առկա տվյալները:*

## СИНТЕЗЫ И БИОЛОГИЧЕСКИЕ СВОЙСТВА БЕНЗО[4′,5′]ИМИДАЗО[2′,1′: 6,1]ПИРИДО[2,3-d]ПИРИМИДИНОВ: МИНИ-ОБЗОР

**А. А. АРУТЮНЯН**[1,2]

[1]Российско-Армянский (Славянский) университет, Ереван
[2]Научно-технологический центр органической и фармацевтической химии
НАН Республики Армения
Армения, Ереван, 0014, пр. Азатутян, 26
E-mail: harutyunyan.arthur@yahoo.com

Рассмотрены известные методы синтеза производных гетероциклической системы бензо[4′,5′]имидазо[2′,1′:6,1]пиридо[2,3-d]пиримидина, основанные на реакциях гетероциклизации замещенных бензимидазолов и альтернативные подхо-ды с использованием замещенных пиримидинил-5-пропановых кислот. Показано, что разработанная синтетическая стратегия, основанная на гетероциклизациях за-мещенных пиримидинил-5-пропановых кислот, является удачным дополнением ранее описанных методов, поскольку позволяет обходить существенные ограниче-ния, связанные с использованием замещенных бензимидазолов и вводить в целе-вую гетероциклическую систему различные типы функциональных заместителей и по различным положениям кольца. Обобщены имеющиеся данные по биологиче-ским свойствам синтезированных соединений.

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