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Synthesis, transformations and biological properties of furo[2,3-*b*]pyridines

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Data on furo[2,3-*b*]pyridines published in the last 15 years are integrated and analyzed for the first time. Information on the methods of synthesis, chemical transformations and biological action of these systems is described systematically. Particular attention is paid to the preparation and study of properties of polycondensed derivatives as the most promising and rapidly developing line of research of furo[2,3-*b*]pyridine chemistry. The biological properties of this class of compounds are discussed, and examples of furo[2,3-*b*]pyridines that exhibit high biological activities are given.
The bibliography includes 88 references.

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I. Introduction

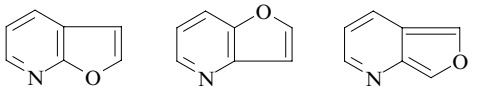
The interest in the heterocyclic compounds comprising fused furan and pyridine rings is caused by two main reasons. First, these systems can be regarded as structural analogues of quinolines and isoquinolines having high biological activities. However, these compounds are rather rare in nature: the furo[2,3-*b*]pyridine moiety is present in furo[2,3-*b*]quinoline alkaloids isolated from *Rutaceae* plants.[1] Second, furopyridines are of theoretical and experimental interest as organic compounds containing simultaneously π-deficient (pyridine) and π-excessive (furan) rings. Diversified derivatives can be used to study the mutual influence of such heterocycles on the reactivity and biological activity of molecules.

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In furopyridines, the rings can be coupled in six different ways, and the compounds thus formed can be classified into two groups. The first group comprises systems connected by pyridine bond *b*, which are quinoline analogues — furo[2,3-*b*]pyridine (**1a**), furo[3,2-*b*]pyridine (**1b**) and furo[3,4-*b*]pyridine (**1c**). The second group includes systems connected by bond *c*: furo[2,3-*c*]pyridine (**1d**), furo[3,2-*c*]pyridine (**1e**) and furo[3,4-*c*]pyridine (**1f**) — isoquinoline analogues.

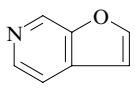
Structures 1



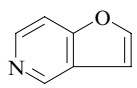
1a

1b

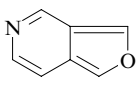
1c



1d



1e



1f

In 1997, a review considering some methods for the preparation of furopyridines **1a–f** was published.[1] Among the chemical transformations of these compounds and their derivatives, the review covered nitration, halogenation, acetoxylation, cyanation, hydrolysis, H–D exchange and the Vilsmeier reaction. However, no detailed reviews devoted to furo[2,3-*b*]pyridine system **1a** can be found in the literature. In view of this fact and considering the results of our studies, we regarded it pertinent to summarize all

data available from the literature published in the last 15 years on both the chemistry and pharmacology of furo[2,3-***b***]pyridines and related fused systems.

II. Methods for the synthesis of furo[2,3-*b*]pyridines

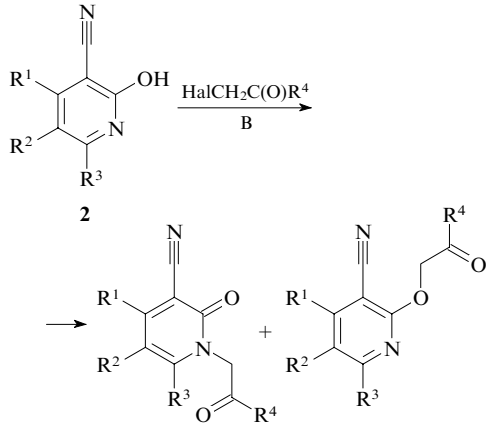
Despite the interest evoked by the biological activity of furo[2,3-*b*]pyridines,[2–6] data on the synthesis of these compounds are scanty. Only a few general methods for their synthesis have been reported. There are two fundamentally different approaches to the synthesis of furopyridines: closure of the furan ring in pyridine derivatives and closure of the pyridine ring in furan derivatives.[1,7]

II.1. Formation of the furan ring from pyridine derivatives

A promising and the most frequently applied strategy for the synthesis of furo[2,3-*b*]pyridines uses 3-cyano-2-hydroxypyridines **2** as the starting compounds. This method has gained rather wide popularity and has been described in a number of papers[8–26] and patents.[2–6,27–29]

3-Cyano-2-hydroxypyridines **2** react with compounds containing an active halogen atom in a basic medium to give a mixture of N- and O-alkylated products **3** and **4** (Scheme 1). In most cases, these structural isomers can be separated using their different solubility in organic solvents. A case of formation of only O-alkylated products **4** has been reported.[9] The only one alkylation pathway was attributed to the presence of bulky groups in the *ortho*-position of the pyridine ring and to the presence of an electron-withdrawing (trifluoromethyl) substituent.

Scheme 1

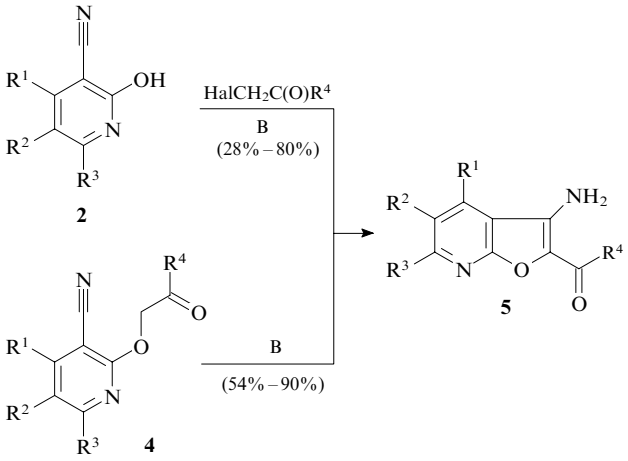


R^1, R^2, R^3 = H, Alk, Ar, CF_3, NHAr, SMe; $R^1–R^2$ = $(CH_2)_n$ (n = 3, 4, 5), $CH_2OCMe_2CH_2$; R^4 = OMe, OEt, Ar, NH_2, NHAr; Hal = Cl, Br, I; B (base) = KOH–DMF, K_2CO_3–DMF, K_2CO_3–Me_2CO, K_2CO_3–Me_2CO–NaI

The O-substituted compounds **4** obtained in this way were then subjected to the Thorpe–Ziegler intramolecular cyclization in a basic medium to give the target furo[2,3-*b*]pyridines **5** (Scheme 2). The process was found to be considerably affected by both a minor amount of water and the time of refluxing. For this reason, cyclization of derivatives **4** is carried out in anhydrous (99.95%) ethanol for 15–20 min. Under other conditions, the ester group is hydrolyzed to the acid group and no cyclization takes place.[13,17–20,22–25]

Furo[2,3-*b*]pyridines **5** were also obtained by one-pot synthesis[10,14,15] from 3-cyano-2-hydroxypyridines **2** and organic halides in the presence of an excess of a base; however, the yields were rather low in some cases (see Scheme 2).

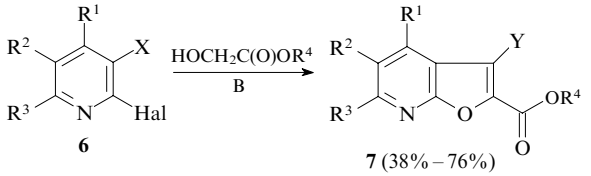
Scheme 2



R^1, R^2, R^3 = H, Alk, Ar, CF_3, NHAr, SMe; $R^1–R^2$ = $(CH_2)_n$ (n = 3, 4, 5), $CH_2OCMe_2CH_2$; R^4 = OMe, OEt, Ar, NH_2, NHAr; Hal = Cl, Br, I; B = NaOMe, NaOEt, KOH–DMF, K_2CO_3–DMF, K_2CO_3–DMF, Cs_2CO_3–Me_2CO

Several publications[7,30–33] report a different method for the furan ring formation according to Thorpe, comprising the reaction of 2-halopyridines **6** with ethyl (or methyl) hydroxyacetate in the presence of a base (Scheme 3). It was shown that the yields of the target furo[2,3-*b*]pyridines **7** depend mainly on the nature and the amount of the base.[7,30]

Scheme 3



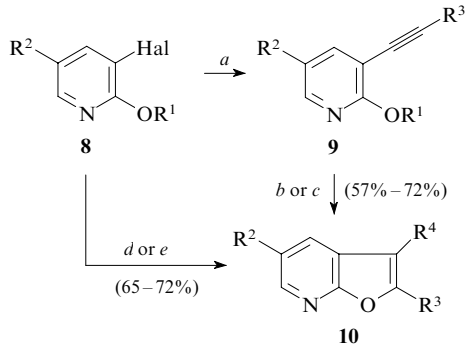
X = CN, Y = NH_2; X = Ac, Y = Me; X = Bz, Y = Ph; X = $C(O)C_6H_4OMe$-4, Y = C_6H_4OMe-4; X = $C(O)C_6H_4CF_3$-4, Y = $C_6H_4CF_3$-4; R^1, R^2, R^3 = H, Ar, NMe_2; R^4 = Me, Et; Hal = Cl, F; B = NaH, Cs_2CO_3, Et_3N, Bu^tOK

Furo[2,3-*b*]pyridines can be synthesized from 5-substituted 3-halopyridines **8**.[34–38] Arcadi *et al.*[34] carried out the reaction between these compounds and trimethylsilylacetylene (Scheme 4, conditions *a*) and then removed the Me_3Si group to give 3-alkynylpyridines **9** (R^1 = H). Then products **9** were cyclized yielding substituted furo[2,3-*b*]pyridines **10** on treatment with various halogen-containing reagents in the presence of catalytic amounts of dichlorobis(triphenylphosphine)palladium (see Scheme 4, conditions *b*). In some cases, the product yields increase to 38% if the reaction is catalyzed by the $Pd_2(dba)_3$–PBu^t_3 system in THF (dba is dibezylideneacetone).[34] Arcadi *et al.*[39] constructed the furo[2,3-*b*]pyridine system based on 2-benzyloxy-3-alkynyl pyridine derivatives **9** (R^1 = Bn). The reaction of these compounds with an excess of iodine and sodium hydrogen carbonate in etha-

nol at room temperature furnishes furo[2,3-*b*]pyridines **10** (see Scheme 4, conditions *c*).

A one-pot synthesis of furo[2,3-*b*]pyridines **10** based on the reaction of 3-halopyridines **8** with acetylene derivatives has been reported.[35–38] This process is catalyzed by Pd^0 complexes (see Scheme 4, conditions *d* or *e*).

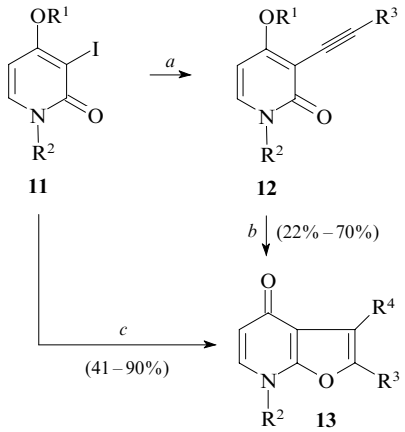
Scheme 4



R^1 = H, Ac, Bn; R^2 = H, CO_2Et, Br, I; R^3 = H, Alk, Ar; R^4 = H, I; Hal = I, Br;
(*a*) 1) $Me_3SiC{\equiv}CH$, Et_3N, THF, rt; 2) KF, MeOH, rt;
(*b*) R^4Hal, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF or DMF, rt; (*c*) I_2, $NaHCO_3$, EtOH, rt; (*d*) $R^3C{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 100 °C; (*e*) $R^3C{\equiv}CH$, $Pd(OAc)_2$, CuI, Bu^nNH_2

Similarly, 4-alkoxy-3-iodopyridin-2(1*H*)-ones **11** were converted, either *via* alkynes **12** or by the one-pot method, to 2,3-substituted 7-methyl(benzyl)furo[2,3-*b*]pyridin-4(7*H*)-ones **13** (Scheme 5).[40–42] It is noteworthy that the yields of products **13** are relatively high if the aryl halides used contain electron-withdrawing substituents.

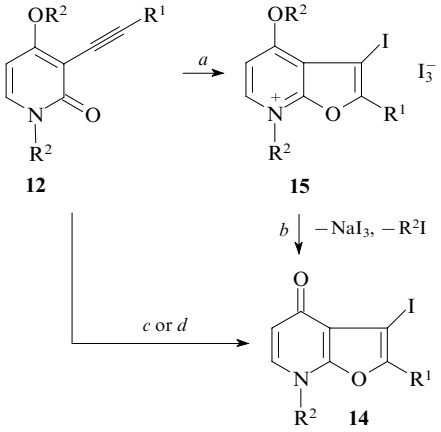
Scheme 5



R^1, R^2 = Me, Bn; R^3, R^4 = Ar; Hal = I, Br;
(*a*) $R^3C{\equiv}CH$, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, MeCN, 60 °C, 24 h;
(*b*) R^4Hal, $Pd(PPh_3)_2Cl_2$, Bu^nLi, THF, MeCN, 60 °C, 48 h;
(*c*) 1) $R^3C{\equiv}CH$, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, MeCN, 60 °C, 24 h; 2) PhI, 60 °C

For the synthesis of iodo-substituted 7-alkylfuro[2,3-*b*]pyridin-4(7*H*)-ones **14**, Aillaud *et al.*[43] and Bossharth *et al.*[44] utilized compounds that already had a triple bond in the side chain: 3-alkynyl-1-alkylpyridin-2(1*H*)-ones **12** (Scheme 6). The latter react with molecular iodine under mild conditions to give the corresponding pyridinium salts **15** (38%–79% yields), which are dealkylated on heating. 7-Methylfuro[2,3-*b*]pyridin-4(7*H*)-ones **14** can be obtained from 3-alkynyl-1-methylpyridin-2(1*H*)-ones **12** in one step by treating the starting compounds with molecular iodine and sodium iodide. The product yields are mainly 79%–92% (see Scheme 6, conditions *c*).[43] Bossharth *et al.*[44] also proposed a simpler reaction procedure requiring only heating of 2-pyridones **12** in acetic acid without a catalyst; the product yields range from 45% to 77 % (see Scheme 6, conditions *d*).

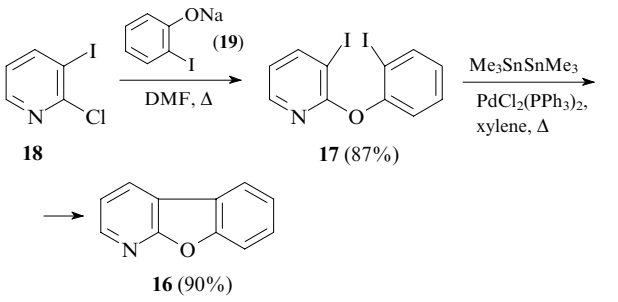
Scheme 6



R^1 = Alk, Ar; R^2 = Me, Bn;
(*a*) I_2, CH_2Cl_2, rt; (*b*) NaI, MeCN, Δ; (*c*) 1) I_2, MeCN, rt; 2) NaI, MeCN, Δ; (*d*) AcOH, Δ

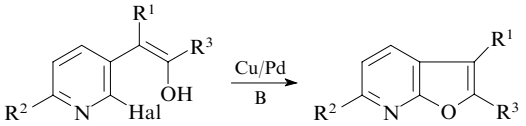
Yue and Li[45] described the synthesis of benzofuro[2,3-*b*]pyridine **16** from 3-iodo-2-(2-iodophenoxy)pyridine (**17**). The latter compound was prepared from 2-chloro-3-iodopyridine (**18**) and sodium *o*-iodophenoxide (**19**). Due to the α-activation of the pyridine nitrogen atom by inductive effect, the chemoselective S_NAr displacement of chlorine located in position 2 by a nucleophile proceeded smoothly, as expected, to give 3-iodo-2-pyridyl ether **17**. This product was subjected to the Stille–Kelly reaction to be converted to compound **16** (Scheme 7).

Scheme 7



Methods for the synthesis of furo[2,3-*b*]pyridines from 2-chloropyridylphenols,[46,47] 2-(2-chloropyridyl)cyclohexanone[48] and other 2-halopyridyl ketones[38,49] have been developed. For example, intramolecular cyclization of the enol form of ketone **20** with hydrogen halide elimination occurring in polar solvents (DMF, MeCN, H_2O–dioxane mixture) under the action of bases (Bu^nONa, KOH, K_2CO_3, K_3PO_4) in the presence of a catalyst [CuI, copper(I) thiophene-2-carboxylate, $Pd_2(dba)_3$] affords compounds **21** in 70%–86% yields (Scheme 8).

Scheme 8



20 **21**

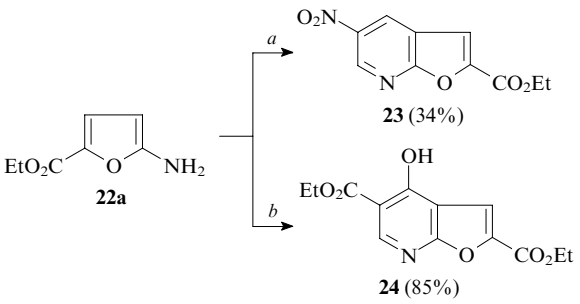
R^1, R^3 = H, Alk; R^1-R^3 = $(CH_2)_n$; R^2 = H, Cl; Hal = Cl, Br

II.2. Formation of the pyridine ring from furan derivatives

The second approach to the construction of the furopyridine skeleton employs the strategy of pyridine ring closure involving furan derivatives.

The synthesis of furo[2,3-*b*]pyridines from ethyl 5-aminofuran-2-carboxylate (**22a**) has been proposed (Scheme 9).[50] Treatment of ester **22a** with the sodium salt of nitromalonaldehyde furnishes the condensation product — ethyl 5-nitrofuro[2,3-*b*]pyridine-2-carboxylate (**23**). Similarly, the use of diethyl ethoxymethylenemalonate leads to the formation of diethyl 4-hydroxyfuro[2,3-*b*]pyridine-2,5-dicarboxylate (**24**) (see Scheme 9).

Scheme 9

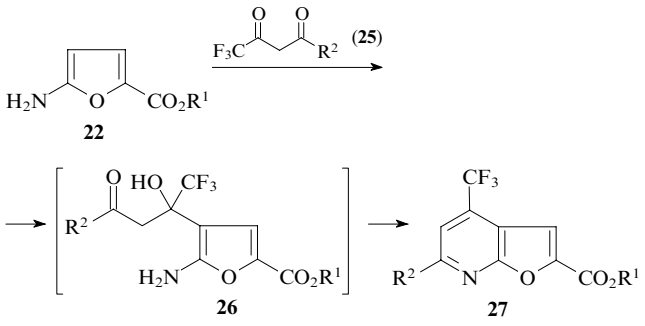


22a **23** (34%) **24** (85%)

(*a*) 1) $NaC(NO_2)(CHO)_2$, H_2O, EtOH; 2) DMF, Δ;
(*b*) $EtOCH{=}C(CO_2Et)_2$, Ph_2CH_2, 240 °C

A felicitous example of annulation of a pyridine ring to furan has been reported by Volochnyuk *et al.*[51] Heating of 2-aminofurans **22** with 4,4,4-trifluoro-1,3-dicarbonyl compounds **25** produces intermediates **26**, which undergo regioselective cyclocondensation yielding 4-trifluoromethylfuro[2,3-*b*]pyridines **27** (Scheme 10).

Scheme 10



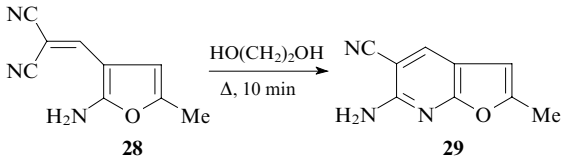
22 **26** **27**

R^1 = Et, Me; R^2 = H, OH, Ph, Th; Th is 2-thienyl

In a similar reaction, 3-formylchromone (4-oxo-4*H*-1-benzopyran-3-carbaldehyde) served as the β-dicarbonyl compound.[52] The reaction was carried out in DMF, and trimethylchlorosilane was used as the catalyst. The product yields were 50%–81%.

The thermal cyclization of 2-(2-amino-5-methylfuran-3-ylmethylidene)malononitrile (**28**) at 200 °C furnishes 6-amino-2-methylfuro[2,3-*b*]pyridine-5-carbonitrile (**29**) in 50% yield (Scheme 11). It is noteworthy, however, that this method is unpractical as the initial dinitrile is difficult to obtain.[50]

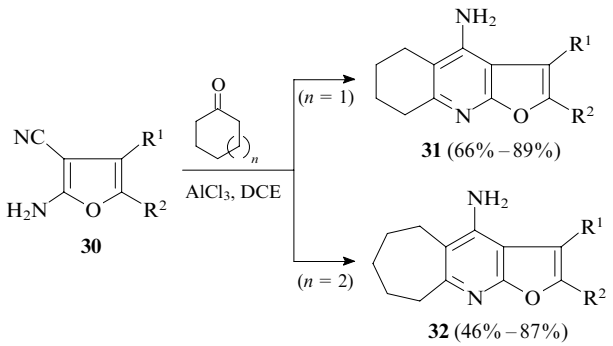
Scheme 11



28 **29**

De los Rios and co-workers[53–55] described an original approach to cyclization of 2-amino-3-cyanofurans **30** with cyclohexanone or cycloheptanone according to the Friedländer reaction pathway. The target products — fused 4-aminofuro[2,3-*b*]pyridines **31** and **32** — are analogues of the known neuroprotective agent called tacrine (Scheme 12).

Scheme 12

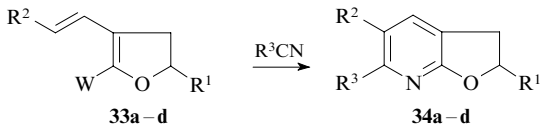


30 **31** (66%–89%) **32** (46%–87%)

R^1, R^2 = H, CN, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4;
DCE is 1,2–dichloroethane

Li *et al.*[56] proposed using the Diels–Alder reaction in which substituted furans **33a–d** serve as dienes {[W] = $CpW(CO)_3$, Cp is cyclopentadienyl}. The [4+2]-cycloaddition involving nitriles affords 2,3-dihydrofuro[2,3-*b*]pyridines **34a–d** (Scheme 13). This reaction can be carried out with nonactivated nitriles, *e.g.*, aliphatic nitriles and benzonitriles, which simultaneously act as solvents. The cyclization proceeds at 23 °C and is activated by $Me_3NO\cdot 2H_2O$ (8 h, conditions *a*) or by photolysis (λ = 300 nm, 2 days, conditions *b*).

Scheme 13



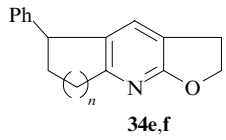
33a–d **34a–d**

Compounds **33**, **34**	R^1	R^2	R^3	Conditions	Yield (%)
a	H	H	Pr^i	*a*	58
				b	47
b	H	H	Ph	*a*	82
c	Ph	H	Et	*a*	67
d	H	Me	Ph	*a*	47

A similar reaction has also been carried out in the intramolecular mode. In this case, substituted furans **33e**,**f** [R^1 = H: R^2 = $CH(Ph)(CH_2)_nCN$, where n = 2 (**e**), 3 (**f**)]

were refluxed in dichloromethane in the presence of $Me_3NO \cdot 2\,H_2O$ to be converted to tricyclic systems **34e**,**f**.

Structures 34e,f

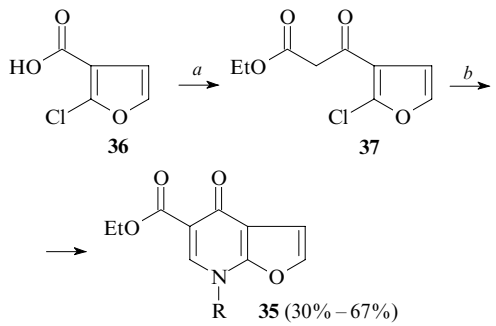


34e,**f**

n = 1 (**e**, 50%), 2 (**f**, 77%)

The synthesis of 4,7-dihydrofuro[2,3-*b*]pyridin-4-ones **35** from 2-chlorofuran-3-carboxylic acid (**36**) (Scheme 14) *via* the formation of compounds **37** has been reported.[57] Note that derivatives **35** exhibit high biological activities (see Section IV).

Scheme 14

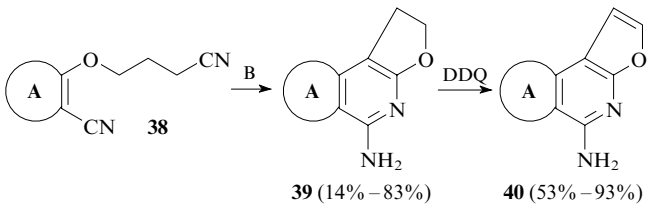


R = Alk, Ar, Py;
(*a*) $EtO_2CCH_2CO_2K$, *N*,*N*-carbonyldiimidazole (CDI), $MgCl_2$, Et_3N, THF, MeCN, 25 °C; (*b*) 1) $(EtO)_3CH$, Ac_2O, 135 °C; 2) RNH_2, Bu^tOK, THF, 30–40 °C; Py is pyridyl

II.3. Miscellaneous methods for the synthesis of furo[2,3-*b*]pyridines

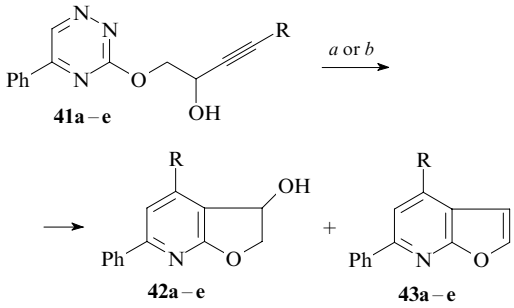
Apart from the above-described major methods for the synthesis of furo[2,3-*b*]pyridines, other miscellaneous routes to these compounds are also known. For example, a method based on the Truce–Smiles rearrangement of cyclic derivatives **38** containing vicinal cyanopropoxy and cyano groups has been developed.[58–63] As the cyclic moiety **A**, benzene and its chloro and nitro derivatives, cycloalkenes, 1,2-dihydronaphthalene, benzo[*a*]cycloheptene, pyridine, benzothiophene, benzofuran and thieno[2,3-*b*]pyridine have been used. The reaction occurs in dioxane under the action of sodium hydride or potassium *tert*-butoxide as a base (Scheme 15). The nature of the base was found to have no significant influence on the yields of tetrahydrofuro[2,3-*b*]pyridines **39**.[59,61] The latter are dehydrogenated to furnish aromatic furo[2,3-*b*]pyridines **40** on treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[59,63]

Scheme 15



Hajbi *et al.*[64] gave an interesting example of [4+2]-cycloaddition involving n-but-3-ynyloxy-5-phenyl-1,2,4-triazines **41**, which was accomplished by two procedures. According to the first one, on refluxing in chlorobenzene (12 h), triazine **41a** undergoes intramolecular Diels–Alder-type cycloaddition to give 3-hydroxy-6-phenyl-2,3-dihydrofuro[2,3-*b*]pyridine (**42a**) in 93% yield (Scheme 16). Substituted analogues **41b–e** undergo similar transformations. The second procedure is based on microwave (MW) irradiation of the same initial compounds in chlorobenzene (45–90 min). In all cases, trace amounts of the corresponding dehydrated products **43a–e** are also formed. The yields of dihydrofuro[2,3-*b*]pyridines **42** are 34%–82%. When the reaction is conducted at low temperatures, longer irradiation times are required.

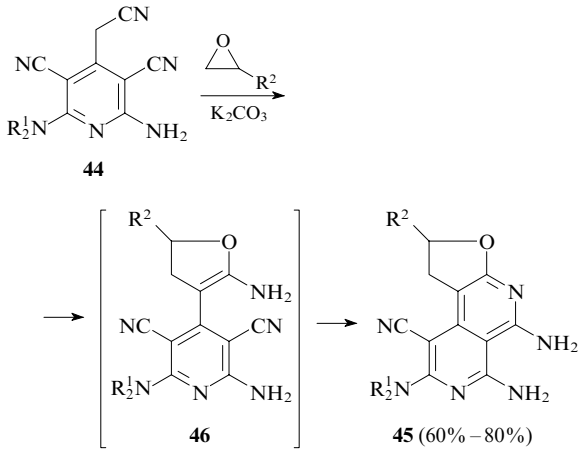
Scheme 16



R = H (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 4-$O_2NC_6H_4$ (**d**), 2-Th; (*a*) PhCl, Δ, 12 h; (*b*) PhCl, MW, 180 °C, 45–90 min

It was shown[65] that polyfunctional pyridines **44** react with substituted oxiranes in ethanol in the presence of potassium carbonate to give tricyclic systems **45** containing a 1,2-dihydrofuro[2,3-*b*]pyridine moiety (Scheme 17). The oxirane ring can be selectively opened from the unsubstituted side, and the subsequent cyclization of intermediate **46** involves the second cyano group of the starting compound.

Scheme 17

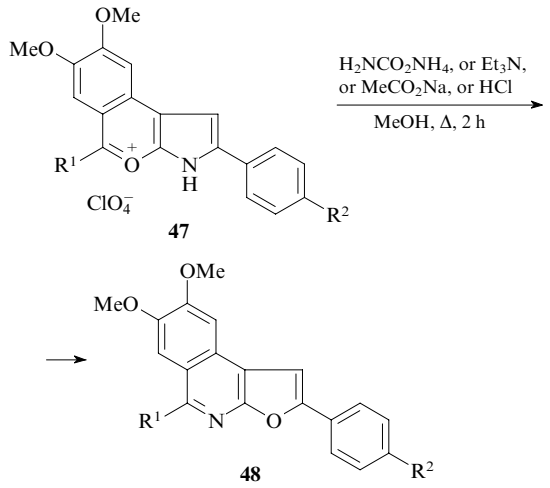


R^1_2N = Et_2N, piperidino, morpholino; R^2 = Et, CH_2Cl, Ph

Tolkunov *et al.*[66] reported an unusual route to furo[2,3-*b*]pyridine derivatives from pyrrolo[3,2-*b*]pyrylium salts **47**. The reaction is induced by nucleophiles, involves the α-position of pyrylium salts **47** and follows the ANRORC mechanism (ANRORC stands for addition of the nucleophile, ring opening and ring closure). However, it

was found that the process does not depend on the nature of the nucleophile, *i.e.*, the pyridine ring is formed with the participation of the pyrrole nitrogen atom rather than the nitrogen atom of the nucleophile used. Finally, the exchange of heteroatoms takes place (O,N for N,O) giving rise to furo[2,3-*b*]pyridines **48** in 30%–50% yields (Scheme 18).

Scheme 18



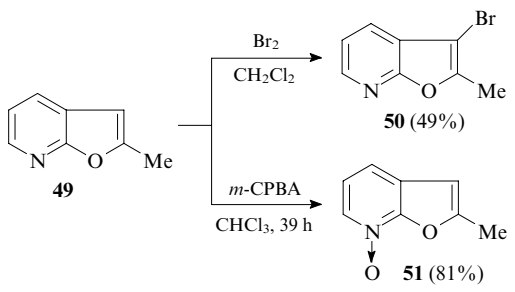
R^1 = Me, Et; R^2 = H, Br

III. Chemical reactivity of furo[2,3-*b*]pyridines

The reactivity of furo[2,3-*b*]pyridine derivatives is described in considerable detail in the publication of Shiotani.[1] Before this author published the results of his own systematic research on the electrophilic reactions of furopyridines **1a**–**f**, only a few studies devoted to the chemical behaviour of furo[2,3-*b*]pyridine (**1a**) had been available from the literature. As noted above, furo[2,3-*b*]pyridines possess a broad range of biological activities in which a substantial role is played by the nature and arrangement of substituents. Hence, the introduction of new groups or modification of the groups present in the molecule is of obvious practical interest. As a rule, exactly this aspect stimulates the study of the chemical transformations of furo[2,3-*b*]pyridines.

Bromination of 2-methylfuro[2,3-*b*]pyridine (**49**) by molecular bromine in dichloromethane involves position 3 and affords 3-bromo-2-methylfuro[2,3-*b*]pyridine (**50**). The reaction of the same initial compounds with *m*-chloroperoxybenzoic acid (*m*-CPBA) in chloroform with long-term stirring at room temperature produces 2-methylfuro[2,3-*b*]pyridine *N*-oxide (**51**) (Scheme 19).[67] However, upon nitration with a mixture of fuming nitric and sulfuric acids, 2-methylfuro[2,3-*b*]pyridine (**49**) decomposes.[67]

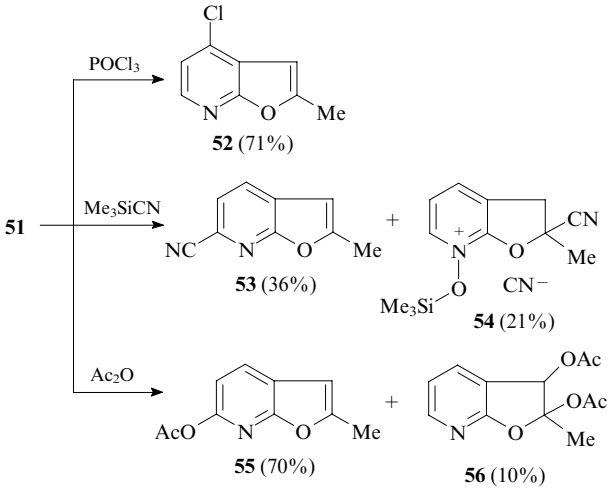
Scheme 19



The reactivity of *N*-oxide **51** has been studied. Chlorination with phosphorus(V) oxychloride in chloroform involves only position 4 and results in the formation of chloro derivative **52**. Meanwhile, the reactions with either trimethylsilyl cyanide in the presence of triethylamine in acetonitrile or with acetic anhydride afford mixtures of compounds **53**, **54** and **55**, **56**, which are separated by chromatography (Scheme 20).

It was shown[67] that the bromination or nitration of 2-cyanofuro[2,3-*b*]pyridine (**57**) or preparation of its *N*-oxide cannot be performed under analogous conditions.

Scheme 20

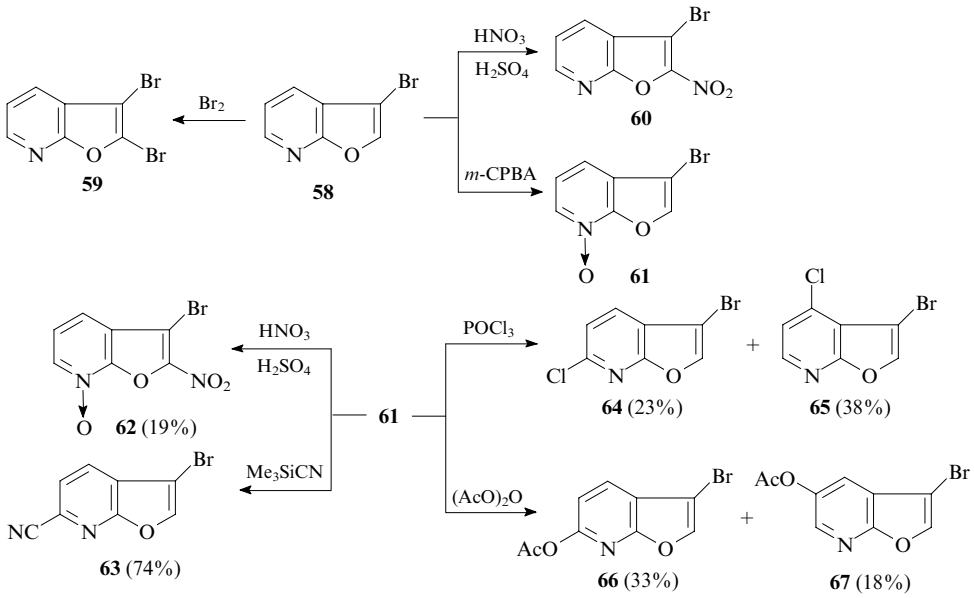


Shiotani and co-workers[68] described the bromination and nitration reactions of 3-bromo derivative **58**, resulting in the formation of compounds **59** and **60**, and the reactions involving furo[2,3-*b*]pyridine *N*-oxide **61**. Whereas the nitration and cyanation of this compound give derivatives **62** and **63** as the only products, the chlorination and acetoxylation result in the isolation of mixtures of compounds **64**, **65** and **66**, **67**, which were separated by chromatographic methods (Scheme 21).

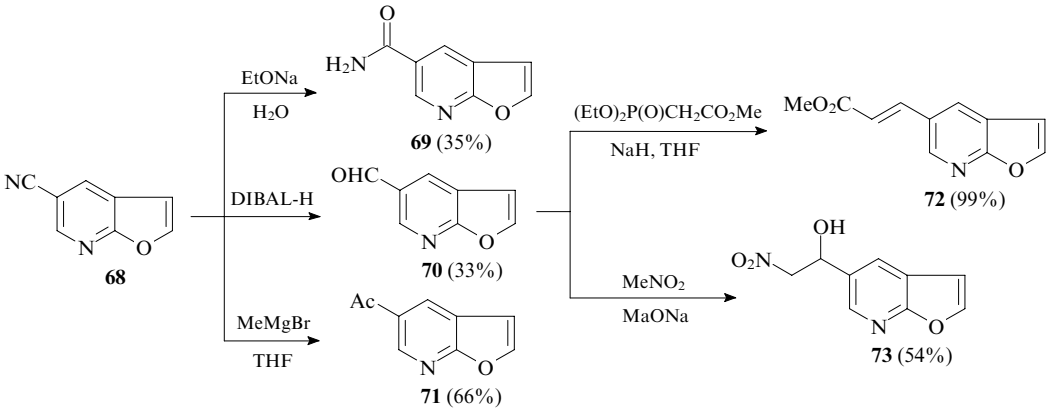
Some transformations of 5-cyanofuro[2,3-*b*]pyridine (**68**) (Scheme 22) have been studied.[69] For example, this compound was converted to 5-carbamoyl- (**69**) and 5-formyl (**70**) derivatives, while the Grignard reaction gave 5-acetyl-substituted furo[2,3-*b*]pyridine **71**. The condensation of 5-formylfuro[2,3-*b*]pyridine (**70**) with methyl diethylphosphonoacetate (Wittig–Horner reaction) and with nitromethane resulted in the synthesis of β-(5-furo[2,3-*b*]pyridyl)acrylate (**72**) and 5-(1-hydroxy-2-nitroethyl)furo[2,3-*b*]pyridine (**73**), respectively.

A number of reactions involving isomeric 6-cyanofuro[2,3-*b*]pyridine (**74**) have also been reported (Scheme 23).[70] Nitration of **74** with a mixture of fuming nitric and sulfuric acids furnishes 2-nitro derivative **75**, while its bromination leads to 2,3-dibromo-2,3-dihydro derivative **76**. Treatment of dibromide **76** with sodium hydroxide in methanol gives a mixture of *trans*-3-bromo-2-methoxy-2,3-dihydro- (**77**) and 3-bromo-6-carbamoylfuro[2,3-*b*]pyridines (**78**), as well as methyl 3-bromofuro[2,3-*b*]pyridine-6-carboxylate (**79**). This mixture was separated into components by chromatography. It is noteworthy that refluxing of dibromide **76** in methanol (4–7 h) or xylene (24 h) results in the recovery of the initial compound **74** in a 15% or 70% yield.

Scheme 21

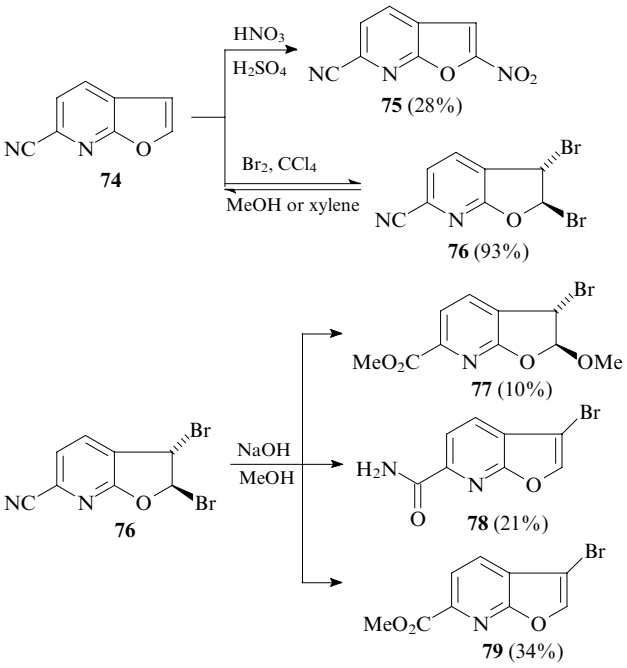


Scheme 22



DIBAL-H is diisobutylaluminium hydride

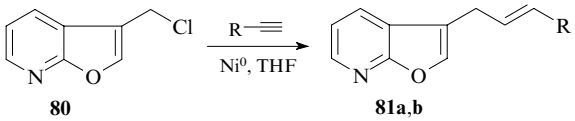
Scheme 23



The attempts to oxidize 6-cyanofuro[2,3-*b*]pyridine (**74**) at the nitrogen atom with *m*-chloroperoxybenzoic acid in chloroform have not met with success.[70]

The reactions of 3-chloromethyl derivative **80** with alkynes conducted in THF at room temperature in the presence of a Ni^0 catalyst were used to prepare 3-alkenyl derivatives **81a**,**b** (Scheme 24).[71]

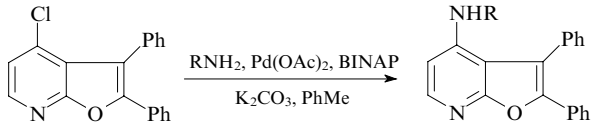
Scheme 24



R = n-C_6H_{13} (**a**, 80%), $(CH_2)_3CH_2OSiBu^tPh_2$ (**b**, 68%)

High reactivity of the chlorine atom in position 4 of 4-chloro-2,3-diphenylfuro[2,3-*b*]pyridine (**82**) towards nucleophilic substitution reactions can be utilized to introduce amino groups into this molecule. For example, various 4-amino derivatives **83** were synthesized by reactions with amines (Scheme 25).[41]

Scheme 25



82 **83** (82%–91%)

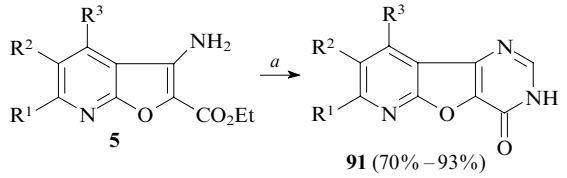
R is 2-(piperazino)ethyl, 2-(tetrahydrofuran-2-yl)methyl; 2-(4-pyridyl)ethyl, 2-(3-pyridyl)ethyl, 3-(1*H*-imidazol-1-yl)propyl; BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binapthalene

Van de Poël *et al.*[36] proposed a multistep procedure for the preparation of a structural analogue of the well-known hormone melatonin.[72] As the initial compound, the authors used 5-bromo-2-phenylfuro[2,3-*b*]pyridine (**84**), which was successively converted to intermediate compounds **85**–**89** and then to product **90** (Scheme 26).

IV. Synthesis of tri- and polycyclic systems based on furo[2,3-*b*]pyridines

Among the chemical transformations of furo[2,3-*b*]pyridines, a special place is occupied by annulation reactions, resulting in the formation of tri- and polycyclic systems. In recent years, enhanced interest in annulated furo[2,3-*b*]pyridines has been observed related to their high biological activity. Amino esters **5** are often used as building blocks for the synthesis of these compounds. This is due, first of all, to the easy preparation of these compounds by the Thorpe–Ziegler reaction and to the presence of two vicinal functional groups (amino group and ester group), which facilitates the formation of annulated rings. For the formation of the pyrimidine ring, most convenient is the condensation of furo[2,3-*b*]pyridines **5** with formamide[2,12,13,17–21,23,24] or triethyl orthoformate.[5,16] The cyclization gives high yields of oxo-substituted pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidines **91** (Scheme 27).

Scheme 27



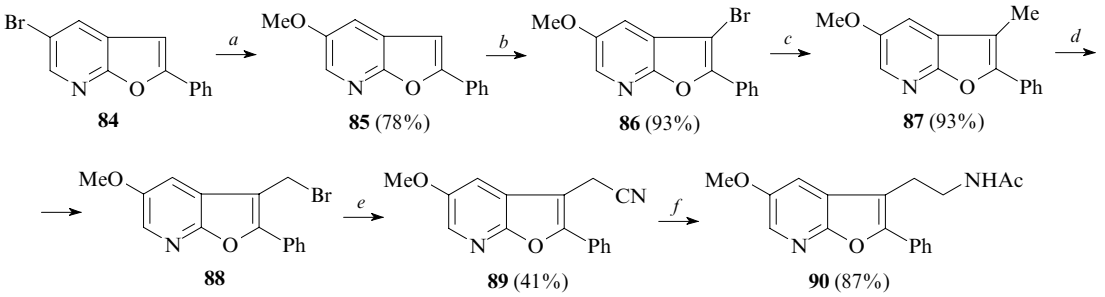
5 **91** (70%–93%)

R^1, R^2, R^3 = H, Alk, Ar; R^1–R^2, R^2–R^3 = $(CH_2)_n$ (n = 3, 4, 5), $CH_2OCMe_2CH_2$; (*a*) 1) $HC(O)NH_2$ or $HC(OEt)_3$, Δ; 2) NH_3, EtOH, Δ

The reaction of amino esters **5** [R^2–R^3 = $(CH_2)_n$] with 2-pyrrolidone (**92**) in the presence of phosphorus(V) oxychloride is accompanied by the closure of two rings.[25] This affords pentacyclic pyrrolo[1,2-*a*]pyrimidinones **93** (Scheme 28). The first stage is the reaction of 2-pyrrolidone with $POCl_3$ to give imido chlorides, which react with amino ester to give amidines **94**. This is followed by intramolecular cyclization to give products **93**.

Condensation of methyl 3-amino-4-(dimethylamino)-furo[2,3-*b*]pyridine-2-carboxylate (**95**) with dimethylacetal dimethylformamide furnished methyl 4-dimethylamino-3-{[(1*E*)-(dimethylamino)methylene]-amino}furo[2,3-*b*]pyridine-2-carboxylate (**96**) in a quantitative yield.[31] Cyclization of this product with amines catalyzed by *p*-toluenesulfonic acid (TsOH) in toluene results in the formation of N-substituted pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidines **97** (Scheme 29).

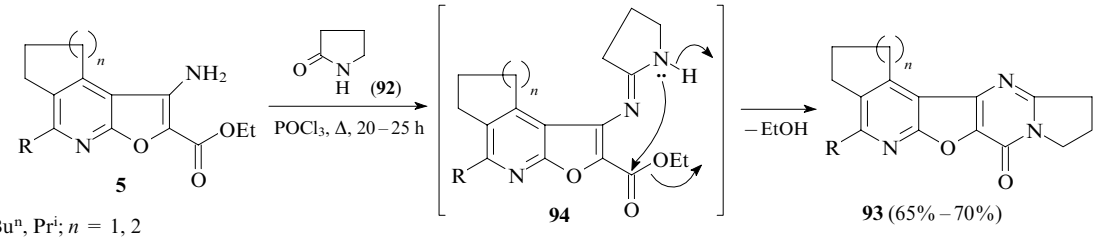
Scheme 26



84 **85** (78%) **86** (93%) **87** (93%) **88** **89** (41%) **90** (87%)

(*a*) MeONa, CuBr, MeOH, DMF; (*b*) 1) Br_2, CCl_4; 2) NaOH, MeOH; (*c*) Me_4Sn, $Pd(PPh_3)_2Cl_2$, HMPA; (*d*) NBS, CCl_4; (*e*) KCN, DMF; (*f*) H_2, Ni-Ra, Ac_2O, AcONa; HMPA is hexamethylphosphotriamide, NBS is *N*-bromosuccinimide, Ni-Ra is Raney nickel

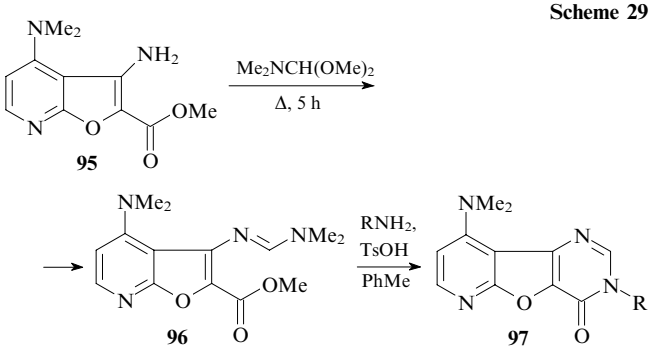
Scheme 28



5 **94** **93** (65%–70%)

R = Bu^n, Pr^i; n = 1, 2

Scheme 29

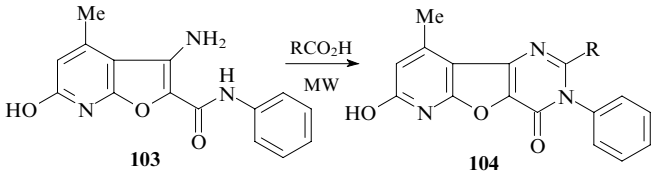


R = 4-EtC$_6$H$_4$ (18% yield), 4-MeC$_6$H$_{10}$ (44%)

In order to introduce various substituents into position 2 of the pyrimidine ring, amino esters **5a**,**b** were made to react with aryl chlorides **98** to give aromatic acid amides **99**.[2, 32] Then the ester group in **99** was also transformed into the amide group. The intermediate diamides **100** were cyclized by treatment with bases to give tricyclic systems **101**, which were converted to the desired compounds, 2-phenyl-substituted 4-morpholinopyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidines **102**, by successive chlorination and amination reactions (Scheme 30).

In recent years, microwave radiation markedly accelerating chemical processes has been often used in organic synthesis. This approach was utilized in the cyclization of 3-amino-6-hydroxy-4-methylfuro[2,3-*b*]pyridine-2-carboxamide **103** with equimolar amounts of various carboxylic acids (Scheme 31).[15] This gave rise to 2-substituted 7-hydroxy-9-methyl-3-phenylpyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidin-4(3*H*)-ones **104**. The reactions were completed in 4–7 min and give products in high yields (69%–93%).

Scheme 31

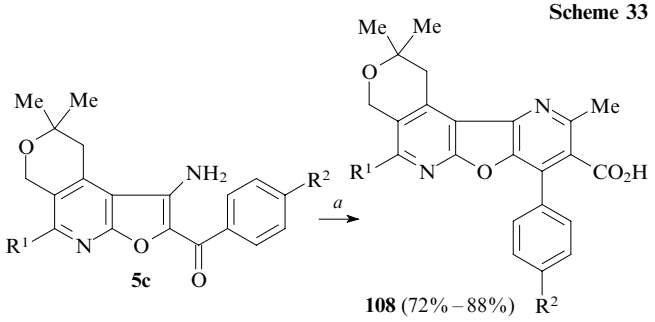


R = $CH_2C_6H_4Cl$-4, $CH_2C_6H_4Br$-4, C_6H_4F-4, C_6H_4F-3, $C_6H_3Me_2$-3,5

The Claisen–Schmidt condensation of *o*-amino ketones **105** based on furo[2,3-*b*]pyridines with aromatic aldehydes in the presence of an ethanol solution of sodium hydroxide gives compounds **106**.[73] The latter undergo Michael-type intramolecular cyclization upon heating with orthophosphoric acid in acetic acid to form pyrido[3′,2′:4,5]furo[3,2-*b*]pyridines **107** (Scheme 32).

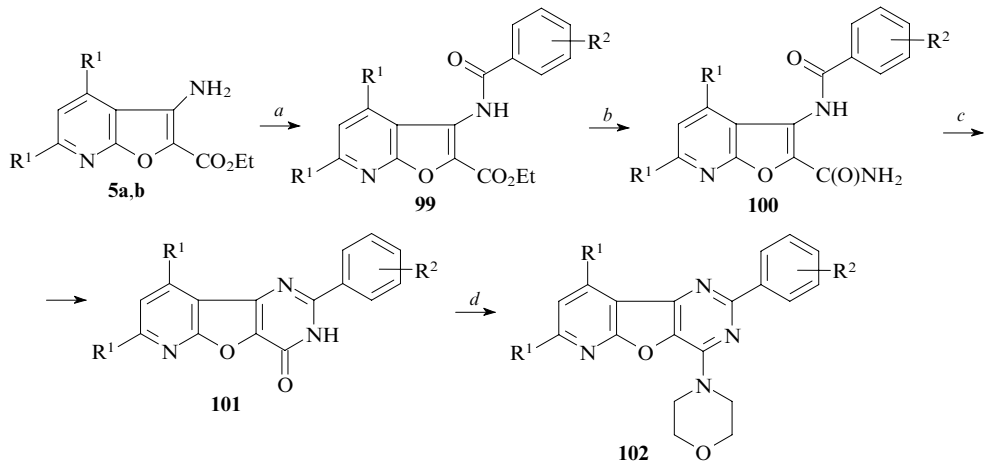
Noteworthy is also a publication [74] describing a similar method for the one-step formation of the pyridine ring (compounds **108**) (Scheme 33).

Scheme 33



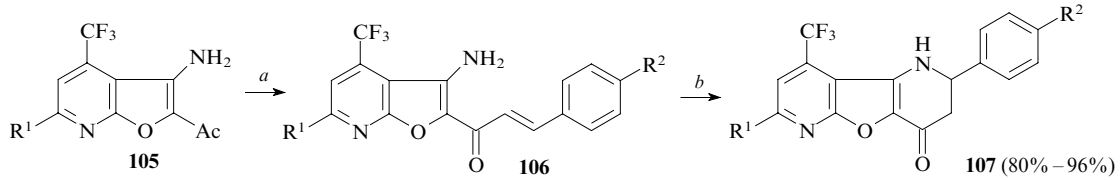
R^1 = Alk, Ar; R^2 = H, Br; (*a*) $AcCH_2CO_2Et$, $ZnCl_2$, *m*-xylene, Δ, 20 h

Scheme 30



5: R^1 = H (**a**), Me (**b**); R^2 = H, Alk, OH, OMe, OAc, NH_2, NO_2, NHAlk; (*a*) R$^2C_6H_4C(O)Cl$ (**98**), Et_3N, $CHCl_3$; (*b*) 1) 1 M NaOH, EtOH; 2) $SOCl_2$, Δ; 3) NH_4OH, THF; (*c*) 2 M NaOH, MeOH or Pr^{i}OH, Δ; (*d*) 1) $POCl_3$, Δ; 2) morpholine, PhMe, Δ

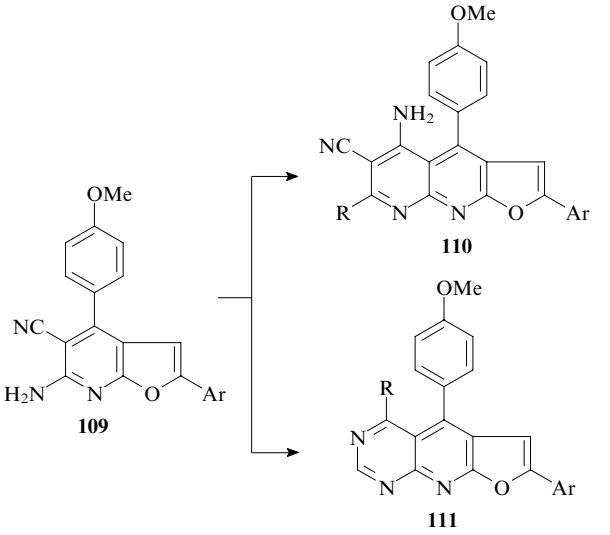
Scheme 32



R^1 = Alk, Ar; R^2 = H, OMe, F, 4-FC_6H_4; (*a*) 4-R$^2C_6H_4CHO$, NaOH, EtOH, 20 °C, 24 h; (*b*) H_3PO_4, AcOH, 110 °C, 3 h

Some publications are devoted to annulation of a new heterocycle to the pyridine moiety. For example, Salman [75] reported the synthesis of two different heterocyclic systems based on a furo[2,3-*b*]pyridine derivative (Scheme 34). Disubstiuted 6-amino-5-cyanofuro[2,3-*b*]pyridines **109** were condensed, in one case, with malononitrile and ethyl cyanoacetate and, in the other case, they were condensed with formamide and a mixture of formic acid and sodium acetate. This resulted in the formation of furo[2′,3′:6,5]pyrido[2,3-*b*]pyridine **110** and furo[2′,3′:6,5]pyrido[2,3-*d*]pyrimidine **111**, respectively.

Scheme 34

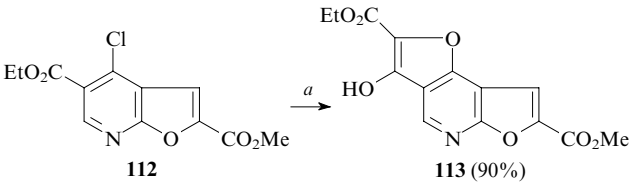


Ar = 2-Me-4-MeOC$_6$H$_3$

Reagent	Conditions	R^1	Yield (%)	
			110	**111**
$CH_2(CN)_2$	Δ, 5 h	NH_2	85	–
$NCCH_2CO_2Et$	Δ, 5 h	OH	60	–
$HC(O)NH_2$	Δ, 4 h	NH_2	–	65
HCO_2H	AcONa, Δ, 4 h	OH	–	70

It is also known that the condensation of 4-chlorofuro[2,3-*b*]pyridine-2,5-dicarboxylate **112** with methyl glycolate in 1,2-dimethoxyethane affords 3-hydroxydifuro[2,3-*b*:2′,3′-*d*]pyridine-2,7-dicarboxylate **113** (Scheme 35).[76]

Scheme 35

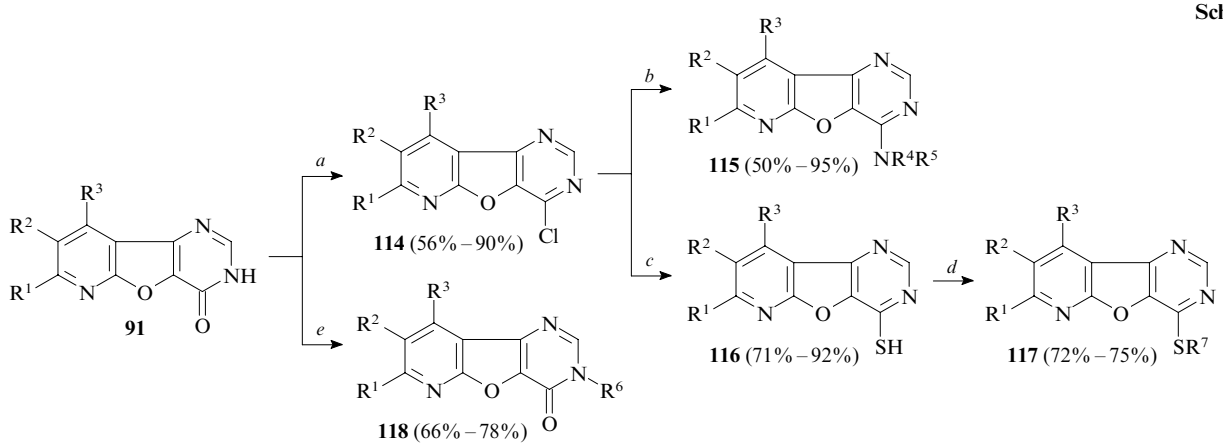


(*a*) 1) $HOCH_2CO_2Me$, NaH, 60–70 °C, 16 h; 2) 10% HCl, $CHCl_3$

As noted above, the interest in derivatives of annulated pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidines is due to their valuable biological properties. This accounts for the thorough investigations of some reactions of these compounds reported in numerous papers [12, 13, 16–21, 23, 24, 77–80] and patents.[2–5, 27–29] In particular, compounds **91** were treated with phosphorus(V) oxychloride to be converted to derivatives **114** with an active chlorine atom. This was followed by nucleophilic substitution with displacement of chlorine to give amino- (**115**) and sulfanylpyridofuro[3,2-*d*]pyrimidines (**116**) (Scheme 36) (see Refs 21 and 21). For comparative estimation of the biological activity, the corresponding S-alkylated derivatives **117** and N-alkylated pyrimidinones **118** were also synthesized.

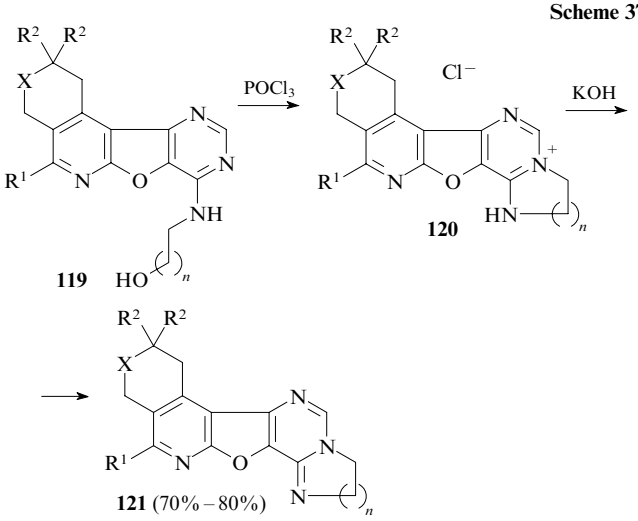
A special place among these reactions is occupied by annulation, resulting in pentacyclic fused systems. In this case, the fifth ring is closed at bond *c* of pyrimidine. Thus hydroxyethylamino and hydroxypropylamino derivatives of fused furo[3,2-*d*]pyrimidines **119** were made to react with phosphorus(V) oxychloride.[24] The reactions occur *via* the intermediate pyrimidinium salts **120**, which are converted to desired products **121** on treatment with potassium hydroxide (Scheme 37).

Scheme 36



R^1, R^2, R^3 = H, Alk, Ar; R^1–R^2, R^2–R^3 = $(CH_2)_n$ (n = 1, 2), $CH_2OCMe_2CH_2$; R^4, R^5 = H, Alk; R^4–R^5 = $(CH_2)_n$ (n = 1, 2); R^6, R^7 = Et, $CH_2C(O)NH_2$, $CH_2C_6H_4Cl$-4, $CH_2C_6H_4F$-4, $CH_2C_6H_3Cl_2$-2,4; (*a*) 1) $POCl_3$, Δ; 2) KOH or NH_3; (*b*) HNR^4R^5, EtOH, Δ; (*c*) 1) $NH_2C(S)NH_2$, EtOH, Δ, 3 h; 2) AcOH; (*d*) R^{7}Hal, K_2CO_3, DMF, Δ, 0.5 h; (*e*) R^{6}Hal, K_2CO_3, DMF, Δ, 1 h

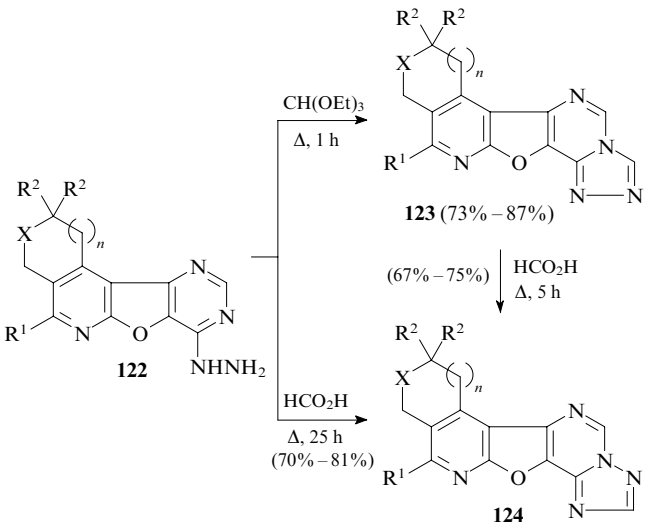
Scheme 37



X = CH_2, O; R^1 = Alk, Ar; R^2 = H, Me; n = 1, 2

Worthy of note are the annulation reactions in which hydrazine pyridofuro[3,2-*d*]pyrimidine derivatives **122** serve as building blocks. Under the action of triethyl orthoformate, these compounds are converted to pyrido[3′,2′:4,5]furo[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **123**, while under the action of formic acid, they are converted to pyrido[3′,2′:4,5]furo[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **124**.[18, 19, 23, 77, 78] The Dimroth rearrangement of triazolo[4,3-*c*]pyrimidines **123** to isomeric triazolo[1,5-*c*]pyrimidines **124** performed in acid medium (Scheme 38) also deserves attention.[18, 19, 77, 78]

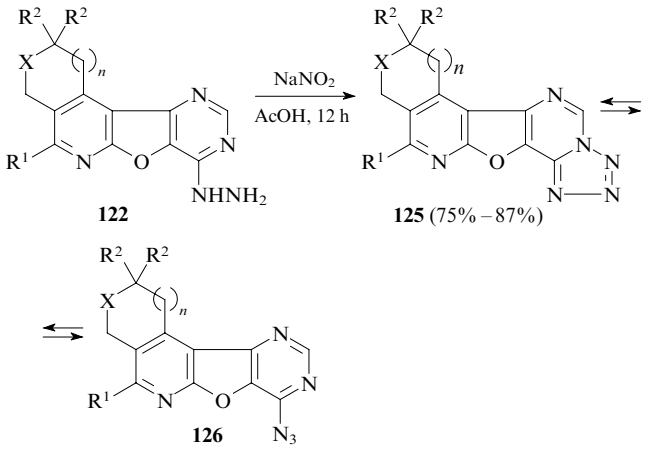
Scheme 38



X = CH_2, O; R^1 = Alk, Ar; R^2 = H, Me; n = 0, 1

Treatment of compounds **122** with an aqueous solution of sodium nitrite at room temperature in acetic acid gives pyrido[3′,2′:4,5]furo[2,3-*e*][1,2,3,4]tetrazolo[1,5-*c*]pyrimidines **125** (Scheme 39).[19, 23, 80] By ^{1}H NMR spectroscopy, it was found that in DMSO solution, tetrazolo[1,5-*c*]pyrimidines **125** exist as mixtures of two isomeric forms, namely, tetrazole (**125**) and azide (**126**) forms, in 3 : 2 ratio. X-Ray diffraction data unambiguously prove that in the crystalline state, tetrazole form **125** predominates.

Scheme 39

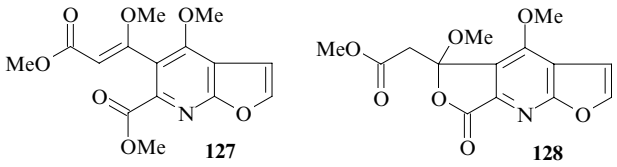


X = CH_2, O; R^1 = Alk, Ar; R^2 = H, Me; n = 0, 1

V. Biological activity of furo[2,3-*b*]pyridines

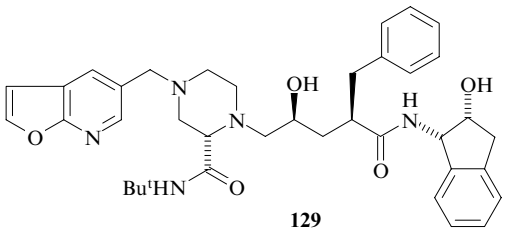
Furo[2,3-*b*]pyridine derivatives possess diverse biological activities. First of all, natural compounds deserve mention: the alkaloids furomegistines I (**127**) and II (**128**) isolated from the bark of *Sarcomelicope megistophylla* and exhibiting cytotoxic activity are known best of all.[81]

Structures 127, 128



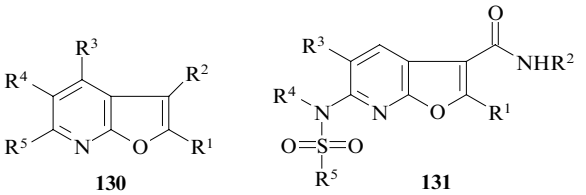
According to published data, the piperazinomethyl derivative of furo[2,3-*b*]pyridine **129** (commercial code L-754,394) is a potent and selective inhibitor of HIV protease[82] and cytochrome P450.[83]

Structure 129



Furo[2,3-*b*]pyridines **130** are known to be selective inhibitors of protein tyrosine kinases such as Lck, Fyn (B), Fyn (T), Lyn, Src, Yes, Hcb, FGR and BLK and other protein kinases such as ACK.[84] Therefore, they can be used to treat immunological and tumour diseases.[41, 42] Derivatives **131** possess high antiviral activities. In particular, they are active against *Flaviviridae* viruses and, therefore, they are useful for the therapy of viral infections (for example, hepatitis C).[37]

Structures 130, 131

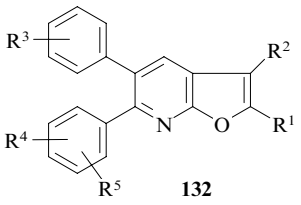


130 **131**

130: R^1, R^2, R^3, R^4 , R^5 = H, Alk, Ar, OH, OAlk, NH_2, NHAlk, Hal, CN, CF_3, NO_2;
131: R^1, R^3 = H, Alk, Ar, Hal; R^2 = Me, Et;
$R^3–R^4$ = $C(O)(CH_2)_n$; R^4 = Alk, OAlk, alkenyl, alkynyl;
R^5 = Alk, CH_2Hal, Ph, CF_3

The results of pharmacological investigations demonstrated that some derivatives of furo[2,3-*b*]pyridine **132** are highly active cannabinoid receptor CB1R modulators and can be used as medicines for treating food-borne diseases.[6, 14]

Structure 132

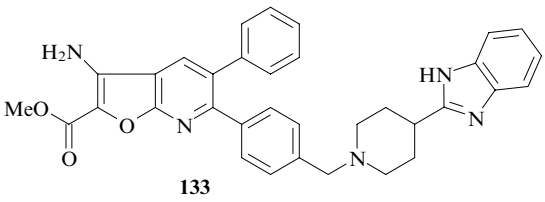


132

R^1 = Ph, Het, C(O)Alk; R^2 = Alk, cyclo-Alk, Het, Ph, NHC(O)Alk; R^3, R^4, R^5 = H, Alk, Ar

Compound **133** based on fluropyridine is a protein kinase B inhibitor and, hence, it may find use for treatment of malignant neoplasms.[33]

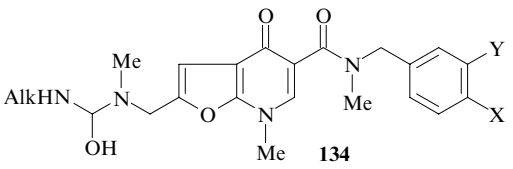
Structure 133



133

It is known from the literature that N-substituted 5-carbamoyl-4-oxo-4,7-dihydrofuro[2,3-*b*]pyridines **134** inhibit the human herpes virus polymerase. Pharmacological investigations demonstrated that the introduction of a chlorine atom into the phenyl moiety substantially enhances the activity of the compound as compared with the effects of both the unsubstituted analogue and some derivatives with other substituents: Br and F atoms and Me and CF_3 groups.[57]

Structure 134



134

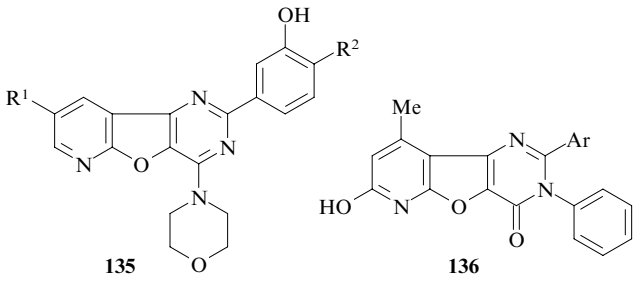
X = H, Hal, Me, CF_3; Y = H, F

Some tricyclic and tetracyclic fused systems based on furo[2,3-*b*]pyridine also have high biological activities. For example, 3-(4-morpholinopyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidin-2-yl)phenol **135** (R^1 = R^2 = H, code PI-103) and its derivatives are selective PI3K (phosphoinositide 3-kinase) inhibitors [2, 29, 32, 85–87] suitable as a therapeutic agent for treating cancer and immune and inflammatory diseases.

2,3-Disubstituted 3,4-dihydropyrido[3′,2′:4,5]-furo[3,2-*d*]pyrimidin-4-ones **136** exhibit antioxidant and antiinflammatory action. It was found that the introduction of substituents — 4-trifluoromethylphenyl, 4-chlorobenzyl, 3,5-dimethoxyphenyl and 3-fluorophenyl groups — in position 2 enhances the biological activity.[15]

It was ascertained [54, 55, 88] that tetrahydrofuro[2,3-*b*]quinoline derivatives **137** (*n* = 1) are potent acetylcholinesterase inhibitors but show no substantial activity against butyrylcholinesterase. Note that similar cyclohepta[*e*]furo[2,3-*b*]pyridines **137** (*n* = 2) are much less active.

Structures 135, 136

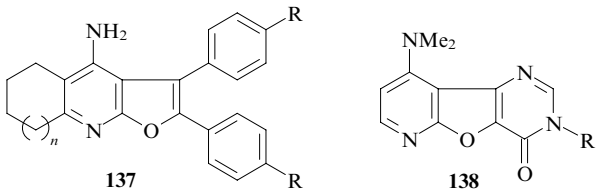


135 **136**

R^1, R^2 = Alk, Ar, NHAlk

N-Substituted furo[3,2-*d*]pyrimidin-4-ones **138** are potent and selective metabotropic glutamate receptor (mGluR1) antagonists.[31]

Structures 137, 138

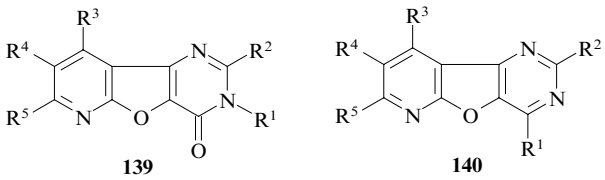


137 **138**

R = H, Me, OMe; *n* = 1, 2 R = Ar, cyclo-Alk

Quite a few published data attest to the physiological activity of substituted pyridofuro[3,2-*d*]pyrimidines.[3–5, 16, 20, 21, 27, 28, 74, 79] For example, biological testing of compounds **139** and **140** showed that many of them possess clear-cut anticonvulsant activity.[20, 21, 74, 79] It was shown that the anticonvulsant action is affected by the

Structures 139, 140



139 **140**

R^1, R^2, R^3, R^4, R^5 = H, Alk, Ar, NHAlk, OH, Hal, *etc.*

nature of substituent R^5 in position 7.[20] Compounds **139** and **140** are also selective and potent phosphodiesterase (PDE-4) inhibitors, which is confirmed by numerous patents.[3–5, 16, 27, 28] Studies of the biological properties of these compounds are currently in progress.

VI. Conclusion

Thus, this review considers and integrates the published data of the last 15 years dealing with the methods of synthesis, chemical transformations and biological activity of furo[2,3-*b*]pyridines. The works covering the most general and promising methods for the synthesis of target structures are analyzed. The data given in the review demonstrate that there exist general and facile methods for the preparation of various substituted furo[2,3-*b*]pyridines.

As can be seen from the studies considered in the review, a promising and the most widely applied strategy for the synthesis of furo[2,3-*b*]pyridines is based on the Thorpe–Ziegler reaction. In some cases, this process is substantially affected by both minor traces of water and the time of reactant refluxing. It is also noteworthy that the one-pot multicomponent condensation strategy for the synthesis of furo[2,3-*b*]pyridines with thorough adjustment of reaction conditions (temperature, solvent, catalyst), obviously, requires further development.

A special place among the chemical reactivity of furo[2,3-*b*]pyridines are occupied by annulation reactions, which afford polyheterocyclic systems possessing high biological activities. Diversified types of biological activity in combination with the ease of the synthesis of many furo[2,3-*b*]pyridine derivatives make these compounds attractive objects for the search for new highly effective medicines.

The summarized published data provide the conclusion that furo[2,3-*b*]pyridine derivatives are of interest from both chemical and pharmacological standpoints.

We hope that our review will be useful for the researchers who are engaged in the chemistry of fused heterocycles.

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