Recent Advances in the Synthesis and Biological Activity of Pyrrolo[2,3-c]pyridines

Abstract

Pyrrolo[2,3-c]pyridines (6-azaindoles) are the most promising nitrogen-containing heterocyclic compounds in the field of drug development. Exhibiting extraordinary versatility as pharmacophores, they are widely used in the development of kinase inhibitors, antiproliferative agents, and as potential therapeutic agents for the treatment of various diseases, including cancer and Alzheimer’s disease. A large number of works focusing on new methods and approaches in the synthesis of 6-azaindoles, as well as on the study of their biological activity, have been published worldwide. In our review, we tried to classify all currently known strategies for the construction of the 6-azaindole core, which were published within the last 15 years, the chemical diversity of the derivatives obtained, and their therapeutic potential in the context of medicinal chemistry. We hope that this work will generalize and facilitate the understanding of the strategy for the synthesis of pyrrolo[2,3-c]pyridines, as well as help scientists in their further research in the direction of 6-azaindoles.

Keywords: pyrrolo[2,3-c]pyridines; 6-azaindoles; biological activity; medicinal chemistry; heterocyclic compounds; drug development

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Introduction

Nitrogen-containing heterocyclic compounds play one of the central roles in the realm of drug development, mainly thanks to their inherent molecular polarity, water solubility, and the ability to permeate cellular membranes. The analysis of FDA-approved drugs reveals that an astonishing 59% of unique small-molecule drugs contain at least one nitrogen heterocycle, which demonstrates their importance in drug design and discovery [1]. This predominance is attributed not only to the versatility of nitrogen heterocycles in mimicking the biological landscape, but also to their structural diversity, which offers myriad possibilities for the modulation of pharmacokinetic and pharmacodynamic properties.

Among all of the nitrogen-containing heterocycles, pyrrolo[2,3-c]pyridines stand out as a very promising scaffold due to its unique structural features and considerable biological activity. This class of compounds with the condensed pyrrole and pyridine ring has long attracted a widespread interest from the research community. This interest is demonstrated by the vast list of literature on synthetic methodologies, structural modifications, and the study of the medicinal and biological potential of the 6-azaindole core. The review by Popowycz et al. (2007) meticulously summarized this data, highlighting the versatility of 6-azaindoles in drug development and underscoring the synthesis of compounds via diverse strategies, including the Reissert, Batcho-Leimgruber, Hemetsberger-Knittel syntheses, and their functionalization in various positions to enhance the biological activity [2]. It delves into the design of 6-azaindoles as biological targets and demonstrates their potential across a range of applications, from therapeutic agents to key synthetic intermediates.

However, since 2007, the synthesis and functionalization capabilities of pyrrolo[2,3-c]pyridines have significantly expanded due to advancements in synthetic chemistry, the availability of new reagents, increased technical capabilities, and so on. This synthetic versatility combined with the inherent biological relevance of the pyrrolo[2,3-c]pyridine core has led to the emergence of an immense amount of research, publications, and scientific works over the past 17 years.

Therefore, it seems to be very reasonable to complement the work of Popowycz, conduct a thorough analysis of all the new scientific achievements and provide a fresh thorough overview of the current state of research on pyrrolo[2,3-c]pyridines, encompassing their synthesis, structural modifications, and pharmacological potential. By studying the current scientific developments in this field and identifying promising areas for future research, we hope to contribute to the ongoing efforts to use pyrrolo[2,3-c]pyridines in the search for new therapeutic agents.

Results and discussion

Pyrrolo[2,3-c]pyridines and their annulated derivatives can be synthesized by various synthetic strategies. However, it makes sense to highlight three main principal approaches that stand out due to their efficiency and versatility: (1) the annulation of the pyrrole nucleus to the pyridine cycle; (2) the annulation of the pyridine nucleus to the pyrrole cycle; (3) the synchronous formation of the 6-azaindole system where both the pyrrole and pyridine rings are constructed in a single, concerted step. Each of these methods offers its own unique advantages in terms of reaction conditions, functional group tolerance, and overall yield.

Initially, we propose focusing on the first method, namely the annulation of the pyridine nucleus to the pyrrole cycle.

1. Annulation of the pyrrole nucleus to the pyridine cycle

The first and one of the most common methods for forming the pyrrolo[2,3-c]pyridine framework 3 involves the Bartoli reaction of 2-halogen-3-nitropyridines 1 with vinyl magnesium bromide 2 in the THF solution [3–6] or using toluene as a solvent in the presence of a base [7] (Scheme 1).

The widespread application of this method can be attributed to its versatility, the high yields of targeted compounds it can achieve, and, of course, the possibility of using halogenated nitropyridines as precursors. The Bartoli reaction is a classic, described in an immense number of scientific studies and publications.

However, a two-step alternative approach allows the synthesis of 2,3-unsubstituted 6-azaindoles with much higher yields. For example, the reaction of 4-methyl-3-nitropyridines 4 with dimethylacetamide dimethyl acetal (DMF DMA) [8–11], lithium methylate in the DMF solution [12] or 1-tert-butoxy-N,N,N’,N’-tetramethylmethanediamine [13] gives enamines 5, which reductive cyclization leads to the target pyrrolo[2,3-c]pyridines (Scheme 2) with up to 100% yields.
The Bartoli reaction is also used and described for synthesizing 2-alkyl-substituted or 2,3-dialkyl-substituted pyrrolo[2,3-c]pyridines 7, among the functionalized derivatives of which potent potassium-competitive acid blockers (P-CABs) have been identified (Scheme 3) [14].

It is worth noting that this approach facilitates the incorporation of versatile alkyl groups in critical positions of the pyrrolopyridine core, allowing to fine-tune the molecule interaction with the H⁺/K⁺-ATPase enzyme. The subsequent functionalization of these derivatives has led to the identification of compounds exhibiting remarkable in vitro and in vivo inhibitory activities against gastric acid secretion, positioning them as promising leads for the development of new therapies for diseases associated with the increased stomach acid production.

Thus, the utility of the Bartoli reaction consists not only in constructing complex nitrogen-containing heterocycles, but also in enabling the targeted modification of these molecules to enhance their pharmacological profiles, thereby offering a valuable strategy for the discovery and optimization of novel P-CABs.

The next described method for constructing the 6-azaindole core is the Sonogashira reaction. The interaction of tert-butyl (4-iodopyridine-3-yl) carbamate 8 with a terminal alkyne 9 at room temperature gave the alkylation product 10; its heating at 80 °C provided a smooth cyclization to 2-benzyl-oxymethylpyrrolo[2,3-c]pyridine 11, from which a new tricyclic diamine 12 could be synthesized by further functionalization [15].

In addition, to implement a tandem Sonogashira coupling/intramolecular cyclization reaction and obtain 6-azaindole 11 in one stage, the reaction mixture of iodopyridine 8 with a terminal alkyne 9 was heated (Scheme 4).

Undoubtedly, our review would be incomplete without mentioning the study from 2005 [16] where the authors described a one-step method for constructing a combinatorial library of 6-azaindole derivatives 15, it involves the direct diliithiation of unprotected 3-amino-4-picoline 13. The condensation of the dianion A obtained with carboxylic acid esters, thioester, or dihydrofurane 14 led to a number of 2-substituted pyrrolo[2,3-c]pyridines with quite good and competitive yields (Scheme 5).
Another convenient method for synthesizing 2-alkyl(aryl, heteroaryl)-substituted 6-azaindoles is the palladium-catalyzed reaction of gem-dichloro olefins and boronic acids, which includes a tandem intramolecular C-N coupling and the intermolecular Suzuki process (Scheme 6) [17].

In work [18] an example of obtaining 2-phenyl-1H-pyrrolo[2,3-c]pyridine using a Pd-catalyzed and carbon monoxide mediated reductive cyclization of 3-nitro-4-styrylpyridine (Scheme 7) was described. In a similar transformation, authors of work [19] used phenyl formate as a CO source (Scheme 7).

Another example of the Pd-catalyzed synthesis of 6-azaindoles was developed based on the Sonogashira reaction followed by a tandem C–N coupling and cyclization with amines. The interaction of 3,4-dibromopyridine with alkynes led to 3-bromo-4-(arylethynyl)pyridines, the treatment with aromatic amines produced a range of pyrrolo[2,3-c]pyridines (Scheme 8) [20].

The work documented in [21] outlines a one-pot method for synthesizing 3-substituted...
6-azaindoles 28 by the Pd-catalyzed direct annihilation of ortho-chloroaminopyridine 26 with aldehydes 27 (Scheme 7). It is noteworthy that the authors of [22] used the Fischer cyclization of 3-hydrazinyl-2-methoxypyridine 29 and protected phenylacetaldehyde 30 as an alternative metal-free method for obtaining 3-phenyl-6-azaindole 28 (Scheme 9).

A series of works [23–25] describe the condensation of nitropyridines 31 with diethyl oxalate followed by the reductive cyclization of the resulting product 32 to yield ethyl 1H-pyrrolo[2,3-c]pyridine-2-carboxylates 33, which are used as building blocks in the synthesis of an immense range of biologically active compounds (Scheme 10).

The synthesis of isomeric ethyl 1H-pyrrolo[2,3-c]pyridine-3-carboxylates 36 was achieved by the condensation of 3- and 5-nitropyridines 34 with diethyl malonate in the presence of NaH in the DMF solution, yielding the corresponding diethyl 2-pyridylmalonates 35. The reduction of the nitro group in these compounds followed by the heterocyclization with 25% aqueous ammonia solution in situ led to the formation of the target products 36 (Scheme 11). Derivatives of

![Scheme 7](image)

**Scheme 7.** The synthesis of 2-phenyl-1H-pyrrolo[2,3-c]pyridine with the reductive cyclization

![Scheme 8](image)

**Scheme 8.** The method for the synthesis of aryl substituted pyrrolo[2,3-c]pyridines

![Scheme 9](image)

**Scheme 9.** The one-pot method for the synthesis of 3-substituted 6-azaindoles

![Scheme 10](image)

**Scheme 10.** The synthesis of 1H-pyrrolo[2,3-c]pyridine-2-carboxylates as the starting building block for obtaining the biologically active compounds
diethyl malonates 35 were converted into ethyl esters of acetic acid 37 by the decarboxylation treated with LiCl in a water/DMSO mixture at reflux. The reductive cyclization of derivatives 37 with zinc in acetic acid produced 5-amino- and 7-amino-6-azaindoles 38 (Scheme 11) [26]. On the example of the synthesis of ethyl 5-amino-2-hydroxy-1H-pyrrolo[2,3-c]pyridine-3-carboxylate 36, the authors of work [27] tried the heterocyclization in a Parr hydrogenator using a catalytic amount of Pd on carbon in ethanol and the treatment with 18% solution of hydrochloric acid, as well as treating diethyl malonate 35 with an excess of SnCl$_2$·$H_2$O in ethanol under ultrasound activation (Scheme 11) [27].

Meanwhile, the condensation of 4-chloro-3-nitropyridine 39 with ethyl cyanoacetate yielded ethyl 2-cyano-2-(3-nitropyridin-4-yl)acetate 40; its intramolecular cyclization upon the treatment with powdered zinc in acetic acid led to the formation of ethyl 2-amino-1H-6-azaindole-3-carboxylate 41 (Scheme 12) [28, 29].

The Pd-catalyzed cyclization of tert-butyl 2-(5-nitropyridin-4-yl)acrylate 43 obtained by the condensation of the corresponding ethanoate 42 with 1,3,5-trioxane in the presence of calcium oxide and potassium carbonate yielded the expected tert-butyl 6-azaindole-3-carboxylate (Scheme 13) [30].

The authors of work [31] developed a one-pot variant for the synthesis of 2-trifluoromethyl-6-azaindoles 46. The acylation of 2-methoxy-3-nitropyridine 45 with ethyl trifluoroacetate led to the formation of the intermediate 1,1,1-trifluoro-3-(3-nitropyridin-4-yl)propan-2-one (A) cyclized under the action of Zn in acetic acid to 2-(trifluoromethyl)-6-azaindole 46_1. In contrast, the reaction of 2-chloro derivative 45 resulted in a mixture of 6-azaindole 46_2 (yield 33%) and cyclic hemiaminal 47 (yield 49%). An improvement in the yield of the target 7-chloropyrrolo[2,3-c]pyridine 46_2 was achieved by dehydration by stirring the mixture of products in glacial acetic acid for 3 days (Scheme 14).

![Scheme 11. The example of the synthesis of isomeric ethyl 1H-pyrrolo[2,3-c]pyridine-3-carboxylates](image1)

![Scheme 12. The synthesis of 2-amino-1H-6-azaindole-3-carboxylate](image2)

![Scheme 13. The synthesis of tert-butyl 6-azaindole-3-carboxylate](image3)
Another convenient approach to 3-trifluoromethyl-6-azaindoles was described in 2020 [32]. The hydration of trifluoracetyl derivative 48 in hydrochloric acid at 80 °C for 16 hours gave easy removing of the trifluoroacetyl group to give 3-H 2-trifluoromethyl 6-azaindole. This efficient scalable synthetic route to 2-trifluoromethyl 6-azaindole made possible the synthesis of a variety of 3-substituted 2-trifluoromethyl 6-azaindoles and their partially saturated derivatives 49–54 (Scheme 15).

In 1970, the synthesis of 3-formyl-6-azaindole by the Vilsmeier-Haack formylation in 19 % yield was described for the first time. However, in 2024, this work was expanded and supplemented by a study concerning the scope and limitations of the synthesis of 3-formyl-6-azaindoles 56 via the Vilsmeier-Haack formylation of the corresponding 3-amino-4-methyl pyridines 55 (Scheme 16) [33].

This method was demonstrated to be very effective, scalable, and regioselective, requiring no catalysts and quite easy to perform.

Also, the same year, the synthesis of 6-azaindoles via the formal electrophilic [4+1]-cyclization of 3-amino-4-methyl pyridines from the whole set of 3-amino-4-methylpyridine derivatives was described in detail (Scheme 17) [34]. The essential difference compared to all similar reactions previously known is the absence of the activation of the methyl group by a strong base. It allows to provide the cyclization in mildly acidic conditions and significantly enlarges its scope. 3-Methylamino-4-methylpyridine and 3-hydroxy-4-methylpyridine were preparatively entered into the reaction, giving the corresponding fused pyrrolo-/furano-derivatives though in hydrated form.

While pyrrolo[2,3-c]pyridines themselves are of substantial interest mainly due to their potential as pharmacophores, the move towards synthesizing their annulated derivatives opens new possibilities in drug design. Approaches to them include strategies, such as intramolecular cyclization reactions, the use of transition metal-catalyzed cross-coupling reactions, and employing...
heteroatom insertions. Each method offers its own set of advantages in terms of selectivity, yield, and the types of annulated structures that can be achieved.

A one-pot, two-step method for synthesizing highly functionalized derivatives of 6-azaindole 61 was developed based on the nucleophilic aromatic substitution reaction of perfluoropyridine 59 with heterocyclic ketene aminals 60 promoted by two bases, K$_2$CO$_3$ and Cs$_2$CO$_3$ (Scheme 18) [35].

A convenient route for obtaining condensed derivatives of 6-azaindoles 63 and 64 is based on a simple four-step cascade sequence; its key stages are Cu-catalyzed coupling of boronic acids 62 with di-tert-butyl diazodicarboxylate (DBAD) and the Fischer indolization (Scheme 19) [36].

The interaction of 3-hydrazinyl-2-methoxypyridine 29 with cyclohexanone under the Fischer cyclization conditions was also effective for the annulation of the tricyclic system 63 (Scheme 19) [22].

An effective method for obtaining β-carbolines 68 involved directed lithiation of 3-fluoropyridines 65 followed by zincation and the Negishi cross-coupling with 2-halogenanilines 66, leading to the formation of 2-aminobariyals 67. Further treatment of derivatives 53 with an excess of NaHMDS facilitated the intramolecular aromatic substitution, yielding the target 9H-pyrido[3,4-b]indoles 68 (Scheme 20) [37].

Another convenient approach to the synthesis of β-carbolines 71 is based on a double C–N coupling catalyzed by copper of 3,4-dibromopyridine 69 with
a series of amines 70 (Scheme 21) [38]. In turn, the authors of work [39] successfully used the Pd-catalyzed Buchwald-Hartwig reaction to obtain β-carbolines 71, and dicarbolines 72 and 73 (Scheme 21).

In work [40], the synthesis of a new electron-deficient 2,5-diazacarbazole (2,5-NCz) (77) was reported for the first time. The synthetic pathway involved the interaction of 2-chloro-3-nitro-pyridine (74) with boronic acid 75 and the cyclization of the resulting 3-nitro-2,4'-bipyridine (76) to 2,5-NCz (77). It is worth noting that compound 77 synthesized possesses a high level of the triplet energy T1 = 2.77 eV and a potential for creating organic electronic materials in the photoelectric field. Through structural modification of product 77, two new materials for electron transport (ETM), p-S2N4NCzDPA and p-D2N4NCzDPA 78, were developed and used to manufacture sky-blue fluorescent OLEDs (Scheme 22).

For the synthesis of pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidine derivatives 82, among which a dual inhibitor of the FMS-like tyrosine kinase 3 (FLT3) and cyclin-dependent kinase 4 (CDK4) were identified, 5-(3-chloropyridin-4-yl)pyrimidine-2,4-diamine 81 was introduced into the Buchwald-Hartwig reaction. This compound was

Scheme 18. The method for the synthesis of annulated pyrrolo[2,3-c]pyridines with EWG in the pyrrole cycle

Scheme 19. The synthesis of condensed 6-azaindoles via the Cu-catalyzed coupling of boronic acids

Scheme 20. An effective method for the synthesis of β-carbolines
obtained by the Negishi cross-coupling of 5-bromo-
moprimidine-2,4-diamine 79 with boronic acid 80 (Scheme 23) [41].

2. Annulation of the pyridine nucleus to the pyrrole cycle

The next strategy for the synthesis of the pyrrolopyridine core is through the annulation of the pyridine nucleus onto the pyrrole cycle. In work [42] a regioselective approach to the synthesis of pyrrole[2,3-c]pyridine 85 was demonstrated by interacting 1H-pyrrole-2-carbaldehydes 83 with propargylamine to form propargyline 84, the reaction of 6n-electrocyclization of which at high temperature gave the target product 85.
(Scheme 24). Also, an effective variant B for obtaining 6-azaindole 85 was implemented by heating 1-methyl-1H-pyrrole-2-carbaldehyde 83 and phenylpropargylamine in the presence of molecular sieves (Scheme 24) [43].

A method for constructing highly functionalized 6-azaindoles 87 involved the iodine-mediated electrophilic cyclization of 2-alkynyl-1-methylene azides 86 (Scheme 25) [44].

The intramolecular cyclization of the poly-substituted 6-azaindole 90 obtained from the reaction of ethyl 1H-pyrrole-3-carboxylate 88 and N-Ts-glycine 89 under LiHMDS treatment led to the highly functionalized pyrrolo[2,3-c]pyridine 91 (Scheme 26) [45].

The Ir(III)-catalyzed reaction of pyrroloxime 92 and α-diazocarbonyl derivative 93 proved to be effective for the synthesis of N-oxide pyrrolo[2,3-c]pyridine 94. It is worth noting that this represents a straightforward method for the synthesis of phosphorylated heterocycles, which are highly important in the organic synthesis and medicinal chemistry (Scheme 27) [46].

In terms of the synthesis of β-carboline derivatives through the annulation of the pyridine nucleus onto the pyrrole cycle, the Pictet-Spengler cyclization is one of the most common methods. The interaction of tryptamine or serotonin 95 with aldehydes in acetic acid led to the formation of tetrahydro-β-carbolines 96; its structural modification yielded derivatives 97 and 98 – potential phosphodiesterase-4 inhibitors (Scheme 28) [47].

A series of tetrahydro-β-carbolines and methyl tetrahydropyrido[3,4-b]indole-3-carboxylates 100 synthesized from tryptamine or the methyl ester of tryptophan 99 and aldehydes were
alkylated and acylated in position 2 to obtain potential antimicrobial agents 101 (Scheme 29) [48].

Tetrahydro-β-carbolines 103 were synthesized via a microwave-assisted version of the Pictet-Spengler reaction from the methyl ester of tryptophan 102 and aldehydes in methanol in the presence of trifluoroacetic acid (TFA). The intermediate products 103 were transformed into the

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**Scheme 27. The synthesis of pyrrolo[2,3-c]pyridine N-oxide**

**Scheme 28. The synthesis of β-carboline derivatives through the Pictet-Spengler cyclization**

**Scheme 29. The synthesis of tetrahydro-β-carbolines**
corresponding N-substituted tetrahydro-β-carbolines 104, hydantoin 105, and pyrazine 106 condensed derivatives (Scheme 30) [49].

The β-carboline derivatives 104–106 obtained were analyzed as potential analgesics and antagonists of TRPM8 binding sites (transient receptor potential melastatin 8 ion channel) [49].

2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylic acids 108 were obtained by the reaction of trimethylamine 107 with glyoxylic acid [50–52]. The subsequent esterification of acids 108 in the presence of thionyl chloride in methanol yielded methyl tetrahydropyrido[3,4-b]indole-1-carboxylates 109; its aromatization with potassium permanganate or sulfur in refluxing xylene led to methyl 9H-pyrido[3,4-b]indole-1-carboxylates 110 (Scheme 31). Otherwise, the authors of [53] used DBN in the air to oxidize alkyl-, aryl-, and heteroaryl-substituted β-carbolines 109 (Scheme 31).

In a series of studies [54–58], a general approach to the synthesis of methyl 9H-pyrido[3,4-b]indole-3-carboxylates 114 is described. This approach includes the Pictet-Spengler reaction of tryptophan 111 and aldehydes 99, esterification of acids 112, and oxidation of tetrahydro-β-carbolines 113 (Scheme 32). A similar synthetic pathway was used to obtain (3S)-methyl-1H-pyridro[3,4-b]indole-3-carboxylates [59, 51].

On the other hand, the authors of study [60] initiated the construction of the β-carboline core 118 by esterifying L-tryptophan 115 with methanol in the presence of SOCl₂ to obtain hydrochloride 116, which was subjected to the Mannich reaction with formaldehyde in an acidic media, yielding tetrahydro-β-carboline-3-carboxylate 117. The oxidation of the latter with trichloroisocyanuric acid (TCCA) in DMF produced methyl 9H-pyrido[3,4-b]indole-3-carboxylate 118 (Scheme 33).

A one-pot method for the synthesis of β-carboline 121 was developed through the reaction of tryptamine 119 and pyridine-2-carboxaldehyde 120 in refluxing anisole followed by reduction with the Pd/C system (Scheme 34). It is noteworthy that the copper(II) complexes 122 based on 1-pyridin-2-yl)-9H-pyrido[3,4-b]indole 121 were tested for the antitumor activity against myeloid leukemia 1 (Mcl-1) [61, 62].
Scheme 31. The synthesis of tetrahydro-1H-pyrido[3,4-b]indole-1-carboxylic acids

Scheme 32. The approach to the synthesis of methyl 9H-pyrido[3,4-b]indole-3-carboxylates

Scheme 33. The synthesis of the β-carboline core through the **Mannich** reaction

Scheme 34. The one-pot method for the synthesis of β-carboline
The authors of work [63] developed a one-step method for synthesizing β-carboline derivatives 124 from substituted methyl ester of tryptophan 123 and aldehydes in a methylene chloride solution in the presence of catalytic amounts of TFA at room temperature, followed by further treatment of the reaction mixture with trichloroisocyanuric acid (Scheme 35).

The biomimetic approach is a convenient alternative to the methods involving the stepwise synthesis of β-carboline. Treating a mixture of substituted tryptophan 125 and amino acids with molecular iodine and trifluoroacetic acid successively undergoes decarboxylation, deamination, the Pictet-Spengler reaction, and oxidation, resulting in the formation of target β-carbolines 127 (Scheme 36). In contrast, the reaction of tryptophan hydrochloride 126 leads to the formation of methyl 9H-pyrido[3,4-b]indole-3-carboxylate 127. This indicates that the carboxylic group esterification in tryptophan blocks the decarboxylation, but does not impede other reactions in the process [64].

The oxidative cyclization mediated by tetrabutylammonium bromide (TBAB) proved to be an effective method for obtaining β-carbolines 129 from readily available tryptophans 128 and aldehydes (Scheme 37) [65].

An efficient approach to the synthesis of β-carbolines 132, 134 was implemented under metal-free conditions starting from heteroaromatic aldehydes 130, propargylamines 131, or but-3-y-n-2-amines 133 (Scheme 38) [43].

The authors of study [66] successfully used a cascade aza-alkylation/Michael addition reaction sequence, exemplified by the interaction of functionalized enones 135 with α-bromoketones 136 to obtain diketoindoles 137, which upon treatment with NH₄OAc in acetic acid yielded 1,3-disubstituted β-carbolines 138 (Scheme 39).

The conditions of the cascade reaction proved to be effective for the synthesis of ethyl 9H-pyrido[3,4-b]indole-3-carboxylate 143 as well. The required enone 141, which was generated by the Wittig olefination of aldehyde 139 with phosphorane 140 in the subsequent one-pot process with 2-bromo-1-phenylethanone 142, gave the target carboxylate 143 with the yield of 63 % (Scheme 40) [66].

![Scheme 35. Another one-step method for synthesizing β-carboline derivatives](image1)

![Scheme 36. The biomimetic approach to the synthesis of β-carbolines](image2)
Scheme 37. The synthesis of β-carbolines from readily available tryptophans and aldehydes

Scheme 38. The synthesis of β-carbolines under metal-free conditions

Scheme 39. The use of a cascade aza-alkylation/Michael addition reaction
The Pictet-Spengler reaction also serves as a general approach to the synthesis of marinoquinolines. The interaction of substituted 2-(1H-pyrrole-3-yl)anilines with a range of aliphatic, aromatic, and heteroaromatic aldehydes resulted in a library of 3H-pyrrolo[2,3-c]quinolines (Scheme 41) [67–69].

2-(1H-Pyrrole-3-yl)anilines have proven to be convenient substrates in the synthesis of pyrroloquinolines through electrocyclization reactions. The interaction of the initial anilines with the pyrrol-3-yl fragment with isocyanates in the DCM solution at room temperature yielded urea derivatives. The treatment of these compounds with CBr4, PPh3, and TEA led to the formation of carbodiimides. The subsequent deprotection of carbodiimides with tetrabutylammonium fluoride (TBAF) was accompanied by the electrocyclization reaction and the in situ formation of the desired marinoquinolines (Scheme 42) [70].

The authors of work [71] developed a Pd-catalyzed cyclization of imines to create the 3H-pyrrolo[2,3-c]quinoline system. It is a part of the natural antimalarial marine products aplidopsamine A and marinoquinoline A. The base-induced deprotection of the phenylsulfonyl fragment from pyrroloquinoline led to the formation of marinoquinoline A with the yield of 96%. For the synthesis of aplidopsamine A, the benzoyl peroxide (BPO) catalyzed bromination of pyrroloquinoline was carried out using NBS to obtain bromide. The reaction of the latter with 6-chloropurine in the DMF solution...
and the treatment of the intermediate with the saturated methanolic ammonia solution led to the formation of aplidopsamine A \(154\) with the yield of 69%. Additionally, bromide \(153\) was used in the synthesis of the hybrid natural product analog NCLite-M1 \(155\) by the alkylation of quinazolinone with bromomethylpyrroloquinoline \(153\) followed by the deprotection allowed for the production of NCLite-M1 \(155\) with the yield of 90% (Scheme 43).

3. The synthesis of the 6-azaindole system with a single-step formation of pyrrole and pyridine rings

A new variant of constructing the 6-azaindole core \(159\) has been developed based on the intramolecular Diels-Alder cycloaddition of oxazole \(158\) obtained from the reaction of oxazole \(156\) with diene \(157\) (Scheme 44) [72].

The reaction of alkyne-allene isomerization of esters \(162\) in situ proved to be convenient for

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\begin{align*}
\text{Scheme 42. Marinoquinolines from 2-(1H-pyrrol-3-yl)anilines} & \\
\text{Scheme 43. The Pd-catalyzed cyclization of imines for the synthesis of 3H-pyrrolo[2,3-c]quinolines} & \\
\text{Scheme 44. The Diels-Alder reaction in the synthesis of the 6-azaindole core} & \\
\end{align*}
\]
the synthesis of ethyl pyrrolo[2,3-c]pyridine-4-carboxylates 163. The Cu(I)-catalyzed interaction of alkyne 160 with ethyl diazoacetate 161 yielded the internal alkyne 162; its further heating in the presence of TEA was accompanied by isomerization into an allene and a spontaneous formation of 6-azaindole-4-carboxylate 163 (Scheme 45) [72].

A one-pot synthesis of polycyclic systems containing the 6-azaindole fragment was carried out by the Pd-catalyzed Sonogashira coupling/intramolecular [2+2+2] cyclization. The reaction of N-alkynyl sulfonamide 164 with alkynyl nitriles 165 under cross-coupling conditions yielded dienyl nitriles 166, from which terminal alkynes 167 were obtained by removing the trimethylsilyl group. The Rh(I)-catalyzed cyclization of the latter led to the formation of the target pyrido[3,4-b]indoles 168 (Scheme 46) [73–75].

4. 6-Azaindoles of high MedChem importance

Pyrrolo[2,3-c]pyridines represent a significant class of heterocyclic compounds that exhibit a wide range of biological activities. Due to their structural similarity to natural alkaloids and their ability to interact with various biological targets, these compounds have attracted considerable interest in medicinal chemistry and drug development. The key areas of the biological activity for pyrrolo[2,3-c]pyridines include the anticancer activity, antiviral properties, neuroprotective effects, anti-inflammatory and analgesic activities, antimarial activity, modulation of ion channels and receptors activity, etc.

The 6-azaindole core is incorporated into the approved antiretroviral drug Fostemsavir 169 (Rukobia™) [76] and its prodrug Temsavir 170 (BMS-626529) [77] (Figure 1). They inhibit the attachment of the viral gp120 and prevent HIV entry. Both structures are widely used in the treatment of patients who have intolerance or resistance to other HIV/AIDS medications.

6-Azaindolylmaleimide 171 (Figure 2) synthesized by the authors of [4] exhibits a high kinase selectivity toward oncogenesis-associated protein kinases VEGFR, FLT-3, and GSK-3β, demonstrating a potent inhibition of angiogenesis and cell proliferation.

Among the functionalized 6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-ones, bromodomain and
an extra-terminal domain (BET) inhibitor [12]. Meanwhile, compound 173 showed an excellent antiproliferative activity against the BxPC3 cell line, strongly induced the degradation of bromodomain-containing protein 4 (BRD4), and inhibited BRD4 BD1 [24] (Figure 3).

3-(2-Fluorophenyl)-N-phenyl-1H-pyrrolo[2,3-c]pyridine-7-amine 174 exhibited a high cytotoxic activity against prostate (PC-3) and colon (HCT116) cancer cell lines, and was found to be non-toxic to normal human fibroblast cells (WI-38) [10] (Figure 4).

Also, pyrrolo[2,3-c]pyridine core is a part of such β-carboline alkaloids as norharmane, harmane, eudistomin [78], trigonelline [79], aplidiosamine A [80], and marinoquinolines [81]. The β-carboline structure is present in such synthetic drugs as Lefetamine 175, which has antibiotic properties and antiproliferative action [82], and the anxiolytic drug Abecarnil 176 [83] (Figure 5).

Figure 1. Antiretroviral drugs Fostemsavir and Temsavir

Figure 2. 6-Azaindolylmaleimide as a potential inhibitor of angiogenesis and cell proliferation

Figure 3. The 6-Azaindole core in BRD4 BD1 and BET inhibitors
1-Substituted β-carbolines have shown a significant fungi activity. Compound 177 is characterized by the high antifungal activity against *G. graminis*, while derivatives 178–180 are active against *B. cinerea* and *F. graminearum* [51] (Figure 6).

Tetrahydro-β-carbolines 169 and 170 demonstrated a good selectivity for inhibiting butyrylcholinesterase (BuChE), disaggregation of Ab1-42, and an excellent neuroprotective activity by alleviating damage induced by H$_2$O$_2$, okadaic acid, and Ab1-42 without cytotoxicity in SH-SY5Y cells. Thus, compounds 169 and 170 are potent multifunctional agents against Alzheimer’s disease and can serve as promising lead candidates for further development [84] (Figure 7).

Compound 183 proved to be a potent, selective, and metabolically stable antagonist of the transient receptor potential melastatin 8 (TRPM8) ion channel (Figure 8). *In vivo*, 183 demonstrated...
a significant target coverage in murine models of icilin-induced wet dog shakes (WDS), cold alldynia induced by oxaliplatin, and thermal hyperalgesia induced by the chronic constriction injury (CCI). These results confirm the tryptophan moiety as a solid pharmacophore matrix for the development of high-potency modulators of the TRPM8-mediated activity [49].

A derivative of pyrido[4′,3′:4,5]pyrrolo[2,3-d]pyrimidine 184 was identified as an effective inhibitor of checkpoint kinases 1 and 2 (CHK1, CHK2) belonging to serine/threonine kinases and playing a central role in the mechanisms of the cellular regulation and DNA repair [41]. It is noteworthy that among compounds of this class of heterocycles, a potent and orally bioavailable dual inhibitor 185 (AMG 925) of cyclin-dependent kinase (CDK4) and tyrosine kinase (FLT3) was found. The derivative 185 inhibits the proliferation of a range of human tumor cell lines, including Colo205 (Rb+) and U937 (FLT3WT), induces cell death in MOLM13 (FLT3ITD), and even in MOLM13 (FLT3ITD, D835Y), which shows resistance to several FLT3 inhibitors. In well-tolerated doses, compound 185 leads to the significant inhibition of the growth of MOLM13 xenografts in mice, and the activity correlates with the inhibition of STAT5 and Rb phosphorylation [41] (Figure 9).

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**Conclusions**

Thus, the analysis of the literature sources for the last 15 years has shown that the construction of the 6-azaindole core and its structural modification remains a topical issue in the organic synthesis and medicinal chemistry. Biologically, pyrrolo[2,3-c]pyridines have emerged as a significant class of compounds with a potent activity across the spectrum of targets. The elucidation of their mechanisms of action and the optimization of their pharmacokinetic profiles are still crucial for drug development. The identification of derivatives with activity against challenging targets, such as protein kinases and viral proteins underscores the potential of pyrrolo[2,3-c]pyridines in addressing unmet medical needs.

In this sense, the future of pyrrolo[2,3-c]pyridine study is promising, and we anticipate new discoveries that will further enrich our pharmacological arsenal and contribute to the advancement of medicinal chemistry. In particular, among the vast array of pharmacophores attached to the pyrrolo[2,3-c]pyridine framework, the promising trifluoromethyl group has been understudied, and we expect the results in the field will appear in the near future.
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