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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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Останні досягнення в синтезі та біологічній активності піроло[2,3-*c*]піридинів

Анотація

Піроло[2,3-*c*]піридини (6-азаіндоли) є одними з найперспективніших серед азотовмісних гетероциклічних сполук у сфері розробки ліків. Виявляючи надзвичайну універсальність як фармакофори, вони відіграють ключову роль у розробці інгібіторів кіназ, антипроліферативних агентів та постають потенційними терапевтичними агентами для лікування різноманітних захворювань, зокрема раку та хвороби Альцгеймера. У світі опубліковано велику кількість робіт, зосереджених на нових методиках та підходах у синтезі 6-азаіндолів, а також на дослідженні їхньої біологічної активності. У нашому огляді ми намагалися класифікувати всі відомі на сьогодні стратегії конструювання 6-азаіндольного ядра, опубліковані за останні 15 років, розглянути хімічне різноманіття одержаних похідних та їх терапевтичний потенціал у контексті медичної хімії. Ми сподіваємось, що ця робота узагальнить та полегшить розуміння стратегій синтезу піроло[2,3-*c*]піридинів, а також допоможе науковцям у їхніх подальших дослідженнях 6-азаіндолів.

Ключові слова: піроло[2,3-*c*]піридини; 6-азаіндоли; біологічна активність; медична хімія; гетероциклічні сполуки; розробка ліків

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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 *Reisert*, *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.

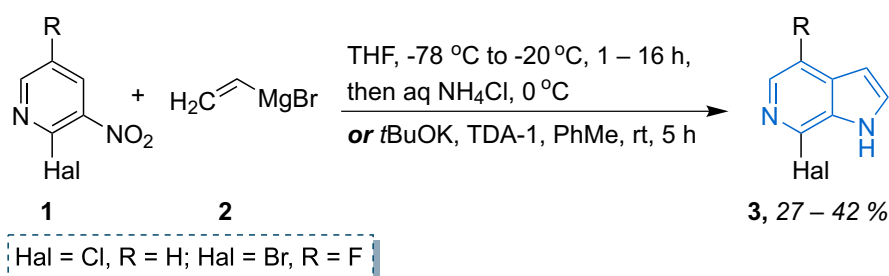
Initially, we propose focusing on the first method, namely the annulation of the pyridine nucleus to the pyrrole cycle.

1. Annulation of the pyrrole nucleus to the pyridine cycle

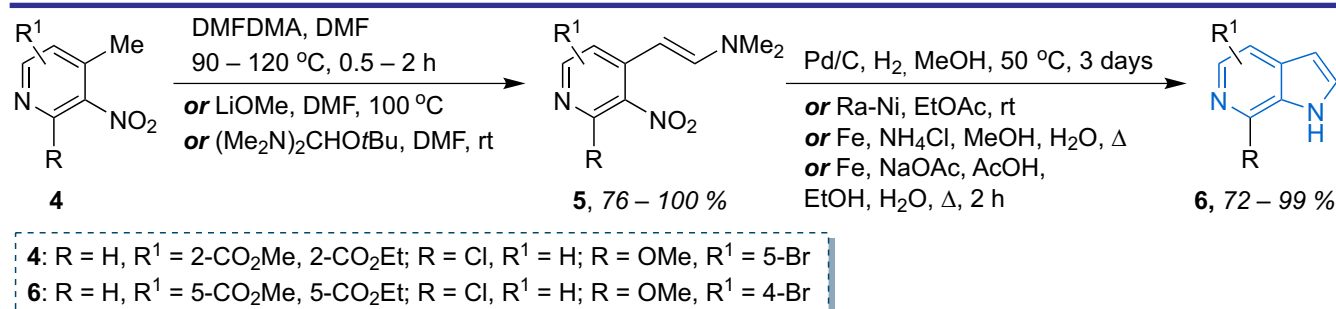
The first and one of the most common methods for forming the pyrrolo[2,3-*c*]pyridine framework **3** involves the *Bartoli* reaction of 2-halogen-3-nitropyridines **1** with vinyl magnesium bromide **2** in the THF solution [3–6] or using toluene as a solvent in the presence of a base [7] (**Scheme 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 (DMFDMA) [8–11], lithium methylate in the DMF solution [12] or 1-*tert*-butoxy-*N,N,N',N'*-tetramethylmethanedi-amine [13] gives enamines **5**, which reductive cyclization leads to the target pyrrolo[2,3-*c*]pyridines (**Scheme 2**) with up to 100 % yields.



Scheme 1. The “classic” *Bartoli* reaction of nitropyridines with a vinyl Grignard reagent



Scheme 2. The alternative two-step approach for increasing the yields to 2,3-unsubstituted 6-azaindoles

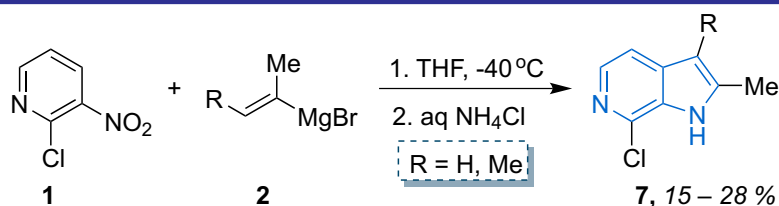
The *Bartoli* reaction is also used and described for synthesizing 2-alkyl-substituted or 2,3-dialkyl-substituted pyrrolo[2,3-*c*]pyridines **7**, among the functionalized derivatives of which potent potassium-competitive acid blockers (P-CABs) have been identified (**Scheme 3**) [14].

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.

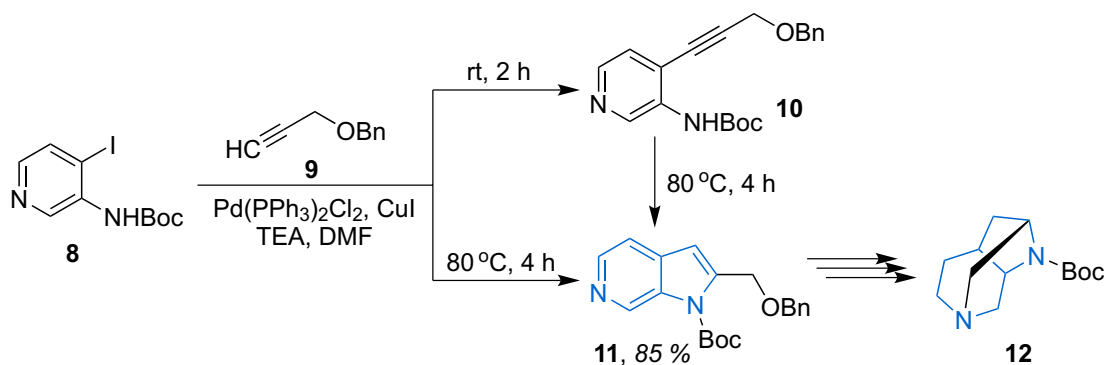
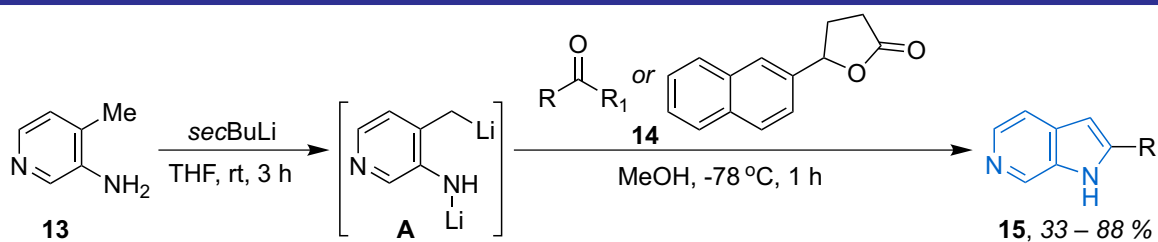
Thus, the utility of the *Bartoli* reaction consists not only in constructing complex nitrogen-containing heterocycles, but also in enabling the targeted modification of these molecules to enhance their pharmacological profiles, thereby offering a valuable strategy for the discovery and optimization 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 dilithiation of unprotected 3-amino-4-picoline **13**. The condensation of the dianion **A** obtained with carboxylic acid esters, thioester, or dihydrofuranone **14** led to a number of 2-substituted pyrrolo[2,3-*c*]pyridines with quite good and competitive yields (**Scheme 5**).

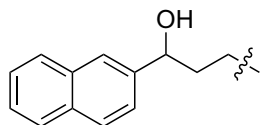


Scheme 3. The use of *Bartoli* reaction for P-CABs synthesis

Scheme 4. The *Sonogashira* reaction in the synthesis of 6-azaindole core

14: R = Me, R¹ = OMe; R = *t*Bu, R¹ = OMe; R = BnCH₂, R¹ = OMe; R = adamantan-1-yl, R¹ = OEt; R = Ph, R¹ = OEt; R = 4-BrC₆H₄, R¹ = OMe; R = 4-CF₃C₆H₄, R¹ = OMe; R = 2-naphthyl, R¹ = OMe; R = 3-furyl, R¹ = OEt; R = 3-thienyl, R¹ = OEt; R = 2-furyl, R¹ = SMe

15: R = Me, *t*Bu, BnCH₂, adamantan-1-yl, Ph, 4-BrC₆H₄, 4-CF₃C₆H₄, 2-naphthyl, 2-furyl, 3-furyl, 3-thienyl



Scheme 5. The scheme of the synthesis of the combinatorial library of 6-azaindole derivatives

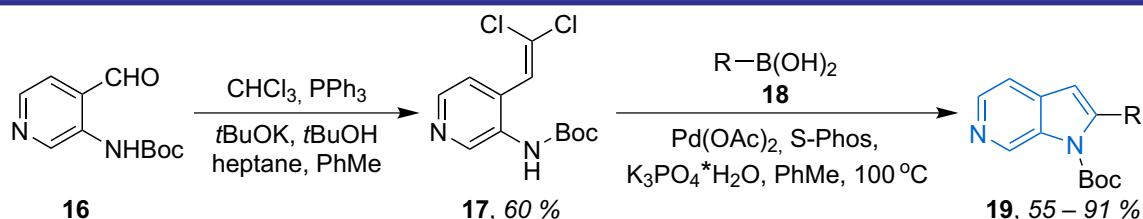
Another convenient method for synthesizing 2-alkyl(aryl, heteroaryl)-substituted 6-azaindoles **19** is the palladium-catalyzed reaction of *gem*-dichloro olefins **17** and boronic acids **18**, which includes a tandem intramolecular C–N coupling and the intermolecular *Suzuki* process (Scheme 6) [17].

In work [18] an example of obtaining 2-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine **15** using a Pd-catalyzed and carbon monoxide mediated reductive cyclization of 3-nitro-4-styrylpyridine **20** (Scheme 7) was described. In a similar transformation,

authors of work [19] used phenyl formate as a CO source (Scheme 7).

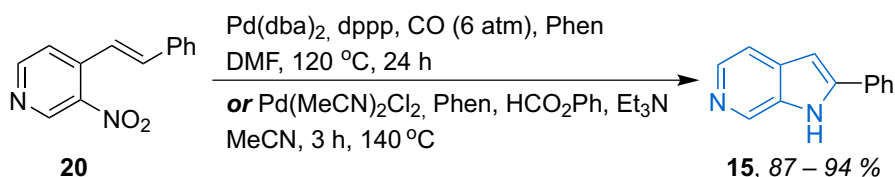
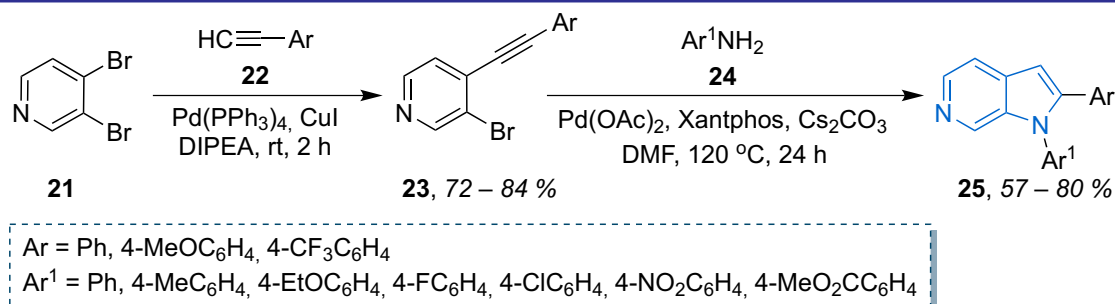
Another example of the Pd-catalyzed synthesis of 6-azaindoles **25** was developed based on the *Sonogashira* reaction followed by a tandem C–N coupling and cyclization with amines. The interaction of 3,4-dibromopyridine **21** with alkynes **22** led to 3-bromo-4-(arylethynyl)pyridines **23**, the treatment with aromatic amines produced a range of pyrrolo[2,3-*c*]pyridines **25** (Scheme 8) [20].

The work documented in [21] outlines a one-pot method for synthesizing 3-substituted



R = *n*PrCH=CH, Ph, 2-MeC₆H₄, 4-MeOC₆H₄, 4-CF₃C₆H₄, 2-naphthyl, 3-thienyl

Scheme 6. The alternative approach to 2-alkyl(aryl, heteroaryl)-substituted 6-azaindoles

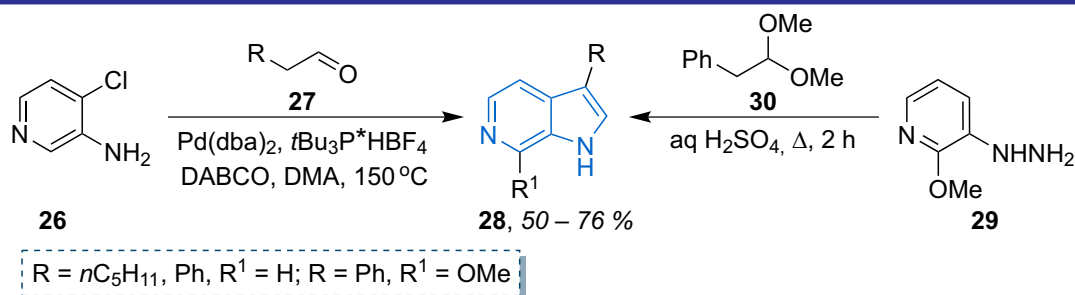
Scheme 7. The synthesis of 2-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine with the reductive cyclizationScheme 8. The method for the synthesis of aryl substituted pyrrolo[2,3-*c*]pyridines

6-azaindoles **28** by the Pd-catalyzed direct annulation of *ortho*-chloroaminopyridine **26** with aldehydes **27** (Scheme 9). 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).

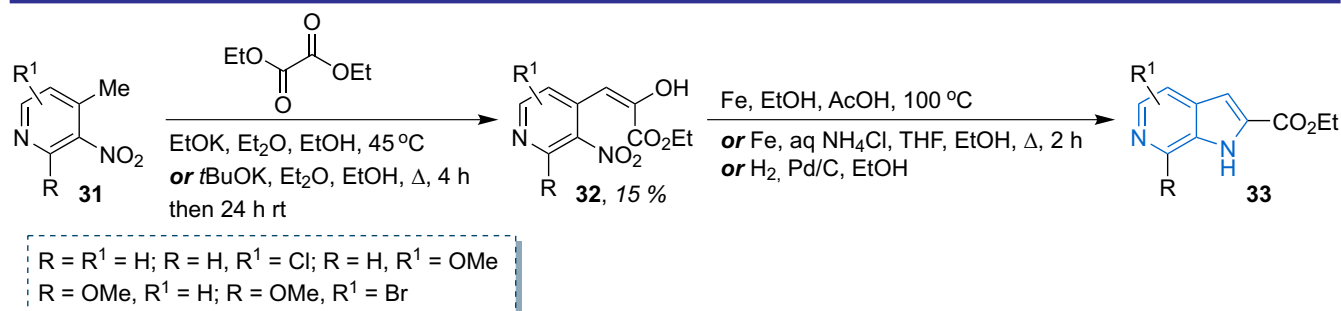
A series of works [23–25] describe the condensation of nitropyridines **31** with diethyl oxalate followed by the reductive cyclization of the resulting product **32** to yield ethyl 1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylates **33**, which are used

as building blocks in the synthesis of an immense range of biologically active compounds (Scheme 10).

The synthesis of isomeric ethyl 1*H*-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 9. The one-pot method for the synthesis of 3-substituted 6-azaindoles

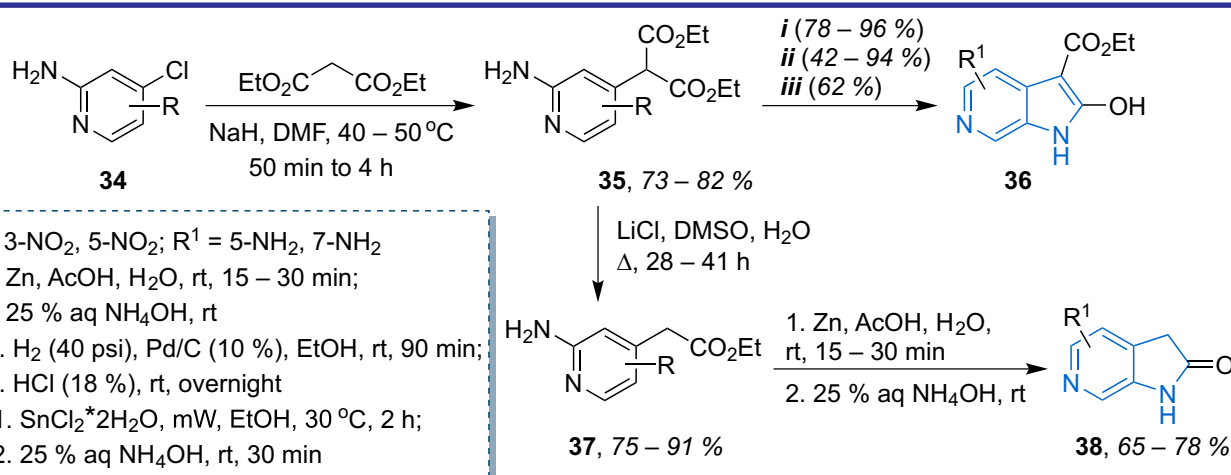
Scheme 10. The synthesis of 1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylates as the starting building block for obtaining the biologically active compounds

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-1*H*-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 the 18 % solution of hydrochloric acid, as well as treating diethyl malonate **35** with an excess of SnCl₂·H₂O in ethanol under ultrasound activation (Scheme 11) [27].

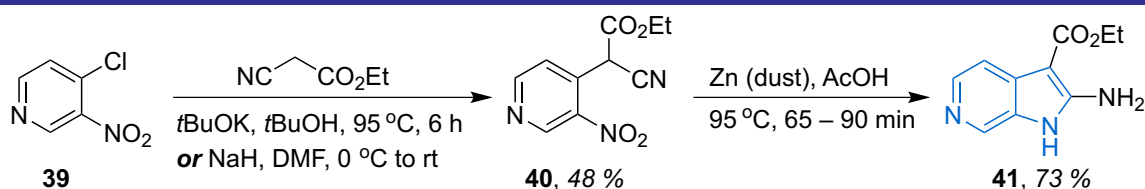
Meanwhile, the condensation of 4-chloro-3-nitropyridine **39** with ethyl cyanoacetate yielded ethyl 2-cyano-2-(3-nitropyridin-4-yl)acetate **40**; its intramolecular cyclization upon the treatment with powdered zinc in acetic acid led to the formation of ethyl 2-amino-1*H*-6-azaindole-3-carboxylate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

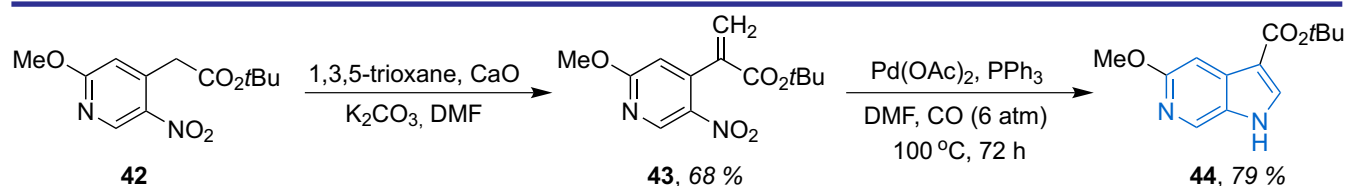
The authors of work [31] developed a one-pot variant for the synthesis of 2-trifluoromethyl-6-azaindoles **46**. The acylation of 2-methoxy-3-nitropyridine **45** with ethyl trifluoroacetate led to the formation of the intermediate 1,1,1-trifluoro-3-(3-nitropyridin-4-yl)propan-2-one (**A**) cyclized 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).



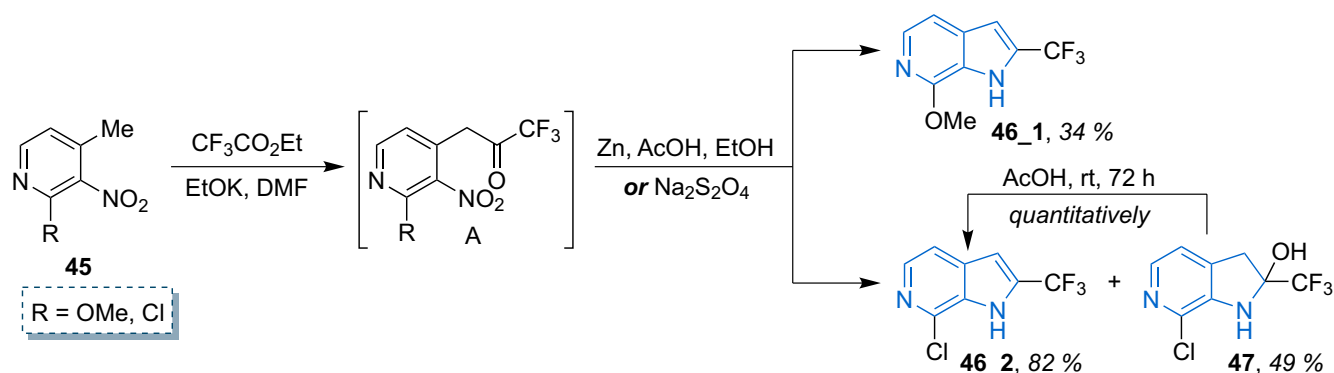
Scheme 11. The example of the synthesis of isomeric ethyl 1*H*-pyrrolo[2,3-*c*]pyridine-3-carboxylates



Scheme 12. The synthesis of 2-amino-1*H*-6-azaindole-3-carboxylate



Scheme 13. The synthesis of *tert*-butyl 6-azaindole-3-carboxylate



Scheme 14. The synthesis of 2-trifluoromethyl-6-azaindoles

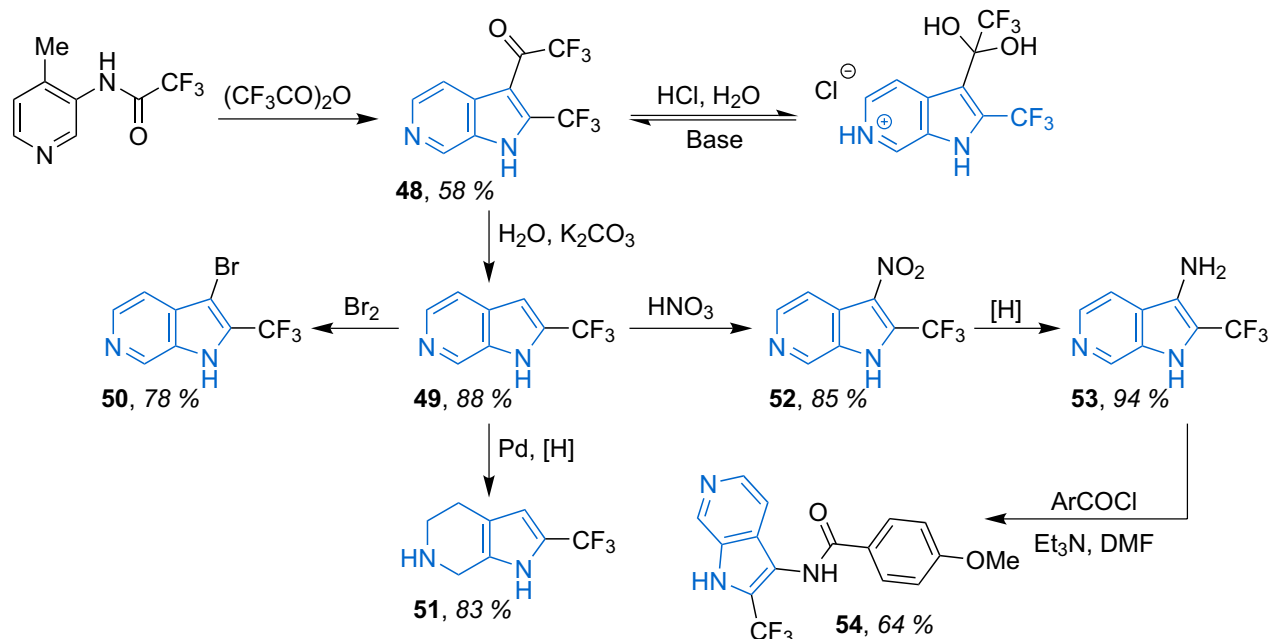
Another convenient approach to 3-trifluoromethyl-6-azaindoles was described in 2020 [32]. The hydration of trifluoroacetyl derivative **48** in hydrochloric acid at 80 °C for 16 hours gave easy removing of the trifluoroacetyl group to give 3-H 2-trifluoromethyl 6-azaindole. This efficient scalable synthetic 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].

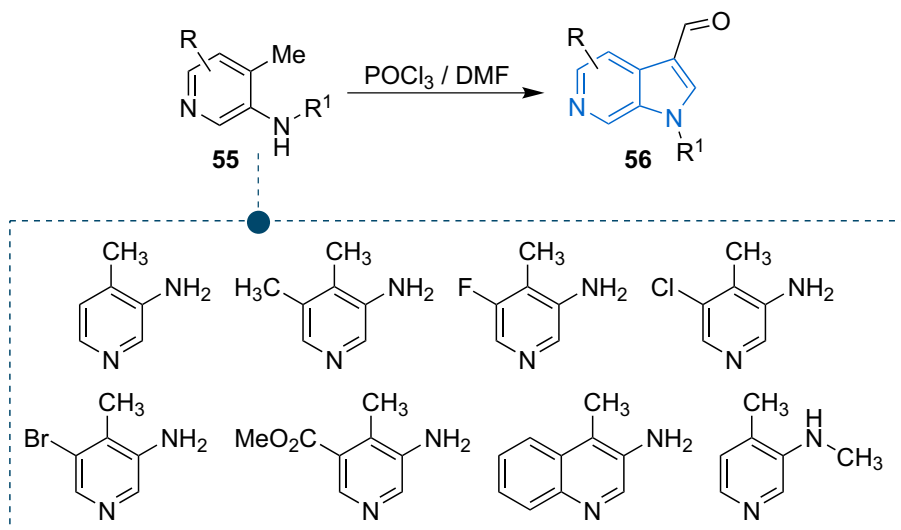
This method was demonstrated to be very effective, scalable, and regioselective, requiring no catalysts and quite easy to perform.

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-/furno-derivatives though in hydrated form.

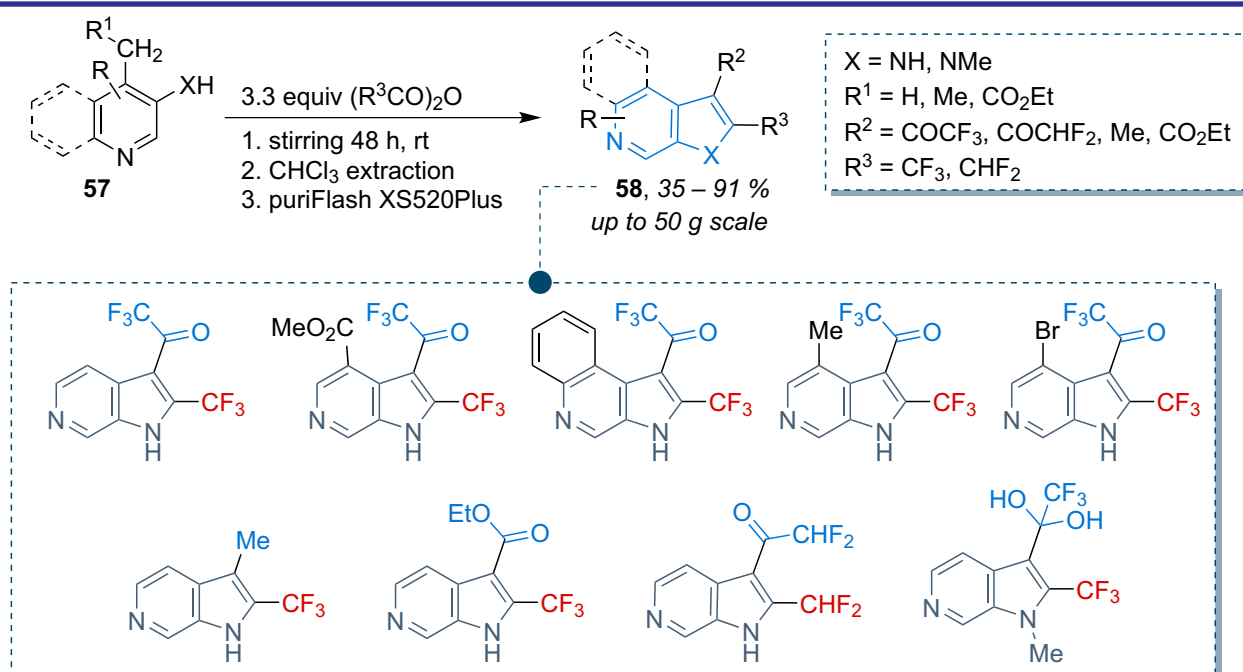
While pyrrolo[2,3-*c*]pyridines themselves are of substantial interest mainly due to their potential as pharmacophores, the move towards synthesizing their annulated derivatives opens new possibilities in drug design. Approaches to them include strategies, such as intramolecular cyclization reactions, the use of transition metal-catalyzed cross-coupling reactions, and employing



Scheme 15. An efficient way to 2-trifluoromethyl 6-azaindole and its derivatives



Scheme 16. The synthesis of 3-formyl-6-azaindoles via the Vilsmeier-Haack formylation



Scheme 17. The [4+1]-cyclization of 3-amino-4-methylpyridines

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.

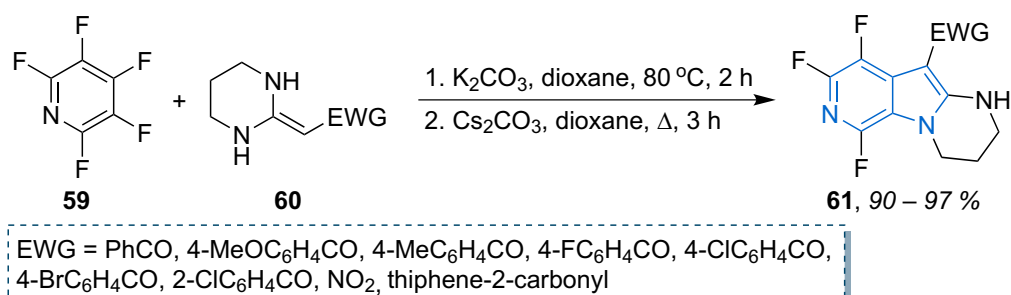
A one-pot, two-step method for synthesizing highly functionalized derivatives of 6-azaindole **61** was developed based on the nucleophilic aromatic substitution reaction of perfluoropyridine **59** with heterocyclic ketene aminals **60** promoted by two bases, K_2CO_3 and Cs_2CO_3 (Scheme 18) [35].

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].

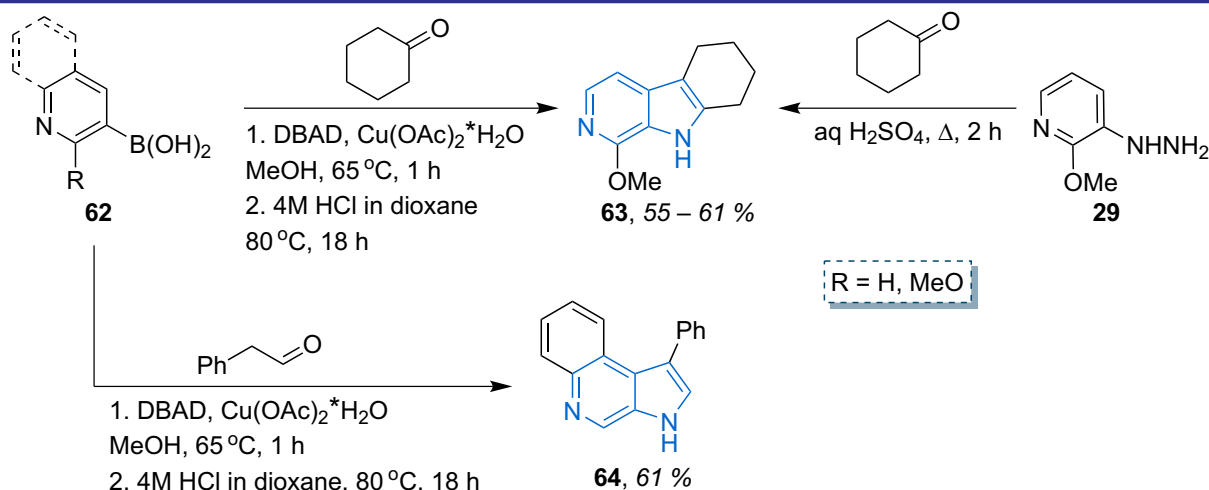
The interaction of 3-hydrazinyl-2-methoxypyridine **29** with cyclohexanone under the Fischer cyclization conditions was also effective for the annulation of the tricyclic system **63** (Scheme 19) [22].

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-aminobiaryls **67**. Further treatment of derivatives **53** with an excess of NaHMDS facilitated the intramolecular aromatic substitution, yielding the target 9*H*-pyrido[3,4-*b*]indoles **68** (Scheme 20) [37].

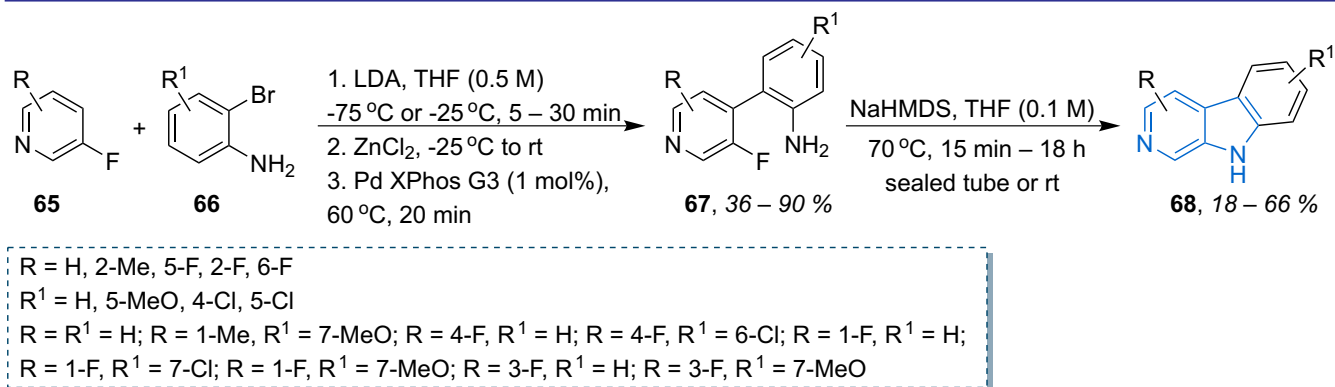
Another convenient approach to the synthesis of β -carbolines **71** is based on a double C–N coupling catalyzed by copper of 3,4-dibromopyridine **69** with



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



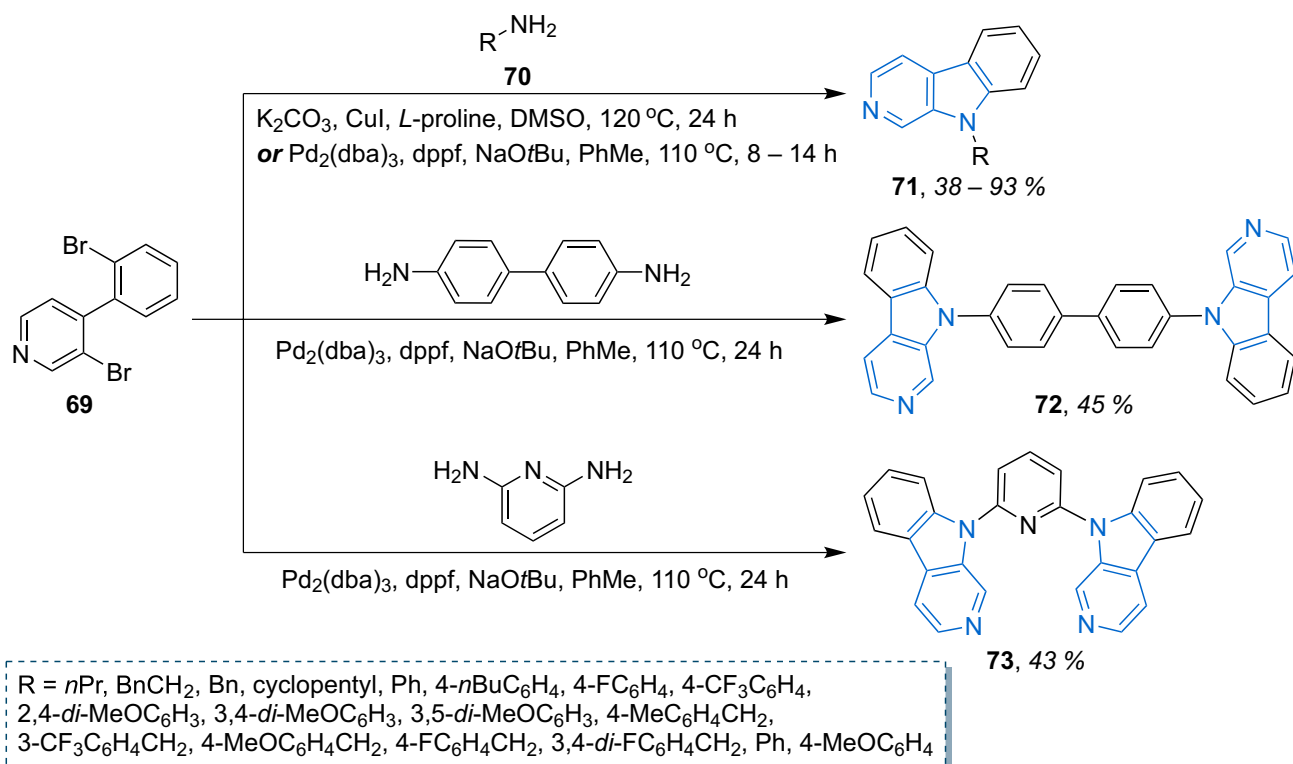
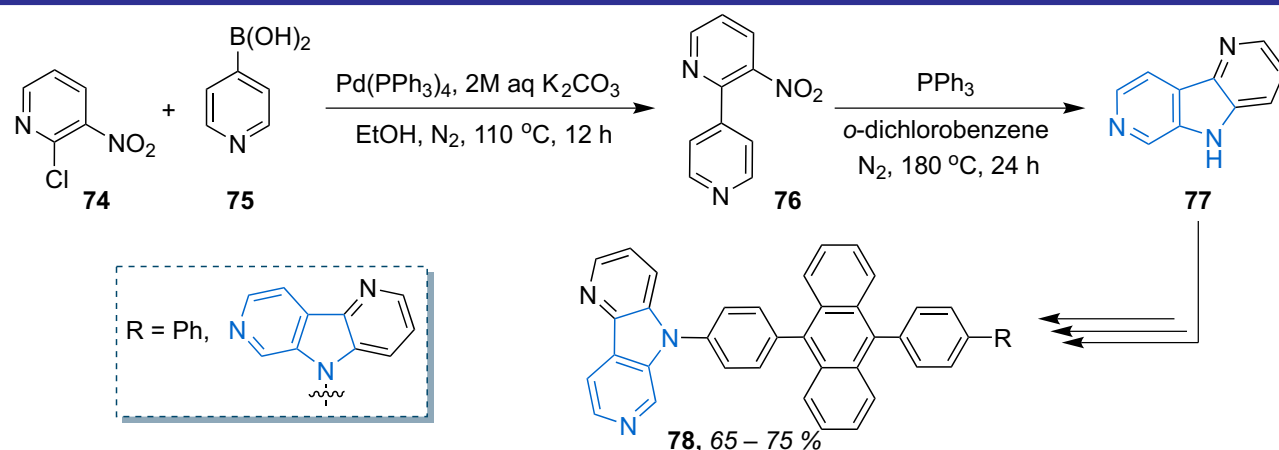
Scheme 20. An effective method for the synthesis of β -carbolines

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-nitropyridine (**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 $T_1 = 2.77$ 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*-S25NCzDPA and *p*-D25NCzDPA **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 21. An alternative route to β -carbolines

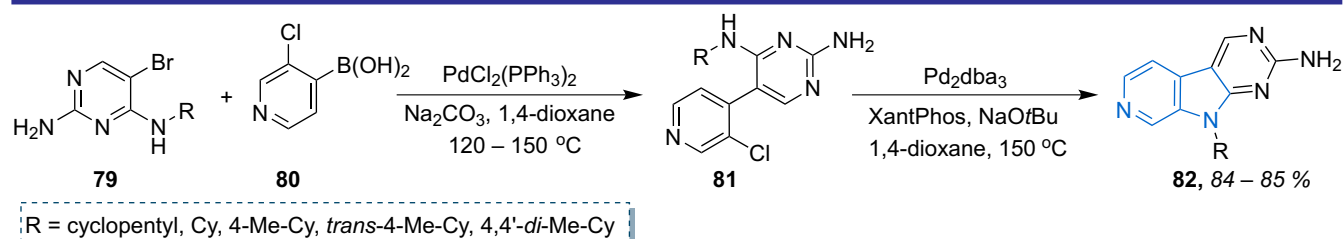
Scheme 22. The synthesis of new electron-deficient 2,5-diazacarbazole

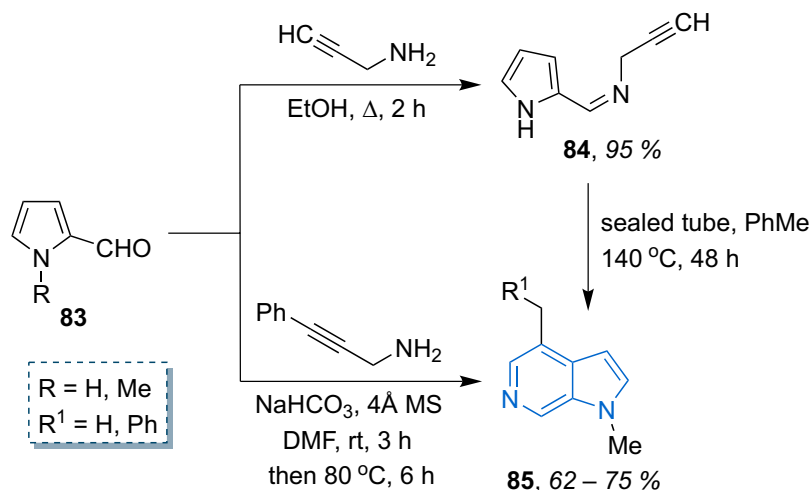
obtained by the *Negishi* cross-coupling of 5-bromopyrimidine-2,4-diamine **79** with boronic acid **80** (Scheme 23) [41].

2. Annulation of the pyridine nucleus to the pyrrole cycle

The next strategy for the synthesis of the pyrolopyridine core is through the annulation of the

pyridine nucleus onto the pyrrole cycle. In work [42] a regioselective approach to the synthesis of pyrrolo[2,3-*c*]pyridine **85** was demonstrated by interacting 1*H*-pyrrole-2-carbaldehydes **83** with propargylamine to form propargylimine **84**, the reaction of 6*π*-electrocyclization of which at high temperature gave the target product **85**

Scheme 23. The synthesis of pyrido[4',3':4,5]pyrrolo[2,3-*d*]pyrimidine derivatives



Scheme 24. A regioselective approach to pyrrolo[2,3-*c*]pyridines

(**Scheme 24**). Also, an effective variant B for obtaining 6-azaindole **85** was implemented by heating 1-methyl-1*H*-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].

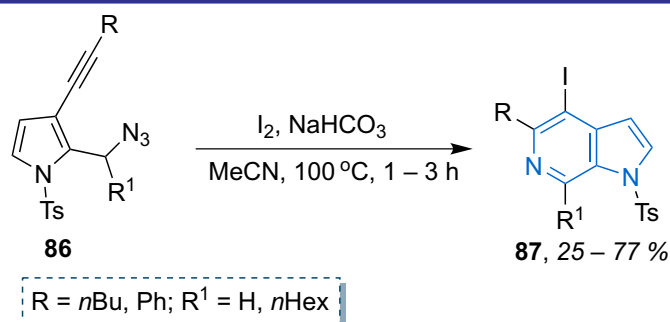
The intramolecular cyclization of the poly-substituted 6-azaindole **90** obtained from the reaction of ethyl 1*H*-pyrrole-3-carboxylate **88** and *N*-Ts-glycine **89** under LiHMDS treatment led to the highly functionalized pyrrolo[2,3-*c*]pyridine **91** (**Scheme 26**) [45].

The Ir(III)-catalyzed reaction of pyrroloxime **92** and α -diazocarbonyl derivative **93** proved to be effective for the synthesis of *N*-oxide pyrrolo-

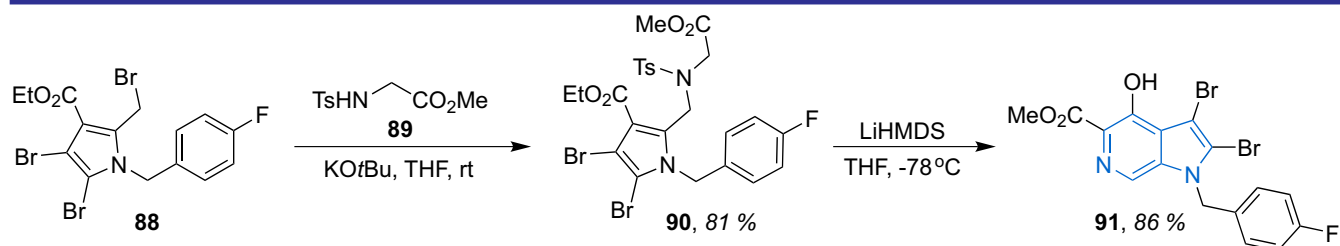
[2,3-*c*]pyridine **94**. It is worth noting that this represents a straightforward method for the synthesis of phosphorylated heterocycles, which are highly important in the organic synthesis and medicinal chemistry (**Scheme 27**) [46].

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].

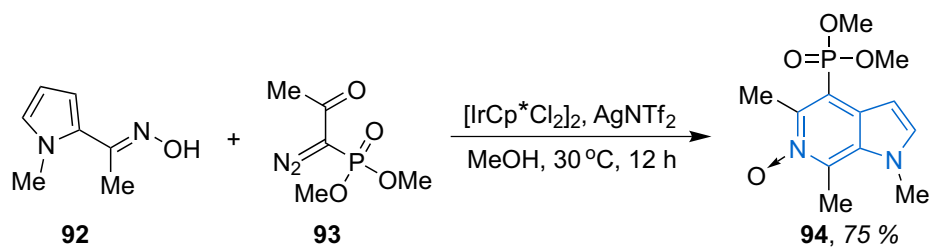
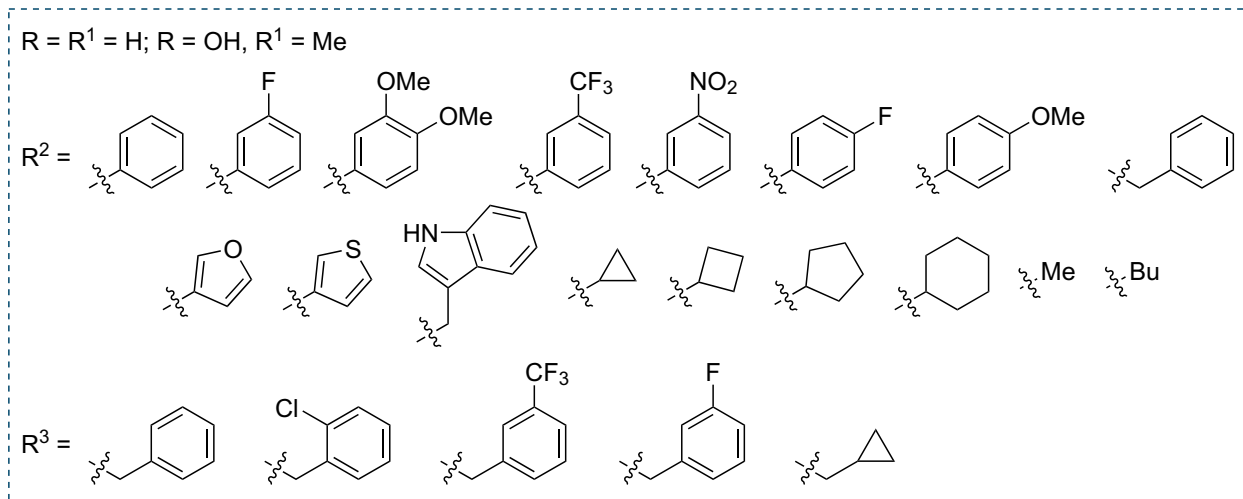
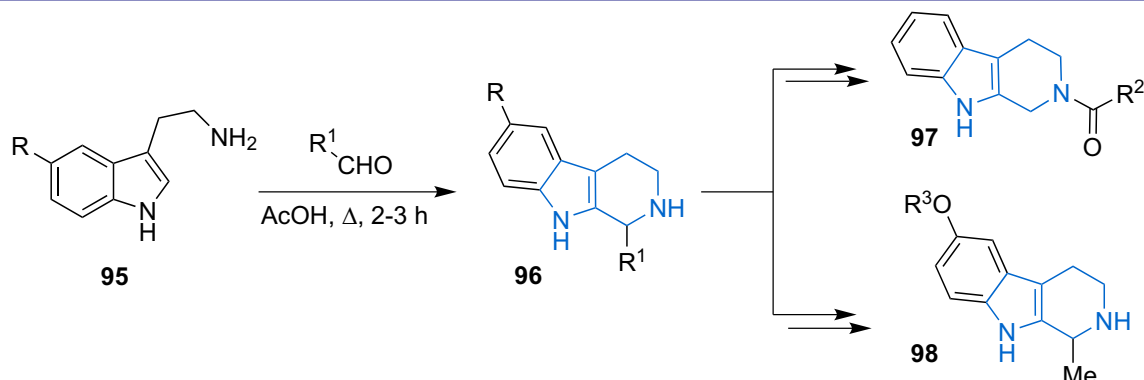
A series of tetrahydro- β -carbolines and methyl tetrahydropyrido[3,4-*b*]indole-3-carboxylates **100** synthesized from tryptamine or the methyl ester of tryptophan **99** and aldehydes were



Scheme 25. The method for obtaining highly functionalized 6-azaindoles



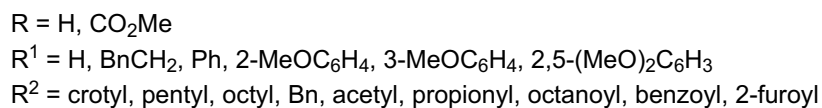
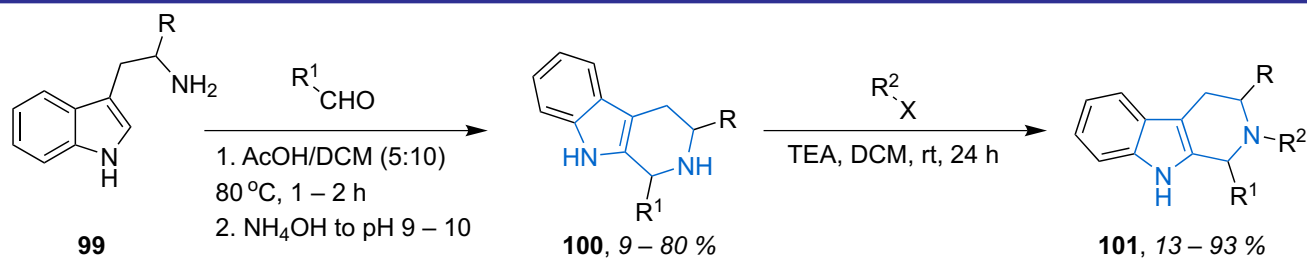
Scheme 26. Another approach to highly functionalized 6-azaindoles

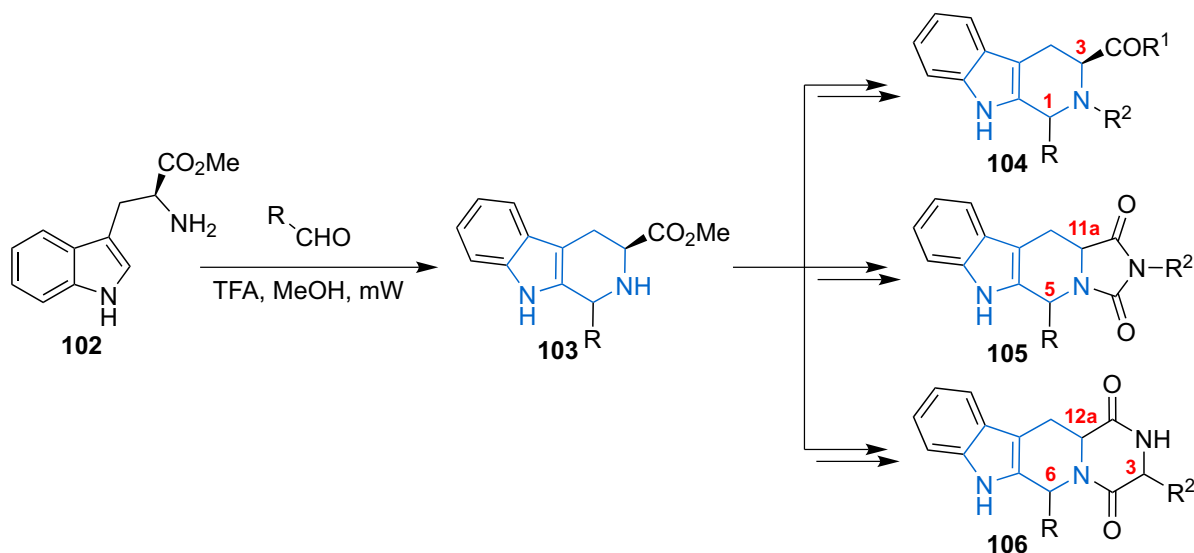

Scheme 27. The synthesis of pyrrolo[2,3-*c*]pyridine *N*-oxide

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

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


Scheme 29. The synthesis of tetrahydro- β -carbolines



104: R, R¹, R²; Ph, OMe, Bn (1*R*,3*S*); Ph, OMe, Bn (1*S*,3*S*); H, NHCH₂(4-F)Ph, H (3*S*); *i*Bu, NHCH₂(4-F)Ph, H (1*R*,3*S*); *i*Bu, NHCH₂(4-F)Ph, H (1*S*,3*S*); CH₂CH₂CO₂Me, NHCH₂(4-F)Ph, H (1*R*,3*S*); CH₂CH₂CO₂Me, NHCH₂(4-F)Ph, H (1*S*,3*S*); CH₂CH₂CO₂H, NHCH₂(4-F)Ph, H (1*R*,3*S*); CH₂CH₂CO₂H, NHCH₂(4-F)Ph, H (1*S*,3*S*); H, OMe, COCH₂CH₂NH₂ (3*S*)

105, 106: R, R²; H, H (12*aS*); H, Bn (3*S*,12*aS*); H, Bn (3*S*,12*aS*); *i*Bu, Bn (3*S*,6*R*,12*aS*); *i*Bu, Bn (3*S*,6*S*,12*aS*); 4-Cl-C₆H₄, H (6*R*,12*aS*); 4-Cl-C₆H₄, H (6*S*,12*aS*); H, CH₂4-F-C₆H₄ (11*aS*); *i*Bu, CH₂4-OMe-C₆H₄ (5*R*,11*aS*); *i*Bu, CH₂4-OMe-C₆H₄ (5*S*,11*aR*); 4-Cl-C₆H₄, CH₂4-Me-C₆H₄ (5*R*,11*aS*); 4-Cl-C₆H₄, CH₂4-Me-C₆H₄ (5*S*,11*aR*); 4-Cl-C₆H₄, CH₂4-F-C₆H₄ (5*R*,11*aS*); 4-Cl-C₆H₄, CH₂4-Me-C₆H₄ (5*R*,11*aS*); 4-F-C₆H₄, Bn (5*R*,11*aS*); 4-F-C₆H₄, Bn (5*S*,11*aR*); 4-F-C₆H₄, (CH₂)₃NH₂ (5*R*,11*aS*); 4-F-C₆H₄, (CH₂)₃NH₂ (5*S*,11*aR*); 4-F-C₆H₄, 3-CF₃-C₆H₄ (5*R*,11*aS*); 4-F-C₆H₄, 3-CF₃-C₆H₄ (5*S*,11*aR*); 4-F-C₆H₄, 2-F-C₆H₄ (5*R*,11*aS*); 4-F-C₆H₄, 2-F-C₆H₄ (5*S*,11*aR*); 4-F-C₆H₄, 4-F-C₆H₄ (5*R*,11*aS*); 4-F-C₆H₄, 4-F-C₆H₄ (5*S*,11*aR*)

Scheme 30. The synthesis of tetrahydro- β -carbolines via the microwave-assisted Pictet-Spengler reaction

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].

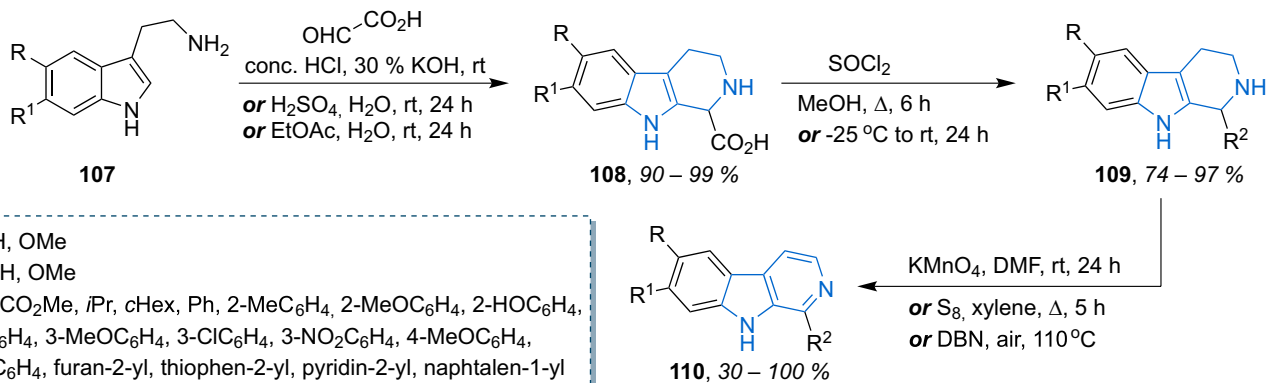
2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic acids **108** were obtained by the reaction of tryptamines **107** with glyoxylic acid [50–52]. The subsequent esterification of acids **108** in the presence of thionyl chloride in methanol yielded methyl tetrahydropyrido[3,4-*b*]indole-1-carboxylates **109**; its aromatization with potassium permanganate or sulfur in refluxing xylene led to methyl 9*H*-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 9*H*-pyrido[3,4-*b*]indole-3-carboxylates **114** is described. This approach includes the Pictet-Spengler reaction of tryptophan **111** and aldehydes **99**, esterification

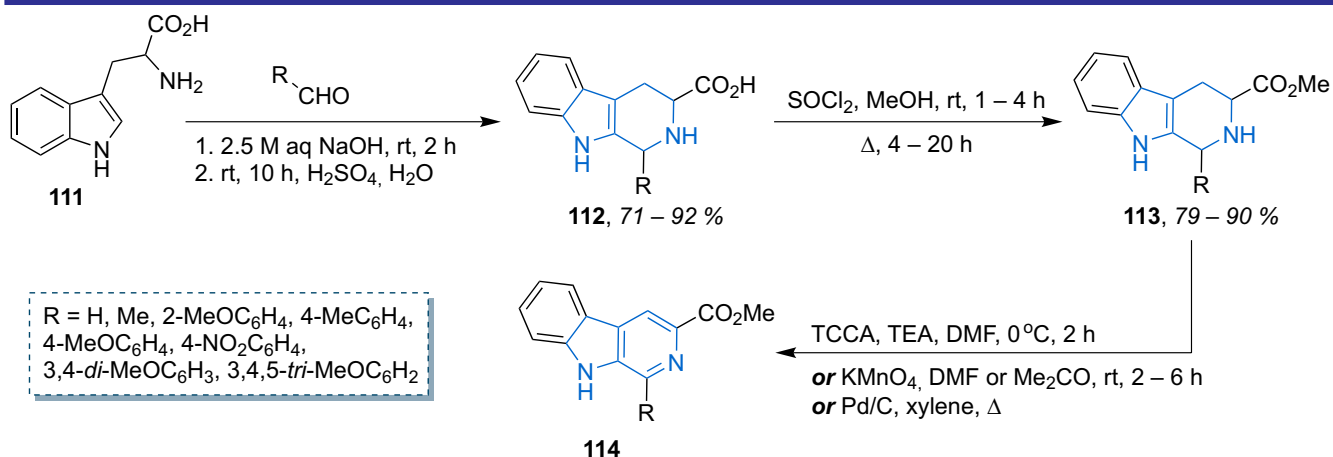
of acids **112**, and oxidation of tetrahydro- β -carbolines **113** (**Scheme 32**). A similar synthetic pathway was used to obtain (3*S*)-methyl-1*H*-pyrido[3,4-*b*]indole-3-carboxylates [59, 51].

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 9*H*-pyrido[3,4-*b*]indole-3-carboxylate **118** (**Scheme 33**).

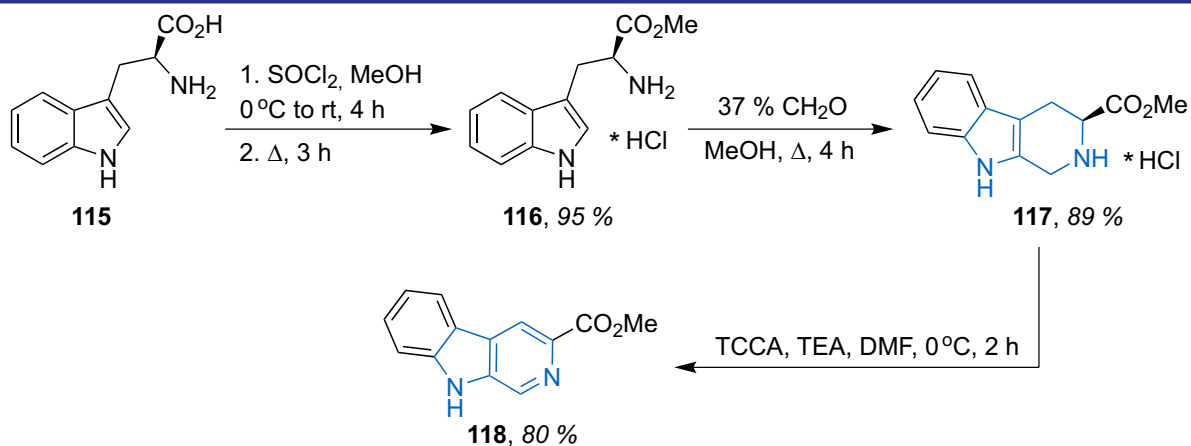
A one-pot method for the synthesis of β -carboline **121** was developed through the reaction of tryptamine **119** and pyridine-2-carboxaldehyde **120** in refluxing anisole followed by reduction with the Pd/C system (**Scheme 34**). It is noteworthy that the copper(II) complexes **122** based on 1-(pyridin-2-yl)-9*H*-pyrido[3,4-*b*]indole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



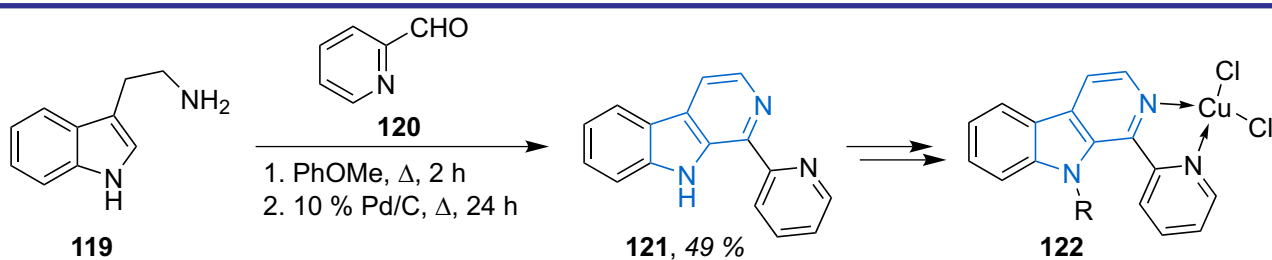
Scheme 31. The synthesis of tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic acids



Scheme 32. The approach to the synthesis of methyl 9*H*-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 -carbolines. 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 9*H*-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].

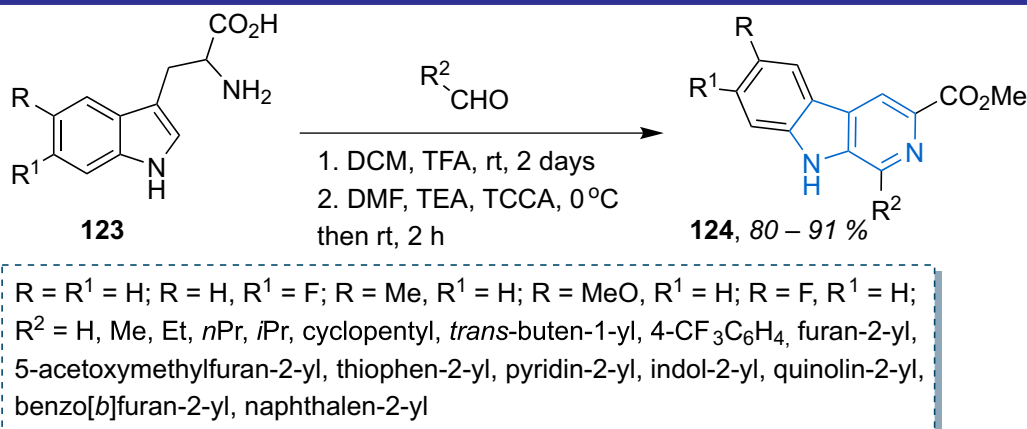
The oxidative cyclization mediated by tetrabutylammonium bromide (TBAB) proved to be an

effective method for obtaining β -carbolines **129** from readily available tryptophans **128** and aldehydes (Scheme 37) [65].

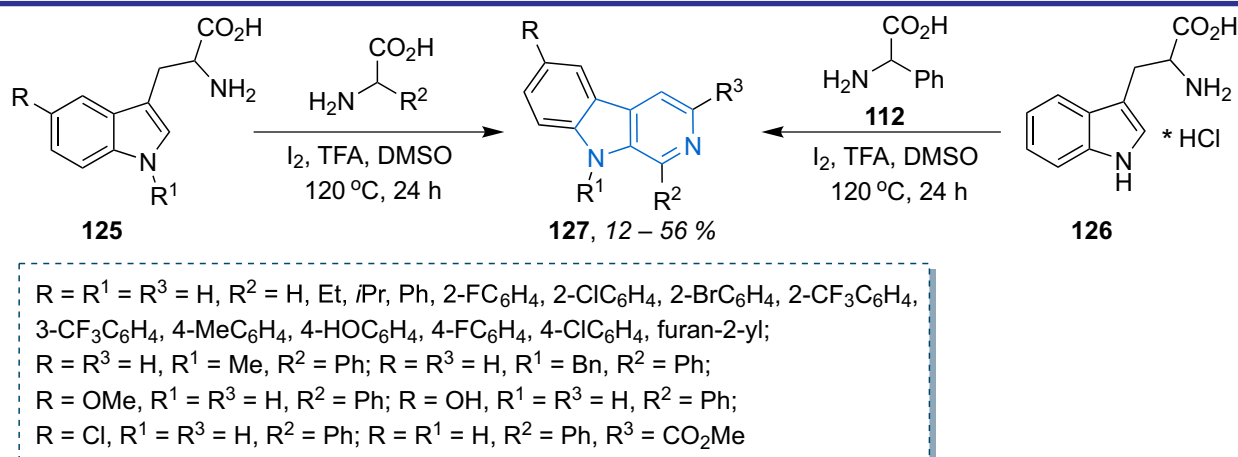
An efficient approach to the synthesis of β -carbolines **132**, **134** was implemented under metal-free conditions starting from heteroaromatic aldehydes **130**, propargylamines **131**, or but-3-yn-2-amines **133** (Scheme 38) [43].

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 NH_4OAc in acetic acid yielded 1,3-disubstituted β -carbolines **138** (Scheme 39).

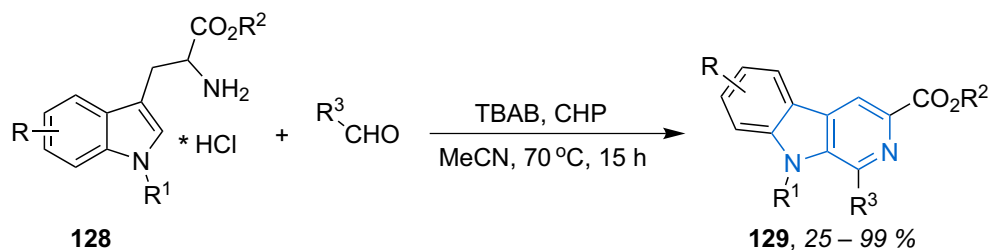
The conditions of the cascade reaction proved to be effective for the synthesis of ethyl 9*H*-pyrido[3,4-*b*]indole-3-carboxylate **143** as well. The required enone **141**, which was generated by the *Wittig* olefination of aldehyde **139** with phosphorane **140** in the subsequent one-pot process 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



Scheme 36. The biomimetic approach to the synthesis of β -carbolines



R = R¹ = H, R² = Me, R³ = H, *n*Pr, Cy, Ph, 2-MeC₆H₄, 2-HOC₆H₄, 2-ClC₆H₄, 3-MeC₆H₄, 3-BrC₆H₄, 3-NCC₆H₄, 4-MeC₆H₄, 4-*i*PrC₆H₄, 4-MeOC₆H₄, 4-BnOC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 4-MeSC₆H₄, 4-MeSOC₆H₄, 4-NO₂C₆H₄, 4-HO₂CC₆H₄, 4-CF₃C₆H₄, 2,4-*di*-ClC₆H₃, 2-HO-6-BrC₆H₃, naphthalen-2-yl, thiophen-2-yl, quinol-2-yl;

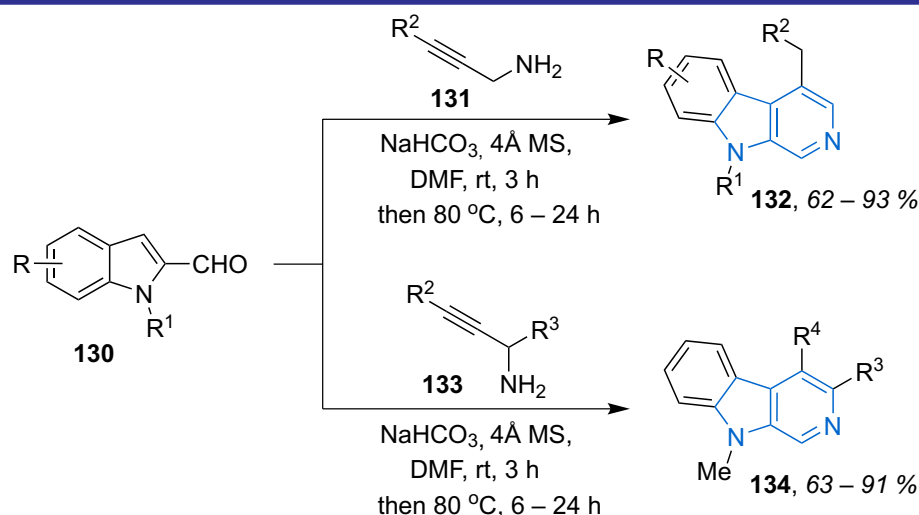
R = R¹ = H, R² = Et, R³ = Ph, 3-NCC₆H₄; R = R¹ = H, R² = OBn, R³ = Ph;

R = 6-Me, R¹ = H, R² = Me, R³ = Ph; R = 6-Br, R¹ = H, R² = OMe, R³ = Ph, 4-NO₂C₆H₄;

R = 6-CN, R¹ = H, R² = Me, R³ = 2-NO₂C₆H₄; R = 7-Cl, R¹ = H, R² = OMe, R³ = Ph, 4-NO₂C₆H₄;

R = H, R¹ = Me, R² = Me, R³ = Ph; R = H, R¹ = Me, R² = NH₂, R³ = Ph

Scheme 37. The synthesis of β -carbolines from readily available tryptophans and aldehydes



130: R = H, 5-MeO, 6-Me, 6-Br, 8-Me; R¹ = H, Me, Bn, Boc, Ph, Ts;

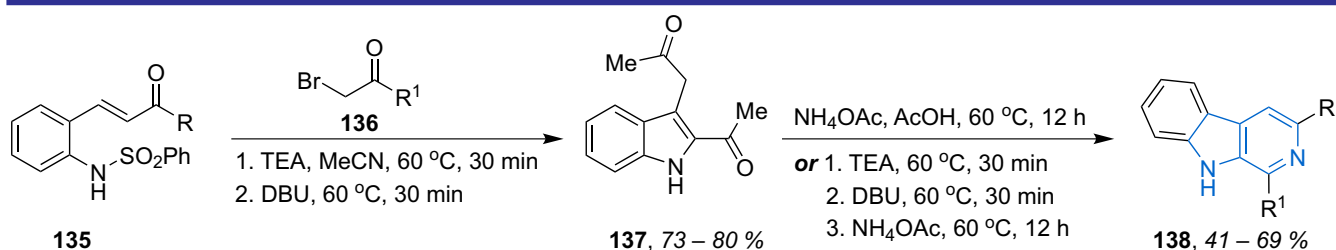
131: R² = H, Ph, 4-MeOC₆H₄, 4-NCC₆H₄, 4-NO₂C₆H₄, 4-AcC₆H₄,

4-CF₃C₆H₄, naphthalen-1-yl, thiophen-2-yl

130: R = H, R¹ = Me; **133**: R² = H, Ph, R³ = Me \rightarrow **134**: R³ = Me, R⁴ = Me

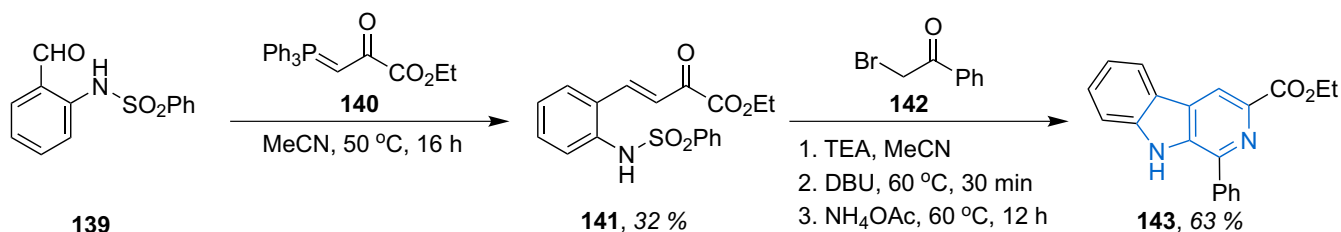
130: R = H, R¹ = Me; **133**: R² = CH₂Cl, R³ = H \rightarrow **134**: R³ = H, R⁴ = vinyl

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



R = Me, Et, Ph; R¹ = Me, Et, Ph

Scheme 39. The use of a cascade *aza*-alkylation/*Michael* addition reaction



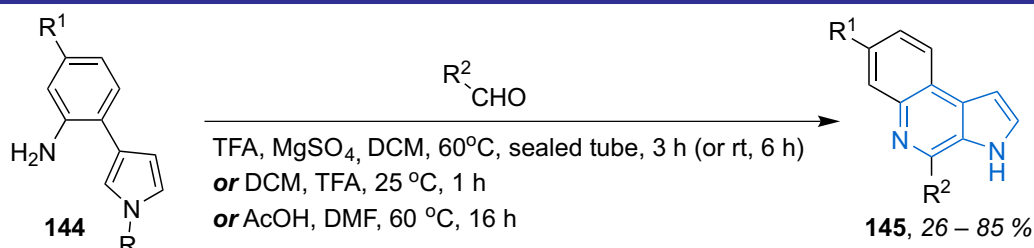
Scheme 40. The synthesis of ethyl 9H-pyrido[3,4-b]indole-3-carboxylate

The *Pictet-Spengler* reaction also serves as a general approach to the synthesis of marinoquinolines **145**. The interaction of substituted 2-(1*H*-pyrrole-3-yl)anilines **144** with a range of aliphatic, aromatic, and heteroaromatic aldehydes resulted in a library of 3*H*-pyrrolo[2,3-*c*]quinolines **145** (**Scheme 41**) [67–69].

2-(1*H*-Pyrrole-3-yl)anilines **146** have proven to be convenient substrates in the synthesis of pyrroloquinolines **149** through electrocyclization reactions. The interaction of the initial anilines with the pyrrol-3-yl fragment **146** with isocyanates in the DCM solution at room temperature yielded urea derivatives **147**. The treatment of these compounds with CBr_4 , PPh_3 , and TEA led to the formation of carbodiimides **148**. The subsequent deprotection of carbodiimides **148** with

tetrabutylammonium fluoride (TBAF) was accompanied by the electrocyclization reaction and the *in situ* formation of the desired marinoquinolines **149** (**Scheme 42**) [70].

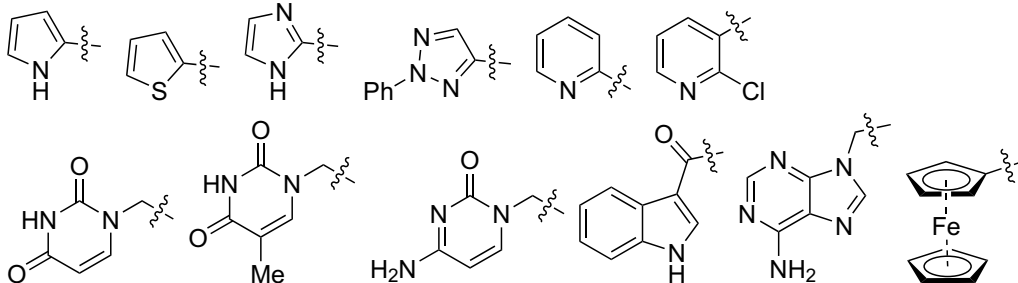
The authors of work [71] developed a Pd-catalyzed cyclization of imines **150** to create the 3*H*-pyrrolo[2,3-*c*]quinoline system **151**. It is a part of the natural antimalarial marine products apidopsamine A and marinoquinoline A. The base-induced deprotection of the phenylsulfonyl fragment from pyrroloquinoline **151** led to the formation of marinoquinoline A **152** with the yield of 96 %. For the synthesis of apidopsamine A **154**, the benzoyl peroxide (BPO) catalyzed bromination of pyrroloquinoline **151** was carried out using NBS to obtain bromide **153**. The reaction of the latter with 6-chloropurine in the DMF solution



R = H, TIPS

R¹ = H

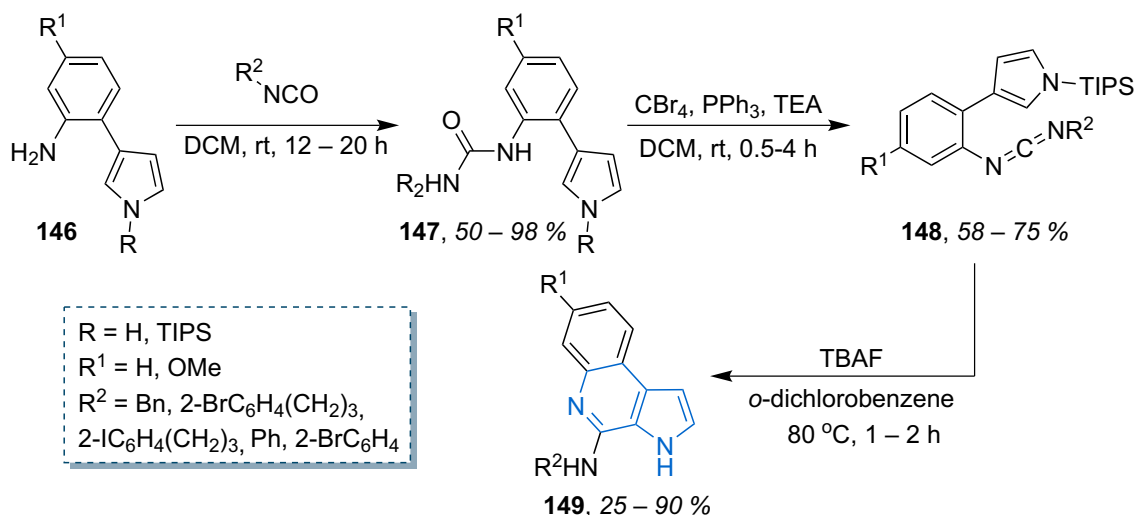
R² = Me, Et, *i*Bu, Bn, Ph, 4- $\text{H}_2\text{NC}_6\text{H}_4$, 4- $\text{Me}_2\text{NC}_6\text{H}_4$, 4- MeOC_6H_4 , 4- ClC_6H_4 , 4- BrC_6H_4 , 4- $\text{NO}_2\text{C}_6\text{H}_4$, 4- $\text{HO}_2\text{CC}_6\text{H}_4$, 4- $\text{MeO}_2\text{CC}_6\text{H}_4$, 4- $\text{F}_3\text{CC}_6\text{H}_4$, 3,5-*di*- MeOC_6H_3 , 3,4,5-*tri*- MeOC_6H_2 , indol-2-yl, indol-3-yl, 5-Br-indol-3-yl, 6-Br-indol-3-yl



R¹ = OMe, R² = Me, Et, *i*Bu, Bn, Ph, 4- $\text{NH}_2\text{C}_6\text{H}_4$, 4- $\text{NMe}_2\text{C}_6\text{H}_4$, 4- ClC_6H_4 , 4- $\text{NO}_2\text{C}_6\text{H}_4$, 4- $\text{HO}_2\text{CC}_6\text{H}_4$, 4- $\text{MeO}_2\text{CC}_6\text{H}_4$, 4- $\text{MeC(O)NHC}_6\text{H}_4$, 4-*t*BuCO₂NHC₆H₄, 3,5-*di*- MeOC_6H_3 , 3,4,5-*tri*- MeOC_6H_2 , indol-3-yl

R¹ = Br, R² = indol-3-yl

Scheme 41. The synthesis of marinoquinolines via the *Pictet-Spengler* reaction



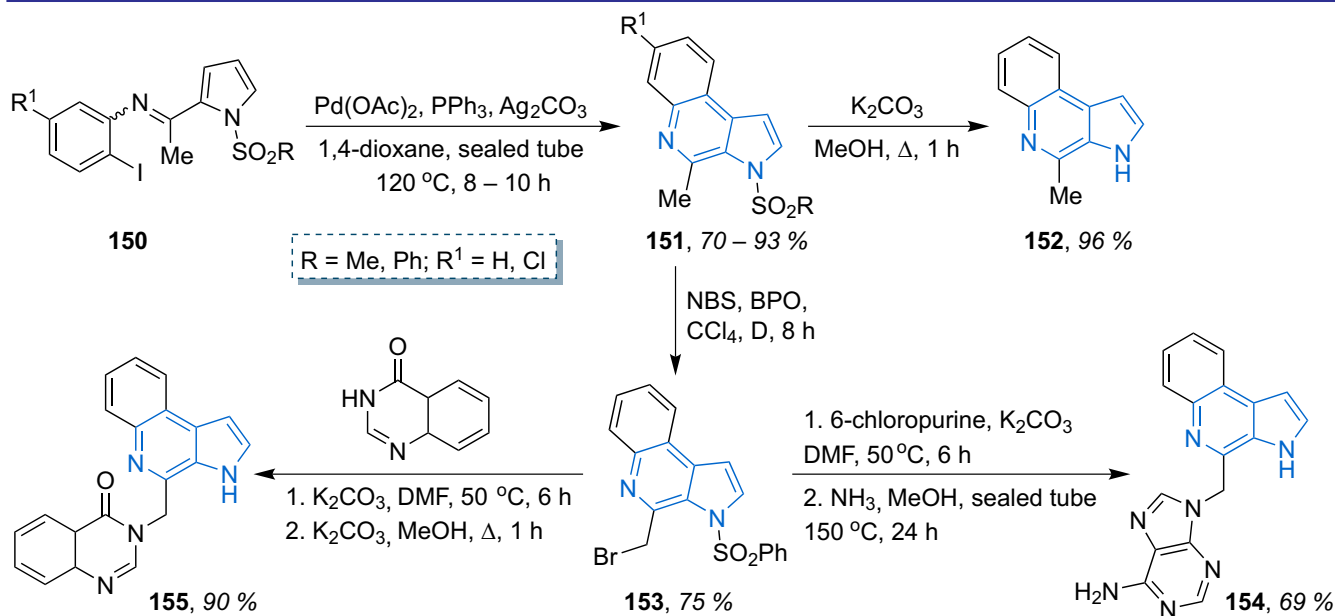
Scheme 42. Marinoquinolines from 2-(1H-pyrrol-3-yl)anilines

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 quinoxalinone with bromomethylpyrroloquinoline **153** followed by the deprotection allowed for the production of NCLite-M1 **155** with the yield of 90 % (Scheme 43).

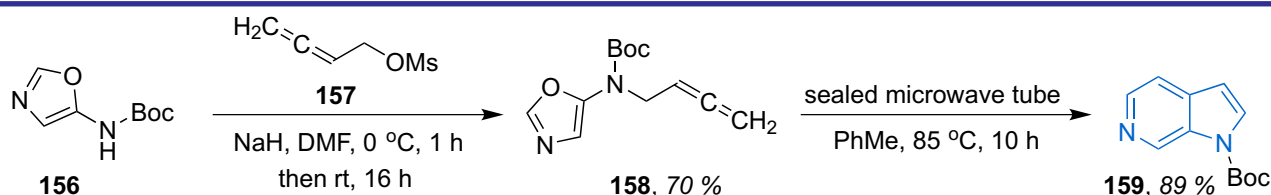
3. The synthesis of the 6-azaindole system with a single-step formation of pyrrole and pyridine rings

A new variant of constructing the 6-azaindole core **159** has been developed based on the intramolecular *Diels-Alder* cycloaddition of oxazole **156** 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



Scheme 43. The Pd-catalyzed cyclization of imines for the synthesis of 3H-pyrrolo[2,3-c]quinolines

Scheme 44. The *Diels-Alder* reaction in the synthesis of the 6-azaindole core

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 di-*enyl* 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

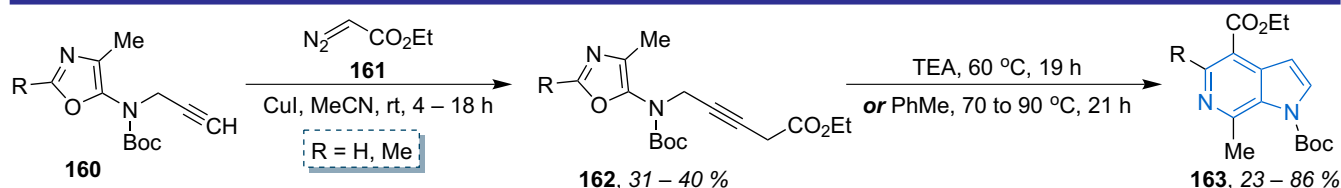
Pyrrolo[2,3-*c*]pyridines represent a significant class of heterocyclic compounds that exhibit a wide range of biological activities. Due to their structural similarity to natural alkaloids and their

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, anti-malarial activity, modulation of ion channels and receptors activity, etc.

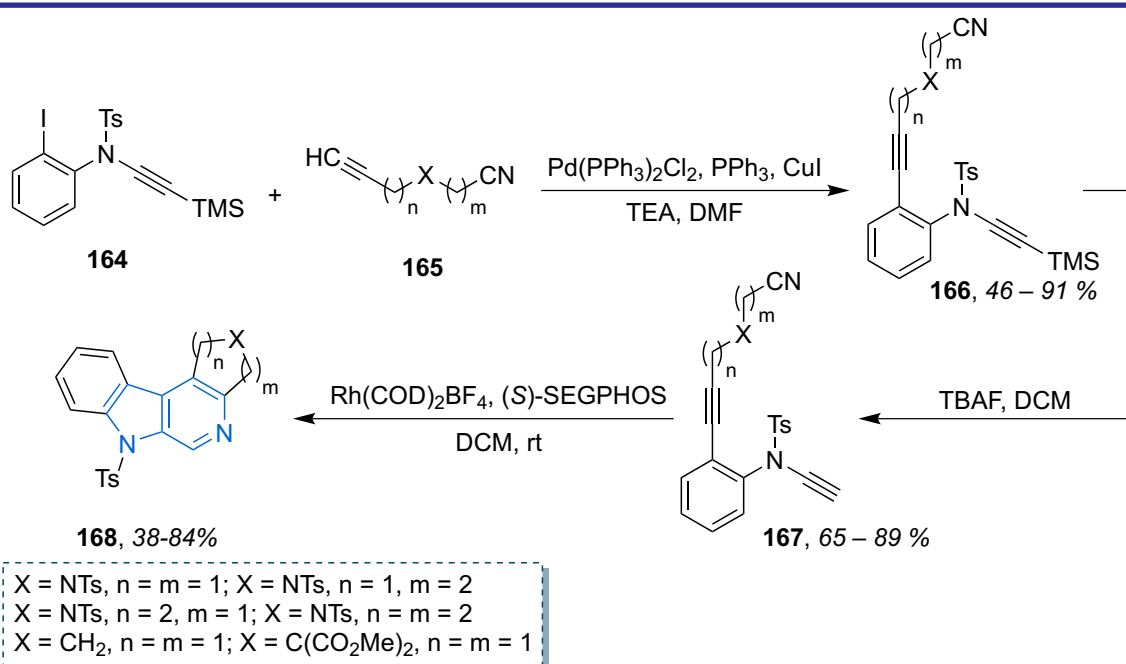
The 6-azaindole core is incorporated into the approved antiretroviral drug Fostemsavir **169** (Rukobia™) [76] and its prodrug Temsavir **170** (BMS-626529) [77] (Figure 1). They inhibit the attachment of the viral gp120 and prevent HIV entry. Both structures are widely used in the treatment of patients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

6-Azaindolyldmaleimide **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-1*H*-pyrrolo[2,3-*c*]pyridin-7(6*H*)-ones, bromodomain and



Scheme 45. The alkyne-allene isomerization and cyclization of esters **150**



Scheme 46. The preparation of 6-azaindoles through the Pd-catalyzed *Sonogashira* coupling/intramolecular [2+2+2] cyclization

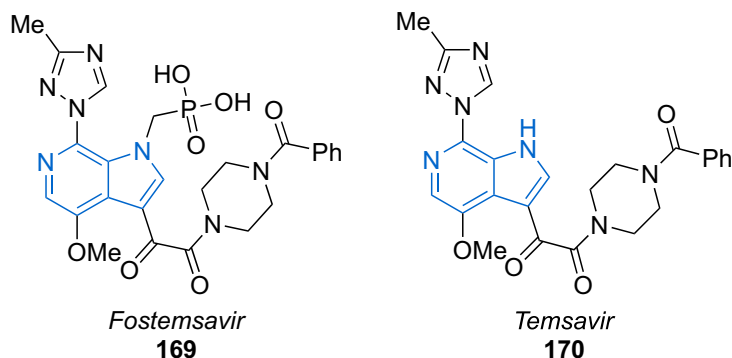
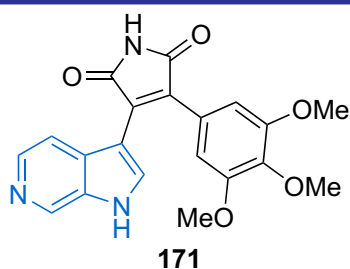


Figure 1. Antiretroviral drugs Fostemsavir and Temsavir



VEGFR-2: $IC_{50} = 48 \pm 3$ nM
FLT-3: $IC_{50} = 18 \pm 5$ nM
GSK-3b: $IC_{50} = 9 \pm 1$ nM

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

an extra-terminal domain (BET) inhibitor **172** (ABBV-075/mivebresib) were found. The latter is characterized by excellent pharmacokinetic properties and is currently undergoing phase I clinical trials [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-1*H*-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], aplidiopsamine 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**).

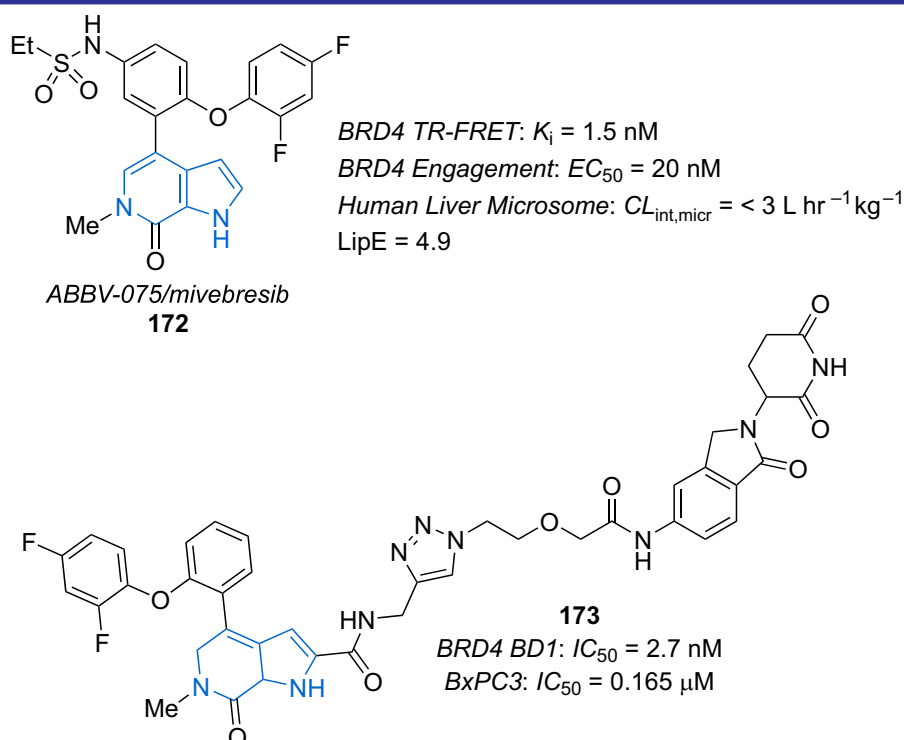


Figure 3. The 6-Azaindole core in BRD4 BD1 and BET inhibitors

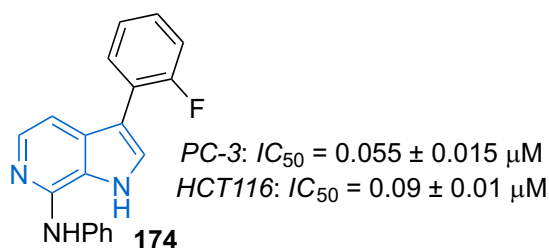


Figure 4. 3-(2-Fluorophenyl)-*N*-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine-7-amine as a potential inhibitor of prostate (PC-3) and colon (HCT116) cancer cell lines

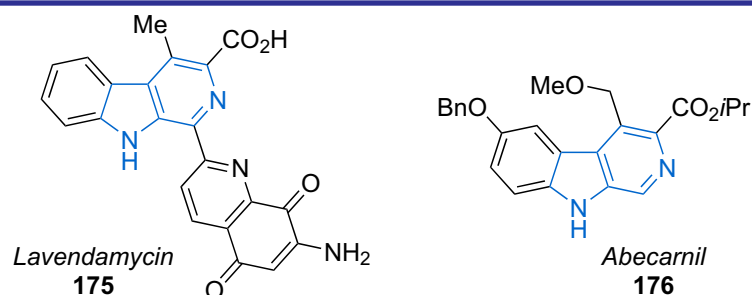


Figure 5. Lefetamine and the anxiolytic drug Abecarnil

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 $A_{\beta 1-42}$, and an excellent neuroprotective activity by

alleviating damage induced by H_2O_2 , okadaic acid, and $A_{\beta 1-42}$, 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

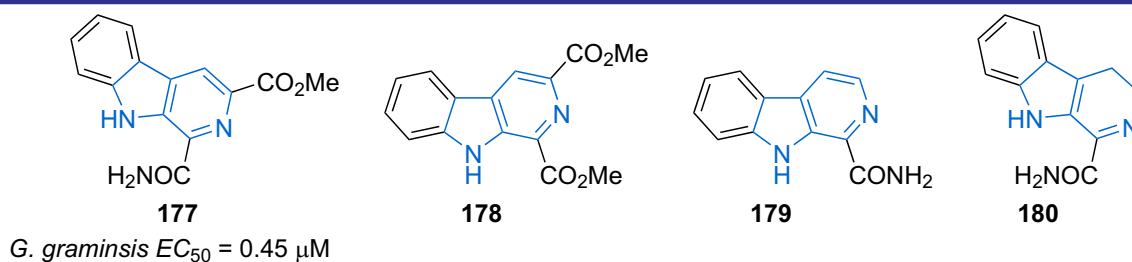


Figure 6. β -Carbolines with the fungicidal activity

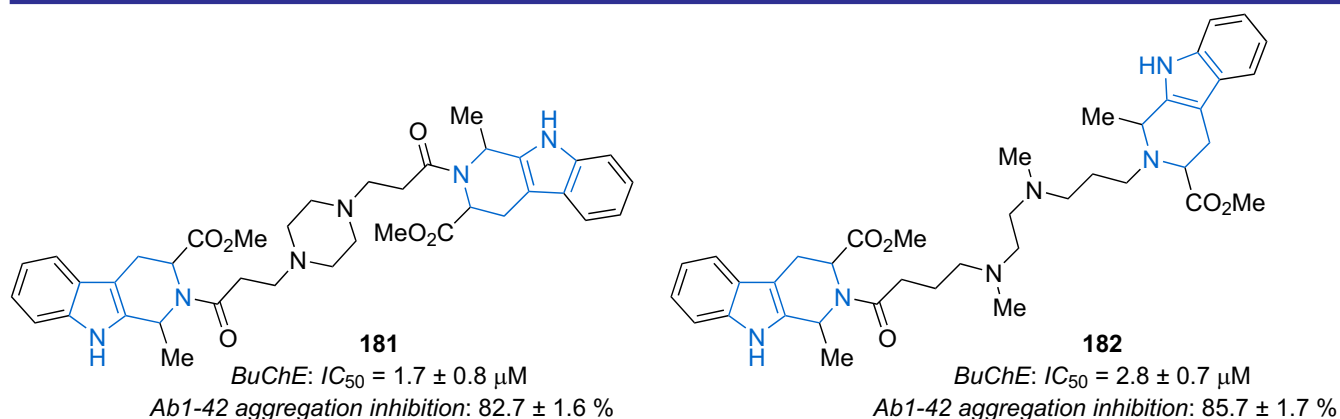


Figure 7. A promising lead candidate among 6-azaindoles against Alzheimer's diseases

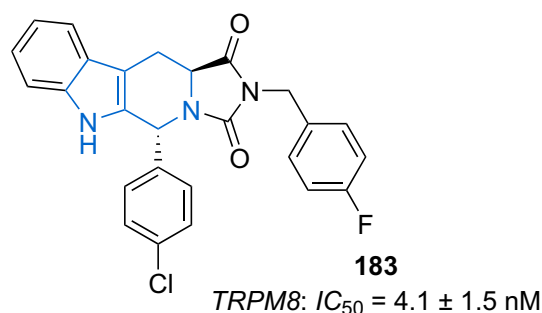


Figure 8. A metabolically stable antagonist of the TRPM8 ion channel

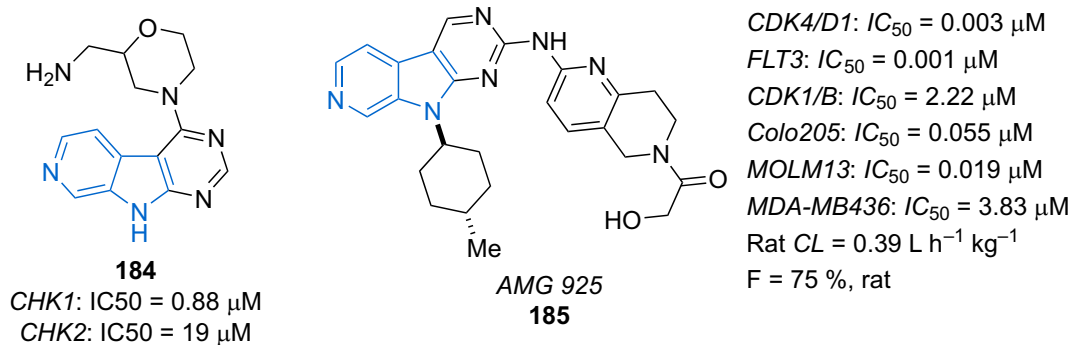


Figure 9. Pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidines and their pharmacokinetic profiles

a significant target coverage in murine models of icilin-induced wet dog shakes (WDS), cold allodynia 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**).

■ 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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