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MINI-REVIEW ARTICLE

Condensed Pyridopyrimidines and Pyridopyrazines Containing a Bridgehead Nitrogen Atom: Synthesis, Chemical Properties and Biological Activity

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Abstract: The investigation of effective and green synthetic routes to approach to novel fused heterocycles with pyridopyrimidine and pyridopyrazine scaffolds stirs up broad interest from scientists as they are capable of providing valuable properties such as anticancer and antimicrobial activities and they are proved γ-secretase modulators, polymers, and corrosion inhibitors. This causes a steady increase in the number of publications on titled condensed systems. The present review article summarizes recent literature data from 2010 to 2020 on the methods of synthesis, chemical transformations and biological properties of condensed bicyclic systems of pyridopyrimidine and pyridopyrazine with a bridgehead nitrogen atom to establish the current state of the art in this area.

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Keywords: Pyrido[1,2-*a*]pyrimidines, pyrido[1,2-*a*]pyrazines, pyrido[1,2-*c*]pyrimidines, bridgehead nitrogen atom, reactivity, biological activity.

1. INTRODUCTION

Fused heteroaromatic compounds with pyridopyrimidine and pyridopyrazine scaffolds have recently occupied a notable place in the work of chemists thanks to their application as anticancer [1-6], anti-diarrheal [7] and antimicrobial agents [8]. Moreover, these compounds could be used as the inhibitors of bacterial biotin carboxylase [9], human carbonic anhydrase [10] and corrosion [11]; γ-secretase modulators [12,13] and polymers [14-17].

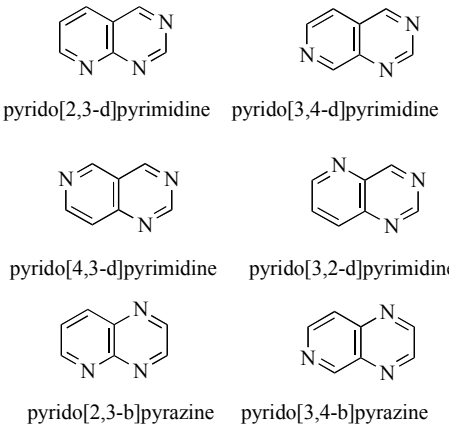

Fig. (1). Examples of fused pyridopyrimidines.

Condensed pyridopyrimidines are also convenient for chemical transformations because of their high reactivity [18-20]. Among the series of bicyclic fused pyridopyrimidines, 6 isomeric structures are known and well-reviewed. These compounds are presented in Fig. (**1**). [21-23].

This review article considers condensed pyridodiazines containing a bridgehead nitrogen atom: pyrido[1,2-*a*]pyrimidine, pyrido[1,2-*a*]pyrazine, pyrido[1,2-*c*] pyrimidine. All the examples of condensed pyridopyrimidine and pyridopyrazine with a bridgehead nitrogen atom are shown in Fig. (**2**).

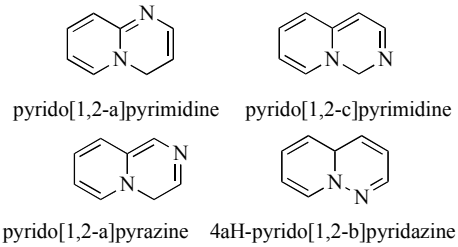

Fig. (2). Condensed pyridopyrimidine and pyridopyrazine with a bridgehead nitrogen atom.

The study on these systems began in the mid-1960s, and since then, methods of their construction, as well as biological properties, have been keenly studied [24-33].

This survey covers the literature of the last ten years that has not been analyzed before. The present review discusses the condensed compounds of pyridopyrimidine and pyridopyrazine, which contain a bridgehead nitrogen atom, which has been analyzed. Among the above described heterocyclic systems, pyrido[1,2-*a*]pyrimidines were the most fully studied both in terms of synthetic methods of preparation and of biological activity, and no literature data for pyrido[1,2-*b*]pyridazine isomeric system is currently present.

2. SYNTHESIS OF CONDENSED PYRIDOPYRIMIDINES AND PYRIDOPYRAZINES CONTAINING A BRIDGEHEAD NITROGEN ATOM

2.1. Synthesis of pyrido[1,2-*a*]pyrimidines and their Benzologs

Synthetic approaches using 2-aminopyridines are the most common methods for the preparation of the pyrido[1,2-*a*]pyrimidines. The reactions of methylene-active compounds and 2-aminopyrdine differ because of ease to perform, high yields, the

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possibility of using non-toxic solvents, which is one of the approaches to green chemistry. The interaction between 2-aminopyridines and malonic acid derivatives at heating in ethanol, toluene, or DMF gives keto-functionalizated pyridopyrimidines **1** (Scheme **1**) [34-39].

Refluxing of 2,6-diaminopyridine with sodium acetate and chloroacetic acid during 10 h led to the formation of 6-amino substituted pyrido[1,2-*a*]pyrimidin-2-one **2** in a high yield (Scheme **1**) [34].

A similar approach was used in an effective one-pot three-component method for the production of 4-amino-pyrido[1,2-*a*]pyrimidines **3** from 2-aminopyridine, aromatic/heteroaromatic aldehydes and malononitrile was proposed in works [40,41].

This pot three-component method can be applied either in the presence of reusable catalytic system [40] or refluxing in isopropanol in the presence of a catalytic amount of triethylamine [41] (Scheme **2**).

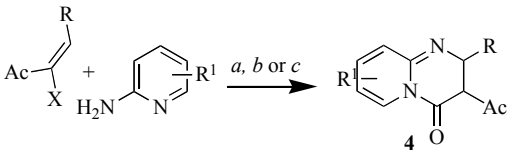
Reactions of 2-aminopyridines with activated alkenes allow to synthesize the substituted pyrido[1,2-*a*]pyrimidines with high yields (Scheme **3**, Table 1). This type of reaction can undergo at both catalytic [42-44] and non-catalytic [44-49] conditions. In some works, the efficiency of using MW irradiation is described [44-47]. This method allows obtaining the target fused pyrido[1,2-*a*]pyrimidines using non toxic solvents [44-48], and in some cases, providing synthesis at room temperature [48,49], which, of course, is an advantage of this approach, as above mentioned conditions are in frame of green chemistry principles.

Zang *et al.* reported the synthesis of substituted pyrido[1,2-*a*]pyrimidin-4-ones **4** by the cyclocondensation of aminopyridines with ketovinyl derivatives in the presence of a copper catalyst, the procedure (*a*), as shown in (Scheme **3**) (Table **1**) [42].

Reaction conditions are listed in Table **1**.

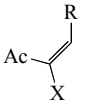
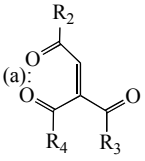
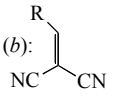
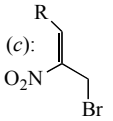
A new method (*b*) (Scheme **3**, Table **1**) was also developed for the synthesis of pyrido[1,2-*a*]pyrimidin-4-ones **4** by reaction of 2-aminopyridines with alkyl/arylidenemalononitriles at heating in presence of a copper catalyst (Scheme **3**) [43].

An efficient work-up procedure (*c*) (Scheme **3**, Table **1**) for access of pyrido[1,2-*a*]pyrimidine **4** was reported via interaction between 2-aminopyridine with substituted nitroalkenes [49]. The possibility of performing of above reaction at room temperature and high yields are some of the advantages of the described procedure.



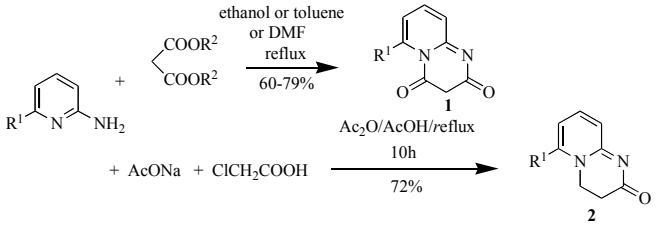
Scheme 3. Synthesis of pyrido[1,2-*a*]pyrimidin-4-ones **4** by Zang *et al.* [42], Mishra *et al.* [43], Satham *et al.* [49].

Table 1. The comparing of synthetic procedures for the obtaining of pyrido[1,2-*a*]pyrimidines 3.

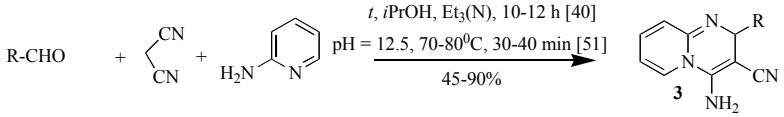
	Conditions [Reference]	Yield,%
		
	Cu^{2+} or Cu/cryptomelane, DMSO, 80^0C, air, 12h [42]	52-93
	CuI / TBAI, DMF, 80^0C O_2 (1 atm) [43]	52-71
	THF, room temperature [49]	80-98

Cyclocondensation reaction for the obtaining of substituted pyrido[1,2-*a*]pyrimidin-2-ones **5**, starting from Baylis-Hillman adducts, is presented in (Scheme **4**) [45-47]. The above transformation includes sequential Michael addition, intramolecular substitution, and [1,3]-proton shift.

An effective approach to 2-[pyrido[1,2-*a*]pyridmidine-3-ylidene]acetic acids **6** was described via reaction of 2-aminopyridines with aconic acid at room temperature in an ethyl alcohol (Scheme **5**) [48]. Simple work up procedure, the usage of non-toxic solvent, room temperature of the reaction, and no column technique for purification of target compounds **6** highlight the presence of green technologies.

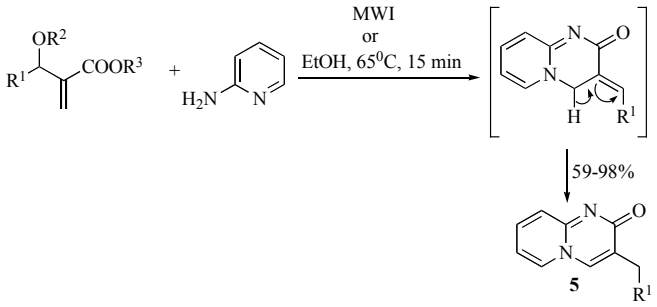


Scheme 1. Synthesis of keto-functionalized pyridopyrimidines **1,2** by authors [34-39].



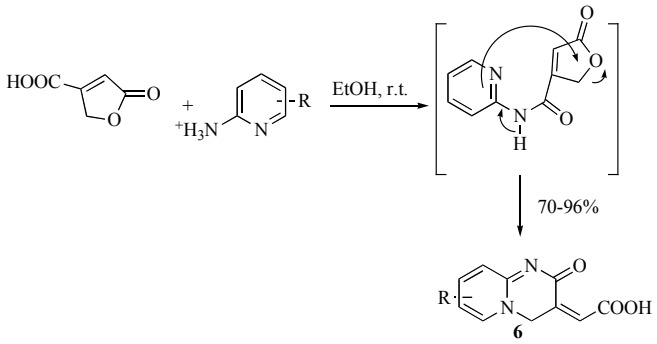
Scheme 2. Synthesis of 4-amino-pyrido[1,2-*a*]pyrimidines **3** by Hese *et al.* [40] and Ivonin *et al.* [41].

Two-step method for the synthesis of pyrido[1,2-*a*]pyrimidin-2-ones **7** under usual conditions or under microwave irradiation (MWI) is presented in (Scheme **6**) [44].



Scheme 4. Synthesis of pyrido[1,2-*a*]pyrimidin-2-ones **5** by authors [45-47].

The interaction of 2-aminopyridines with itaconic acid gives intermediate substituted pyridine derivatives of itaconic acid, which was converted to the target compounds **9** under heating in ethanol at the presence of PTSA or under MWI.



Scheme 5. Synthesis of 2-[pyrido[1,2-*a*]pyridmidine-3-ylidene]acetic acids **6** by Venugopal *et al.* [48].

2-Pyrazolyl-3-dimethylaminoacrylonitriles reacted with 2-aminopyridine in TFA medium in the presence of amberlist-15 as catalyst to form pyrazolyl-substituted pyrido[1,2-*a*]pyrimidin-2-ones **8** (Scheme **7**) [50].

This procedure allows to obtain heteroaryl substituted pyrido[1,2-a]pyrimidin-2-ones **8** from 2-aminopyridine and activated alkenes, which expands its application limits.

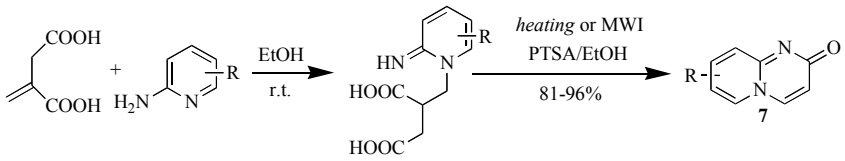
The reaction of N-(2-pyridyl)imines and terminal alkynes results in [4+2]cycloaddition with production of pyrido[1,2-*a*]pyrimidines **9** in high yields (Scheme **8**) [51]. The above reaction includes the derivation of intermediate propargylamino-pyridine derivatives, which undergo 6-endo-dig-cyclization with the formation of target fused system **12**. The advantage of this type of reaction can be considered the possibility of selective introduction of Alk-, Ar- substituents in 2nd and 4th positions of the pyrido[1,2-*a*]pyrimidine system.

The reaction of the benzo[1,3]oxazino[3,2-*b*]isoquinoline-2,6-dione with hydrazine hydrate in boiling dioxane selectively gives the 6-amino-isoquinolino[2,3-*a*]quinazoline **10** (Scheme **9**) [52]. At the same time, the interaction of the above oxazinosoquinoline with ammonium acetate at 170 °C or under microwave irradiation led to the formation of the same system **11**, but without amino group (Scheme **9**) [52].

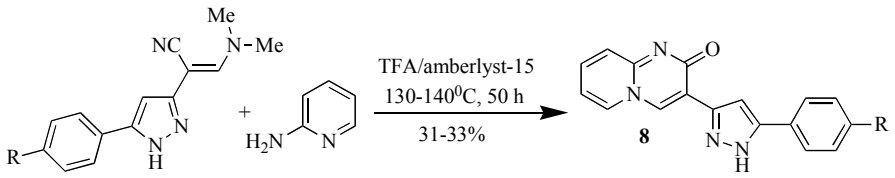
The "click reaction" is a well-known procedure which is used for receiving condensed heterocyclic compounds [53-58]. This strategy was successfully applied for the introduction of useful functionalities, in the form of polar and function-rich moieties, directly attached to the pyrido[1,2-*a*]pyrimidine system.

The one-pot interaction between substituted pyridines, arylisoselenocyanates, and acetylenedicarboxylic acid esters gives 2-selenoxo-pyrido[1,2-*a*]pyrimidines **12** in good yields at room temperature (Scheme **10**) [59,60].

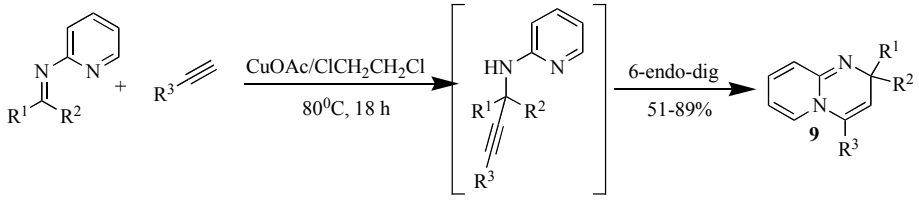
An effective one-step synthetic approach for the preparation of pyrido[1,2-*a*]pyrimidines **13** was developed as four-component



Scheme 6. Synthesis of pyrido[1,2-*a*]pyrimidin-2-ones **7** by Sharulatha *et al.* [44].

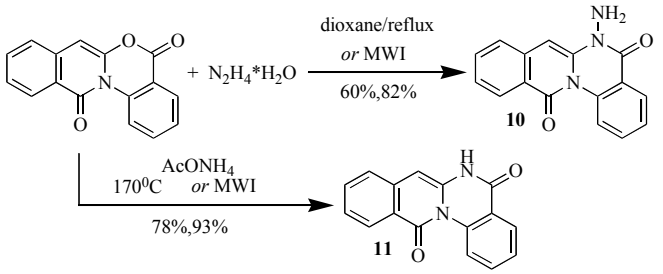


Scheme 7. Synthesis of 2 pyrazolyl-substituted pyrido[1,2-*a*]pyrimidin-2-ones **8** by Maurya *et al.* [50].



Scheme 8. Synthesis of pyrido[1,2-*a*]pyrimidines **9** by Tatsumi *et al.* [51].

reaction, starting from 1,1-bis(methylthio)-2-nitroethylene, 1,3-propanediamine, aldehydes, and nitriles (Scheme **11**) [61-64].



Scheme 9. Synthesis of isoquinolino[2,3-*a*]quinazolines **10** and **11** by Hekal *et al.* [52].

The possibility of providing this reaction under solvent-free conditions is an important advantage of the elaborated procedure (Scheme **11**) [63].

Partially hydrogenated pyrido[1,2-*a*]pyrimidine-7,9-dicarboxylate **14** was synthesized in 98% yield by one-stage three-component procedure via annulation of ethyl acetoacetate, 1,3-propanediamine, and methoxymethanol (Scheme **12**) [65].

The reaction of quinazolinones with diarylacetylenes in the presence of complex catalyst $PdCl_2(MeCN)_2$/CuBr under an oxygen atmosphere leads to stereoselective formation of isoquinolino[1,2-*b*]quinazolinones **15** (Scheme **13**) [66].

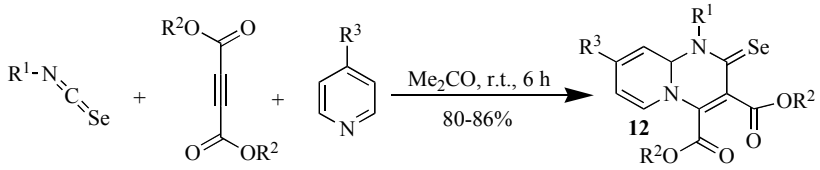
A common approach to the synthesis of pyrido[1,2-*a*]pyrimidines **16** by intramolecular cyclization of N-(pyridin-2-yl)propinamide derivatives at heating in DMSO medium is presented in (Scheme **14**) [67].

Simple procedure, good to excellent yield, and non-column purification are highlights of the present procedure (Scheme **14**) [67].

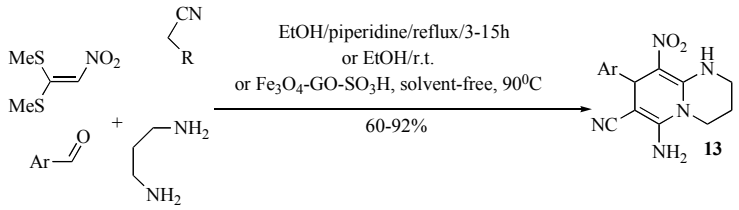
Method for the production of spiro-derived quinolino[1,2-*a*]quinazolines **17,18** based on the interaction of 2-[(3,3-dimethyl-5-oxocyclohexyl)amino]benzo-derivatives with (2-oxo-1,2-dihydro-indol-3-ylidene) nitriles (Scheme **15**) [68].

The above procedure allows to obtain spiro-derivatives of pyrido[1,2-*a*]pyrimidine system **17,18** in good yields (Scheme **15**) [68].

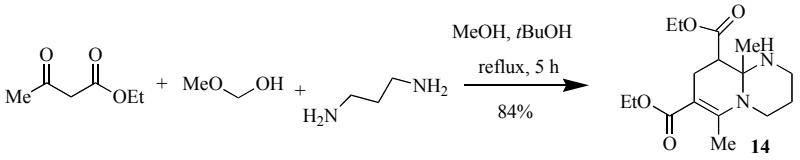
N-Substituted pyrido[1,2-*a*]pyrimidine-4-imines **19** were obtained from α-acyl-β-(2-aminopyridinyl)acrylamides in trifluoromethane sulfonic anhydride in the presence of 2-chloropyridine as an activating agent (Scheme **16**). This approach is characterized by mild reaction conditions, ease of implementation, excellent yields, and high chemoselectivity [69].



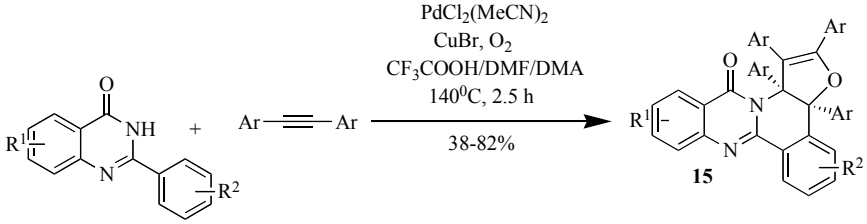
Scheme 10. Synthesis of 2-selenoxo-pyrido[1,2-*a*]pyrimidines **12** by Shahroudia *et al.* [59] and Singh *et al.* [60].



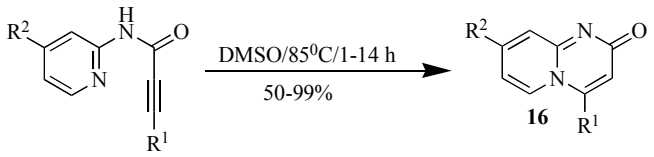
Scheme 11. Synthesis of pyrido[1,2-*a*]pyrimidines **13** by authors [61-64].



Scheme 12. Synthesis of pyrido[1,2-*a*]pyrimidine-7,9-dicarboxylate **14** by Ishmiyarova *et al.* [65].



Scheme 13. Synthesis of isoquinolino[1,2-*b*] quinazolinones **15** by Feng *et al.* [66].



Scheme 14. Synthesis of pyrido[1,2-*a*]pyrimidines **16** by Alanine *et al.* [67].

The reaction of substituted 3,4,4-trichloro-1,1-bis-(3,5-dimethyl-pyrazol-1-yl)-2-nitrobut-1,3-dienes with 2-aminopyridine derivatives in tetrahydrofurane at room temperature led to the formation of pyrido[1,2-*a*]pyrimidines **20** [70-72].

2.2. Synthesis of pyrido[1,2-*c*]pyrimidines and their benzologs

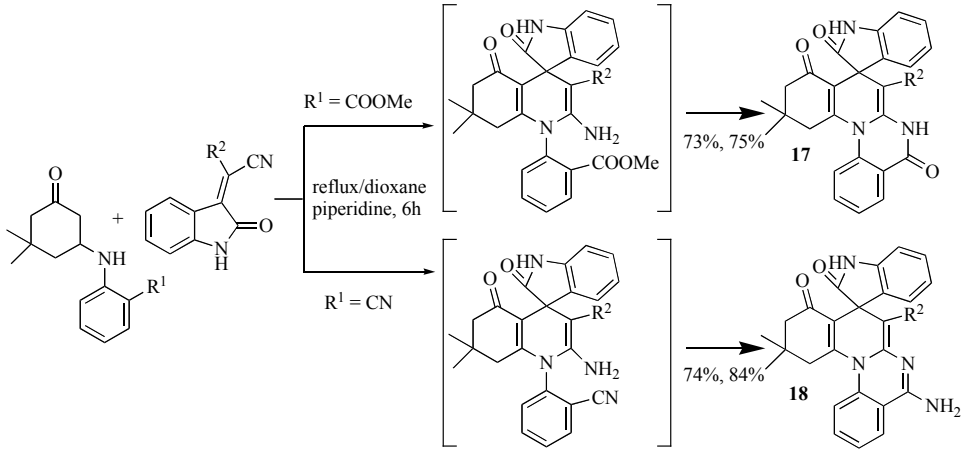
A series of 4-arylpyrido[1,2-*c*]pyrimidines **21** was synthesized by annulation of 2-phenyl-substituted-2- (pyridin-2-yl)acetamides with diethyl carbonate at heating (Scheme **18**) [73].

The above process features by the simple work up and the avoiding of the usage of toxic solvents and can be considered as green procedure.

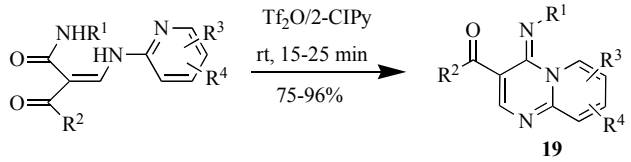
2.3. Synthesis of pyrido[1,2-*a*]pyrazines and their benzologs

A convenient procedure for the synthesis of pyrido[1,2-*a*]pyrazine-7,9-dicarboxylates **22** by a one-step three-component reaction of cyclic enaminones, aromatic aldehydes, and 1,3-dicarbonyl compounds was proposed (Scheme **19**) [74]. Target compounds **22** were obtained in moderate to high yields by refluxing the reaction mixture in alcohol.

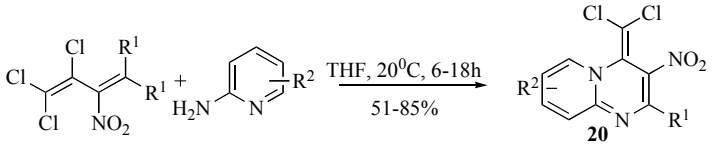
An efficient protocol was developed via cyclocondensation of 3-oxopiperazin-2-ylidene-acetic acid methyl ester with N-substituted maleimides to obtain functionalized pyrido[1,2-*a*]pyrazines **23** [75]. Target products **23** were synthesized by heating of the initial reagents in methanol medium (Scheme **20**).



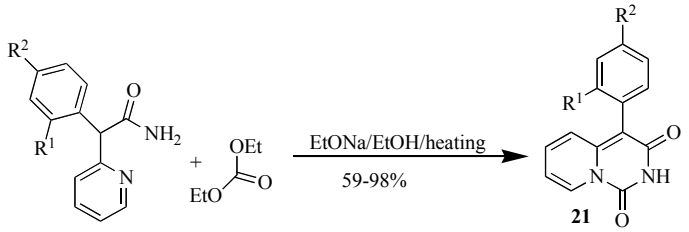
Scheme 15. Synthesis of quinolino[1,2-*a*]quinazolines **17,18** by Ghozlan *et al.* [68].



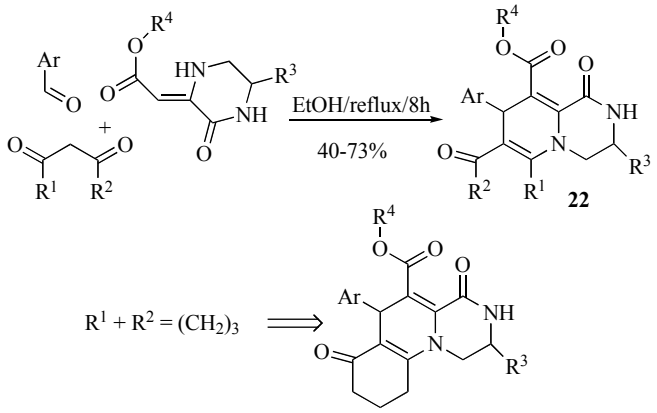
Scheme 16. Synthesis of pyrido[1,2-*a*]pyrimidine-4-imines **19** by Rao *et al.* [69].



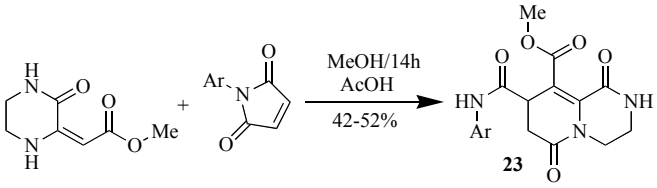
Scheme 17. Synthesis of pyrido[1,2-*a*]pyrimidines **20** by authors [70-72].



Scheme 18. Synthesis of 4-arylpyrido[1,2-c]pyrimidines **21** by Herold *et al.* [73].



Scheme 19. Synthesis of pyrido[1,2-*a*]pyrazine-7,9-dicarboxylates **22** by Eften'eva *et al.* [74].



Scheme 20. Synthesis of pyrido[1,2-*a*]pyrazines **23** by Medvedeva *et al.* [75].

The heating of 2,5-disubstituted pyran-4-ones with 1,2-ethylenediamine or ortho-phenylenediamines in aqueous ethanol gave the corresponding pyrido[1,2-*a*] pyrazine-1,8-dione **24** and its benzologs **25** (Scheme **21**) [76].

3. CHEMICAL TRANSFORMATIONS OF PYRIDO-PYRIMIDINES AND PYRIDOPYRAZINES CONTAINING A BRIDGEHEAD NITROGEN ATOM

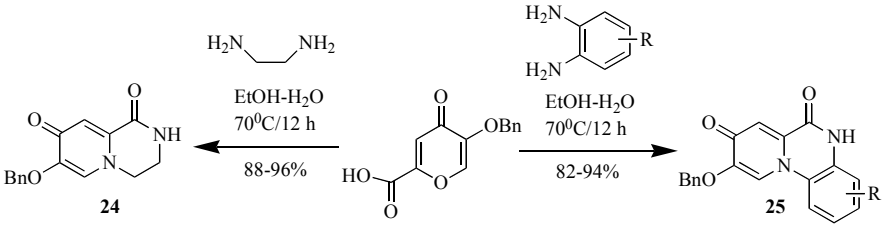
3.1. Pyrido[1,2-*a*]pyrimidine-2,4-dione reactions

Amino-substituted pyrido[1,2-*a*]pyrimidines **1,2** are convenient starting compounds for subsequent chemical transformation. The action of 5-methylfuran-2-carbaldehyde in boiling ethyl alcohol leads to the formation of Schiff compounds **26** (Scheme **22**) [34].

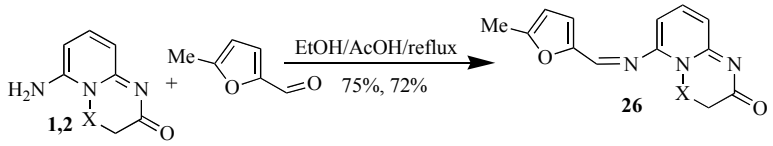
The Claisen reaction of pyrido[1,2-*a*]pyrimidine-2,4-diones **1** can serve as an effective illustration of high reactivity of cyclic methylene group for further chemical transformations. The reaction of compounds **1** with aromatic aldehydes gives corresponding chalcones, which react with aromatic oximes, hydroxylamine and hydrazine hydrate to form the diverse cyclization products **27-29** (Scheme **23**) [35].

Due to the presence of an active cyclic methylene group pyrido[1,2-*a*]pyrimidine-2,4-diones **1** undergoes the annulation of additional pyrane cycle by the action of ethyl acetoacetate in concentrated sulfuric acid at heating with the formation of pyranoannulated derivatives **30** with fluorescent bleaching properties (Scheme **24**) [36].

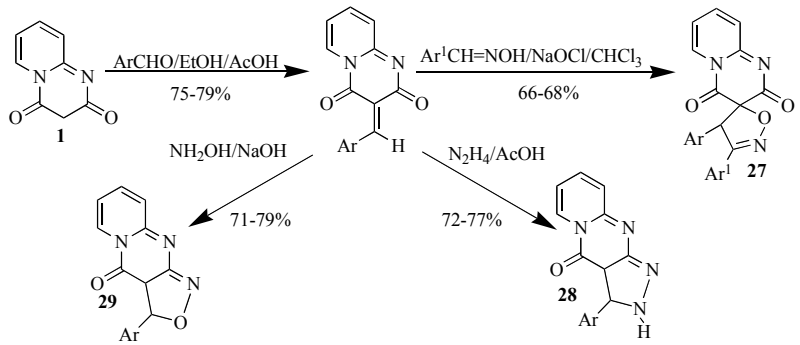
Condensation of compound **1** with 2-aminostyrenes leads to the formation of linear polycyclic structures **31**. The isomeric angular systems **32** were isolated as minor products (Scheme **25**) [38].



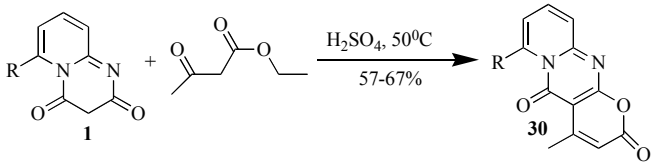
Scheme 21. Synthesis of pyrido[1,2-*a*] pyrazine-1,8-dione **24** and its benzologs **25** by Ma *et al.* [76].



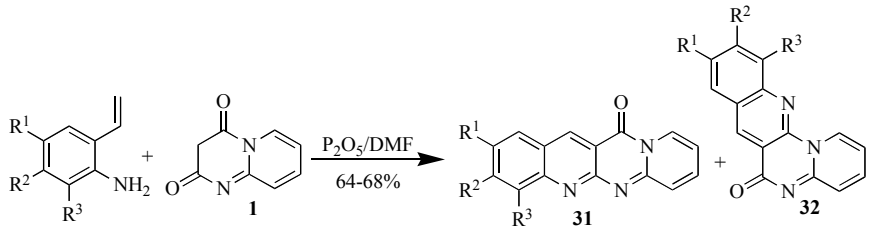
Scheme 22. Synthesis of Schiff compounds **26** by Bassyouni *et al.* [34].



Scheme 23. Synthesis of pyrido[1,2-*a*]pyrimidine derivatives **27-29** by Bishnoi *et al.* [35].



Scheme 24. Synthesis of pyranoannulated derivatives **30** by Gawale *et al.* [36].



Scheme 25. Synthesis of linear polycyclic structures **31** and **32** by Gupta *et al.* [38].

The authors of the study [38] also developed a protocol for the synthesis of symmetric pentacyclic systems **33**, containing pyrido[1,2-*a*]pyrimidine moiety, *via* condensation of compound **1** with aromatic aldehydes in ethylene glycol medium at heating without a catalyst (Scheme **26**).

Enamines **34** were obtained from methylene active pyrido[1,2-*a*]pyrimidine **1** *via* its refluxing with the corresponding amines in the presence of equimolar amount of triethylorthoformiate (Scheme **27**) [39].

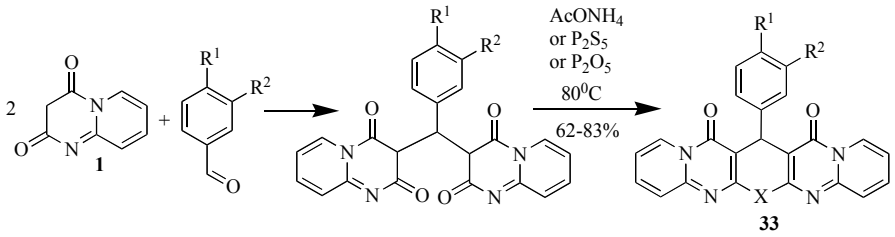
The reaction between pyrido[1,2-*a*]pyrimidin-2,4-dione **1**, isocyanides, and dialkyl acetylenedicarboxylates gives tricyclic fused pyrano[2,3-*d*]pyrido[1,2-*a*]pyrimidines **35** (Scheme **28**) [77].

3.2. Reactions of other pyrido[1,2-*a*]pyrimidine derivatives

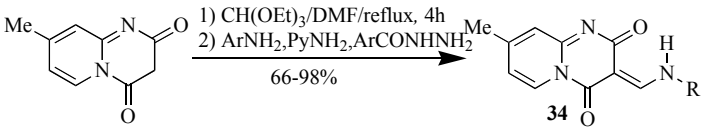
A convenient three-component protocol for obtaining pyrazolyl-substituted pyrido[1,2-*a*]pyrimidines **36** was developed in the presence of $CuFe_2O_4$ nanoparticles under solvent-free conditions (Scheme **29**) [78].

The rearrangement of pyrido[1,2-*a*]pyrimidines **6** in PPA medium, promoted by heating on a steam bath, leads to the formation of seven-membered pyridodiazepines **37** (Scheme **30**) [79].

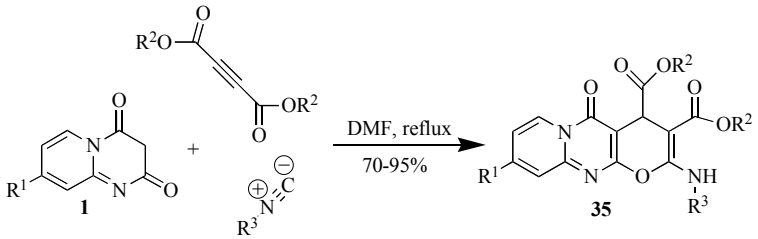
p-Toluoyl chloride interacts with phenylacetylene, and the resulting intermediate product can be converted into the tricyclic fused system **38** under treatment with pyrido[1,2-*a*] pyrimidine (Scheme **31**) [80].



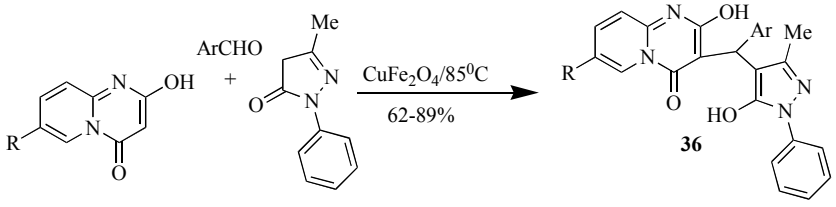
Scheme 26. Synthesis of pentacyclic systems **33** by Gupta *et al.* [38].



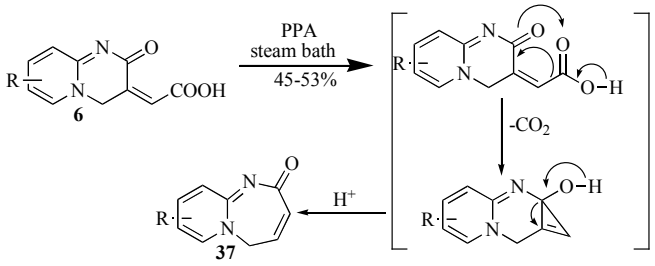
Scheme 27. Synthesis of enamines **34** by Rauf *et al.* [39].



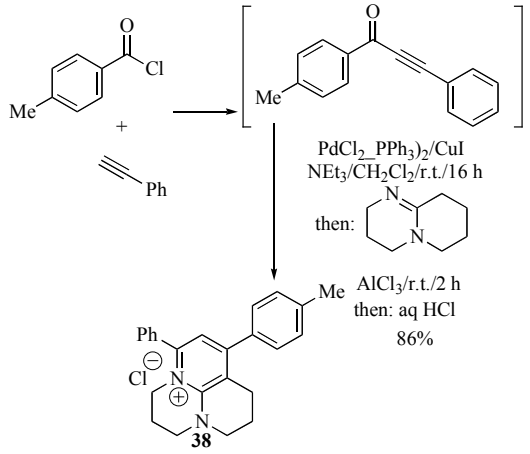
Scheme 28. Synthesis of pyrano[2,3-d]pyrido[1,2-*a*]pyrimidines **35** by Esmaeili *et al.* [77].



Scheme 29. Synthesis of pyrido[1,2-*a*]pyrimidines **36** by Jannati *et al.* [78].



Scheme 30. Synthesis of pyridodiazepines **37** by Yang *et al.* [79].



Scheme 31. Synthesis of fused system **38** by Bakulina *et al.* [80].

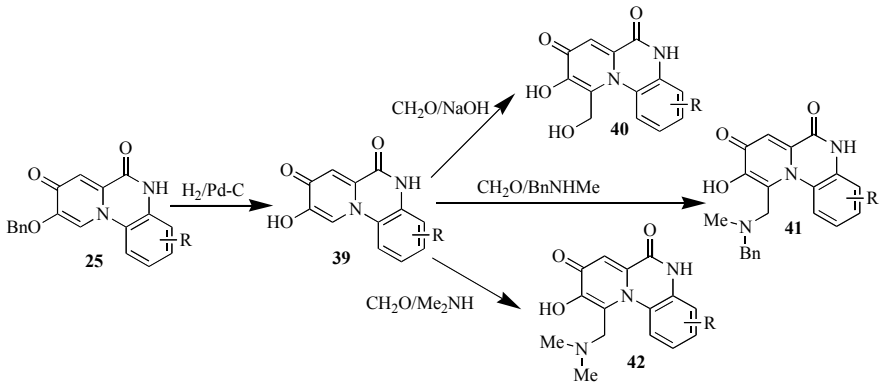
Oxopyrido[1,2-*a*]pyrimidines **25** were subjected to hydrogenolysis in ethanol in the presence of a 5% Pd/C catalyst for 5 h, as a result, fluorescent chelators **39** were obtained in high yields. Upon further functionalization, these products were converted into derivatives **40-42** (Scheme **32**) [76].

4. BIOLOGICAL ACTIVITY OF PYRIDOPYRIMIDINES AND PYRIDOPYRAZINES CONTAINING A BRIDGING NITROGEN ATOM

Biomedical experiments have established that pyridopyrimidines and pyridopyrazines containing a bridgehead nitrogen atom excess pharmacodynamic activity - anti-inflammatory, cytoprotective, bronchodilatory, antithrombotic, anti-atherosclerotic, analgesic, antiallergic action, and they are also phosphodiesterase inhibitors. [81-84].

Compounds **26** were tested for antitumor activity on liver cells (HepG2) [34]. The biochemical action of the compounds on enzymes such as AST, ALT and (ALP), in addition to albumin, globulins, creatinine, total lipids, cholesterol, triglycerides and bilirubin in the serum of mice, was studied in comparison with 5-FU and DOX. The results of antitumor activity showed that these compounds show good growth inhibition activity on the tested cell line, but with different efficacy compared to the known anti-cancer drugs 5-FU and DOX Fig. (**3**).

Compounds **27-29** also exhibit excellent activity against bacterial and fungal strains (Fig. (**4**)). The zone of inhibition for some of these samples was significant against *Staphylococcus aureus* (12-24 mm), *Bacillus subtilis* (11-21 mm) and *Candida albicans* (16-30 mm) [35].



Scheme 32. Synthesis of fluorescent chelators **39** and derivatives **40-42** by Ma *et al.* [76].

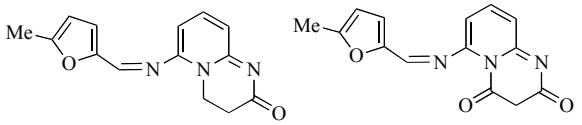
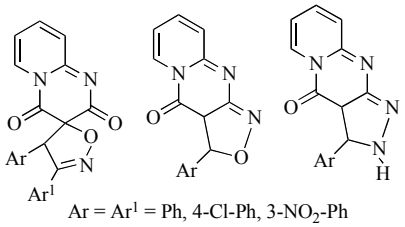


Fig. (3). Examples of compounds **26** that posse antitumor activity.



Ar = Ar^1 = Ph, 4-Cl-Ph, 3-NO_2-Ph

Fig. (4). Examples of compounds **27-29** that posse antibacterial and fungal activity.

The pyrido[1,2-*a*] pyrimidine derivative **34** was found as a potent inhibitor of urease activity compared to thiourea, a standard urease inhibitor as an etalon (Fig. (**5**)) [39]. While at a concentration of 100 μM thiourea reduces the activity of the urease enzyme by 94%, compound **34** reduces its activity by 96%. At a low concentration of 0.01 μM, thiourea reduces the activity of urease by only 8%, while pyridopyrimidine **34** at this concentration reduces the activity by 22%.

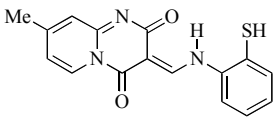


Fig. (5). Compound **34** as an inhibitor of urease activity.

The pyrido[1,2-*a*]pyrimidine-3-carbonitrile derivatives **3** exhibit different patterns of antibacterial and antifungal activity (Fig. (**6**)). The obtained results of antibacterial activity *in vitro* showed that some of the synthesized compounds exhibit equipotent activity compared to the standard drug ampicillin, and also inhibit the growth of *Escherichia coli* (18-24 mm), *Bacillus subtilis* (15-21 mm) and *Staphylococcus aureus* (17-24 mm), as well as fungi *Aspergillusniger* (16-27 mm), *Aspergillusflavus* (14-21 mm) and *Candida albicans* (15-22 mm) [40].

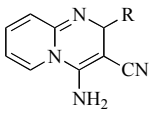


Fig. (6). Compounds **3** that posse antibacterial and fungal activity.

4-Arylpyrido[1,2-*c*]pyrimidines **21** have shown the efficacy of *in vitro* experiments on binding to 5-HT1A receptors and 5-HT transporter proteins in rat cerebral cortex membranes and of *in vivo* experiments on models of induced hypothermia to determine the activity antagonists/agonists against 5-HT1A autoreceptors [73] (Fig. **7**).

Compounds **24** and **25** were developed to replace traditional fluorescent probes for quantifying pools of intracellular labile iron [76]. The relatively low pKa values of the ligands result from the inductive action of the amido group at position 6. As a result of a decrease in competition with protons, the pFe^{3+} values increase. The chelating function forms part of the fluorescent moiety, which makes it possible to develop small fluorescent probes that are capable of rapidly penetrating membranes. ClogP values range from -3.23 to -0.20. The fluorescence of the probe is sensitive to iron, and the addition of an equimolar amount of Fe (III) or Fe (II) completely quenched the fluorescence. The PKa and pFe^{3+} values of these ligands show that they all have lower ionization constants compared to deferiprone and readily bind iron (Fig. **8**).

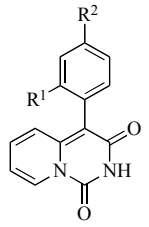


Fig. (7). Compounds **21** that are efficient on binding to 5-HT1A receptors and 5-HT transporter proteins.

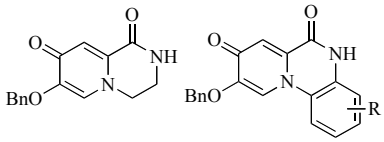


Fig. (8). Compounds **24** and **25** as the fluorescent probes.

The tricyclic salt **38** emits light in dichloromethane, water, and in a crystalline state [80]. A bright blue to turquoise phosphor exhibits a high quantum yield of fluorescence. This salt is a convenient model for the development of specialized fluorescent probes as labels for biomolecules (Fig. **9**).

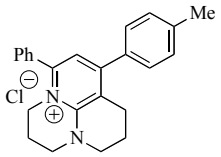


Fig. (9). Compounds **38** that emits light.

CONCLUSION

Pyridopyrimidines and pyridopyrazines are multipurpose intermediates for the receiving of many significant biologically active compounds. This review covered the recent chemistry of the synthetic approaches and chemical properties of condensed pyridopyrimidines and pyridopyrazines containing a bridgehead nitrogen atom, as well as their biological characteristic. Thus, the analysis of literature sources concerning studies on pyridopyrimidine and pyridopyrazine systems with a bridging nitrogen atom allows concluding that, along with various modifications of the classical method of synthesis with the participation of 2-aminopyridines, the range of methods for constructing their new derivatives has been significantly evaluated. "Click-chemistry in production of titled fused heterocyclic systems are also discussed. Expanding the synthetic potential of pyridopyrimidines and pyridopyrazines with a bridgehead nitrogen atom, especially in a frame of the using of green approaches, is a reliable option for searching for bioactive structures. It should be noted that, along with studies of antitumor and antimicrobial activity, the development of fluorescent probes and urease inhibitor activity is of particular importance.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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