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Chemistry and biological activities of 1,8-naphthyridines †

V P Litvinov

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Abstract. Data on the synthetic methods, reactivities, biological activities and other practically important properties of 1,8-naphthyridine derivatives published over the last 15 years are analysed. The bibliography includes 759 references.

I. Introduction

Of the six isomeric pyridopyridines, 1,8-naphthyridine derivatives have received the most study in the last 15 years. This class of compounds has attracted considerable attention primarily because the 1,8-naphthyridine skeleton is present in many compounds which have been isolated from natural substances and exhibit various biological activities. The number of publications (including patents) devoted to the chemical and biological properties of 1,8-naphthyridines which were issued over this period is substantially larger than the number of studies on all other types of isomeric pyridopyridines published in the last 90 years. In the last two years, more than 900 publications appeared, among which were about 200 patents. Most of these studies were devoted to specific aspects of biological activity assays of 1,8-naphthyridine derivatives.

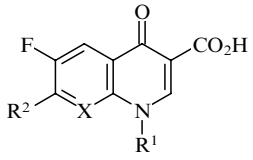
The present article, which completes a series of reviews of the chemistry of pyridopyridines,[1,2] summarises and analyses data on the synthesis methods, reactivities, biological activities and other practically important properties of 1,8-naphthyridine derivatives. For convenience of representation, the data are classified according to the types of the starting substrates, reagents or the nature of the compounds synthesised. In the discussion of the synthetic methods and chemical transformations, the principal data on biological activities of the compounds synthesised are considered. In my opinion, it is reasonable to cite a virtually complete bibliography, including patents, on the synthesis and properties of 1,8-naphthyridine derivatives. However, since the literature on these problems is voluminous, only general and promising synthetic methods and most typical reactions are covered in detail in the present review.

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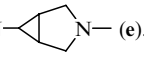
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II. Synthetic methods and biological activities of 1,8-naphthyridine derivatives

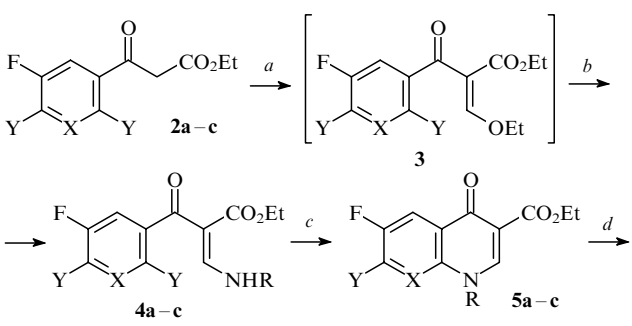
Among 1,8-naphthyridine derivatives, 6-fluoro-substituted 1,8-naphthyridin-4-ones, which are aza analogues of fluoroquinolones, have attracted most attention in the last 15 years. Fluoroquinolone- and fluoronaphthyridonecarboxylic acids provided the basis for the design of highly efficient antibacterial drugs, such as norfloxacin (**1a**),[3] pefloxacin (**1b**),[4] ciprofloxacin (**1c**),[5] enoxacin (**1d**),[6] trovafloxacin (**1e**),[7–10] *etc*.



1a – e

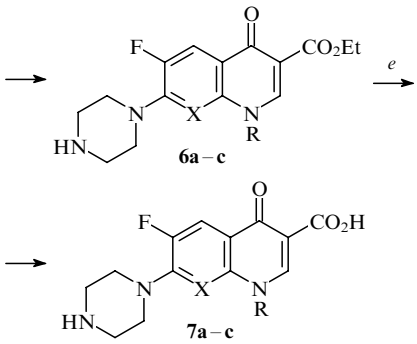
X = CH: R^1 = Et, R^2 = piperazin-1-yl (**a**), *N*-methylpiperazin-1-yl (**b**); R^1 = cyclo-C_3H_5, R^2 = piperazin-1-yl (**c**); X = N: R^1 = Et, R^2 = piperazin-1-yl (**d**); R^1 = 2,4-$F_2C_6H_3$, R^2 =  (**e**).

Fluoronaphthyridones are similar not only in biological activity but also in other properties to fluoroquinolones, whose chemistry has been studied in considerable detail.[11–15] The most commonly used method for the synthesis of fluoro-substituted 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acids is based on approaches developed for preparing fluoroquinolone analogues [16–20] and can be represented by the following scheme:



2a – c **3** **4a – c** **5a – c**

† Dedicated to Academician Oleg Nikolaevich Chupakhin on the occasion of his 70th birthday.



X = N (**a**), CH (**b**), CF (**c**); Y = Cl, F;

R = Et, Pr^i, cyclo-C_3H_5, Bu^t, CH_2=CMe, 4-FC_6H_4;

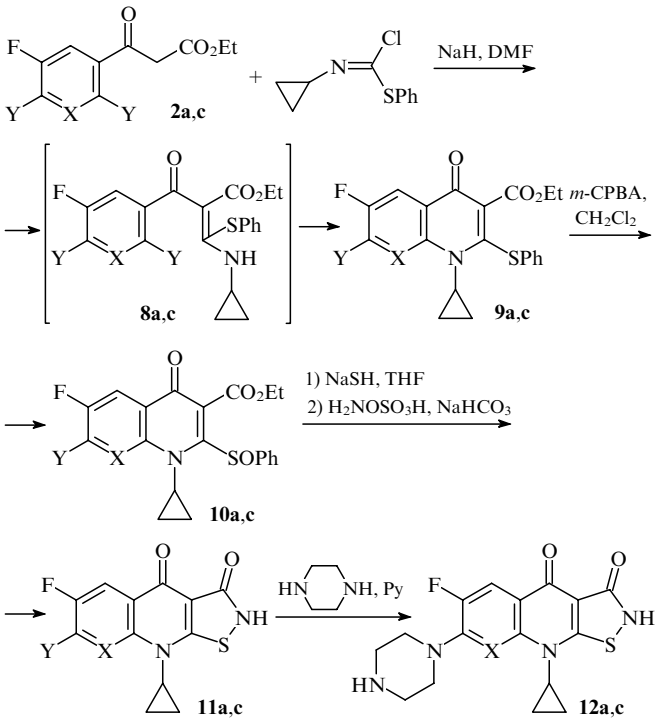
DBU is diazabicyclo[5.4.0]undec-7-ene;

(*a*) $HC(OEt)_3$, Ac_2O; (*b*) RNH_2, EtOH; (*c*) NaH, dioxane;

(*d*) $NH(CH_2CH_2)_2NH$, DBU, MeCN; (*e*) 1) NaOH, H_2O, Δ; 2) H^+.

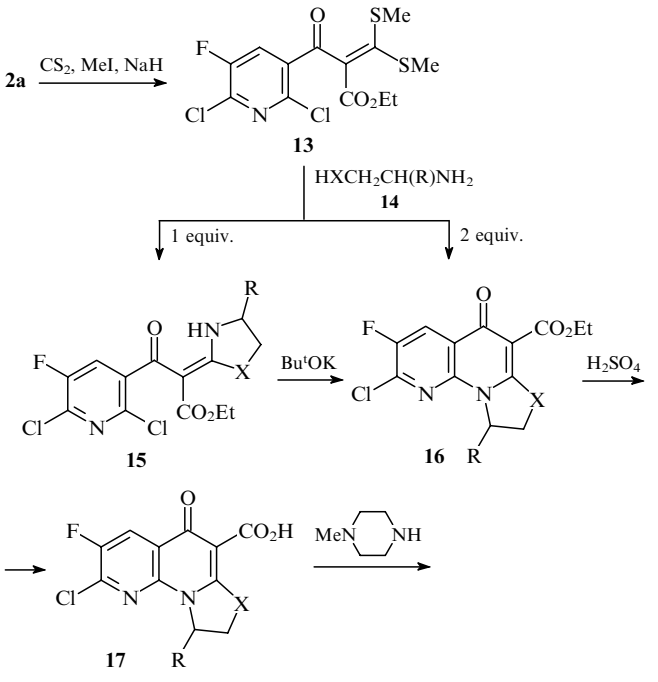
Condensation of ethyl (2,6-dichloro-5-fluoronicotinoyl)acetate **2a** and analogous benzoyl derivatives **2b**,**c** with ethyl orthoformate in acetic anhydride followed by the reaction of intermediates **3** with a small excess of amine (ethanol, 20 °C) yields the corresponding enamino ketoesters **4a**–**c**. Heating of enamines **4b** with sodium hydride in dioxane gives rise to ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylates **5b**. Cyclisation of enamines **4a**, which can be carried out according to three procedures, *viz*., by reaction with sodium hydride in dioxane, with potassium carbonate in acetonitrile or with *tert*-butylammonium fluoride in THF, affords naphthyridones **5a** in good yields.[16–26] The replacement of the halogen atom at position 7 of compounds **5a** under the action of amine in acetonitrile (in some cases, in the presence of DBU as a base) gives rise to esters **6a**, which are hydrolysed to form acids. This procedure was used for the synthesis of naphthyridonecarboxylic acids **7a** (R = Et,[21] Pr^i,[16] isoprenyl,[24] Bu^t,[22] cyclopropyl,[25] 4-fluorophenyl [19]).

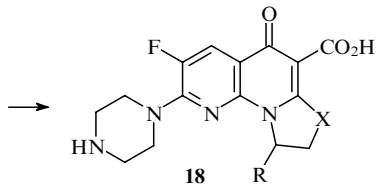
The high synthetic potential of esters **2** is also exemplified by their reactions with thioformates. For example, the reaction of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (**2a**) with phenyl *N*-cyclopropyliminochlorothioformate in the presence of one equivalent of sodium hydride in xylene proceeds through intermediate **8a** to give ethyl 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-2-phenylthio-1,4-dihydro-1,8-naphthyridine-3-carboxylate (**9a**) in 51% yield.[24] An analogous treatment of ethyl 2,3,4,5-tetrafluorobenzoylacetate (**2c**) produces ethyl 1-cyclopropyl-6,7,8-trifluoro-4-oxo-2-phenylthio-1,4-dihydroquinoline-3-carboxylate (**9c**) in 42% yield. Oxidation of 3-carboxylic esters **9a**,**c** with *m*-chloroperoxybenzoic acid (*m*-CPBA) (CH_2Cl_2, 20 °C) affords ethyl 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-2-phenylsulfinyl-1,4-dihydro-1,8-naphthyridine-3-carboxylate (**10a**) (83% yield) or ethyl 1-cyclopropyl-6,7,8-trifluoro-4-oxo-2-phenylsulfinyl-1,4-dihydroquinoline-3-carboxylate (**10c**) (78% yield), respectively. The regiospecific replacement of the sulfinyl group of sulfoxide **10a** with freshly prepared sodium hydrosulfide in aqueous THF gives rise to a 2-mercapto derivative, whose treatment (without purification) with hydroxylamine-*O*-sulfonic acid in the presence of sodium bicarbonate affords the hydrosulfamino derivative. The latter undergoes cyclisation to form 7-chloro-9-cyclopropyl-6-fluoro-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**11a**) (67% yield). The reaction of naphthyridinedione **11a** with an excess of piperazine (pyridine, 60 °C) produces 9-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]-[1,8]naphthyridine-3,4-dione (**12a**) in 98% yield. An analogous sequence of transformations of quinolinedione **11c** gives rise to 9-cyclopropyl-6,8-difluoro-7-(piperazin-1-yl)-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**12c**) (74%). Naphthyridinedione **12a** and quinolinedione **12c** exhibit higher antibacterial activity compared to ciprofloxacin **1c**.[24]



X = N, Y = Cl (**a**); X = CF, Y = F (**c**).

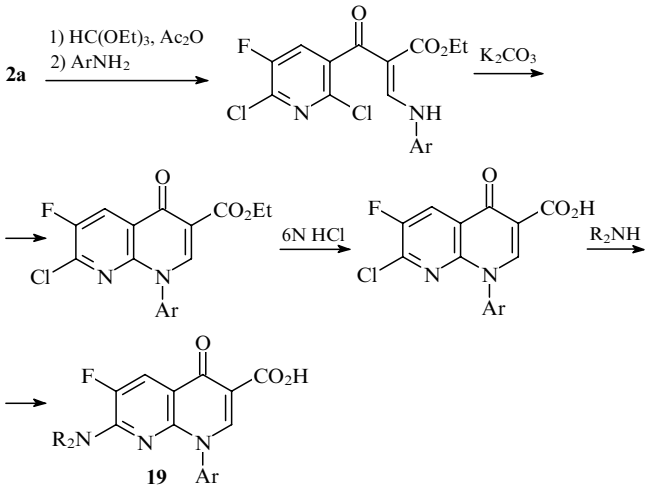
The reaction of ester **2a** with sodium hydride, carbon disulfide and methyl iodide in *N*,*N*-dimethylacetamide produces ketene dimethyl dithioacetal **13** (58% yield). The reactions of the latter with substituted amines **14** in toluene afford derivatives **15** in yields of up to 93%.[27] Their intramolecular cyclisation in the presence of potassium *tert*-butoxide gives rise to ethyl thiazolo-, oxazolo- and imidazolo[3,2-*a*][1,8]naphthyridine-4-carboxylates **16** (35%–92% yields). Condensation of ketene dithioacetal **13** with two equivalents of amines **14** allows one to prepare compounds **16** in one step. Acid hydrolysis of esters **16** gives the corresponding carboxylic acids **17** (55%–91% yields). The reactions of the latter with *N*-methylpiperazine are accompanied by the replacement of the chlorine atom at position 2 to form piperazine derivatives **18**, which exhibit *in vitro* antibacterial activity.





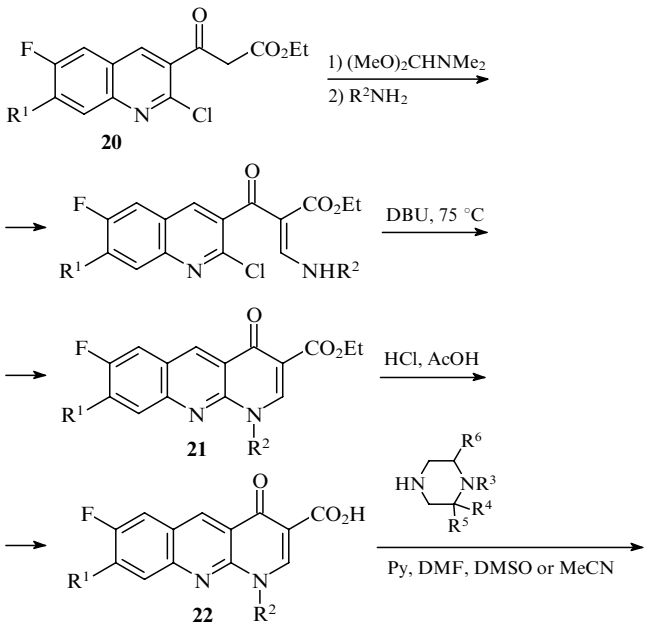
X = S,O, NMe; R = H, Me.

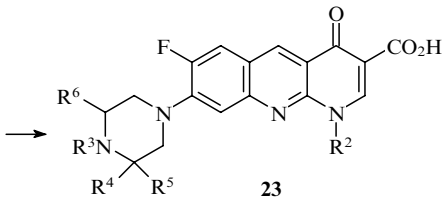
Ester **2a** was also used as the starting compound in the synthesis of previously unknown 7-substituted 6-fluoro-1-(1- or 2-naphthyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acids **19**, which possess pronounced (comparable to that of the drug ataverdine) anti-HIV-RT activity.[28] The synthesis of acids **19** is illustrated by the following scheme:



Ar = 1-naphthyl, 2-naphthyl; R_2NH = piperazine, 2-methylpiperazine, *N*-methylpiperazine, (2*R*,6*S*)-2,6-dimethylpiperazine, (3*S*)-3-aminopyrrolidine.

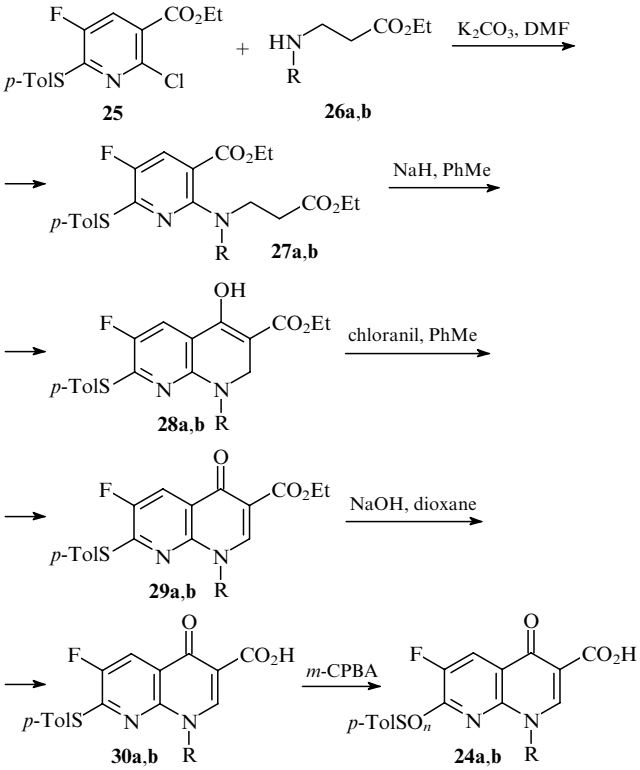
Ethyl (2-chloroquinolyl-3-carbonyl)acetates **20** served as the starting compounds for the preparation of benzo[*b*][1,8]naphthyridines **21**–**23**[29,30] possessing high antibacterial activity against Gram-positive bacteria. These compounds are used for the treatment of skin staphylococcus infections and water purification and also as preservatives and decontaminants.





R^1 = F, Cl; R^2 = Me, MeO, cyclo-C_3H_5; R^3, R^4, R^5, R^6 = H, Alk.

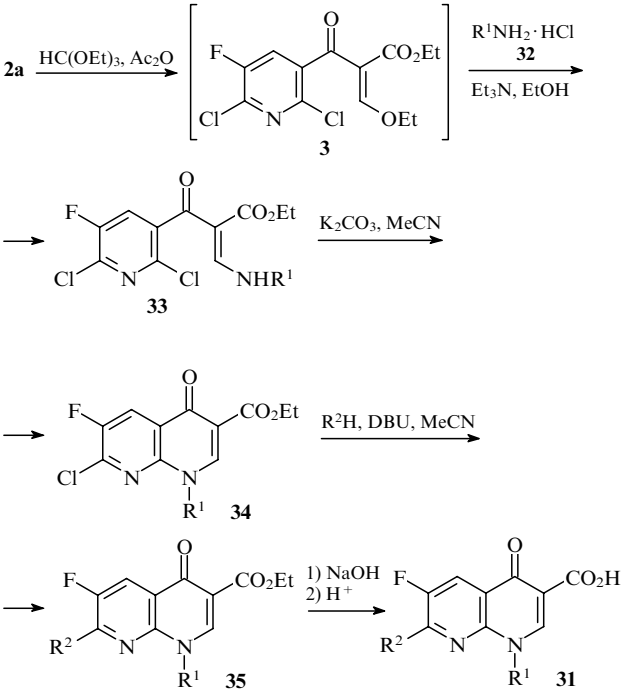
A procedure was developed for the synthesis of 1-ethyl-(or cyclopropyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid derivatives **24** containing the sulfinyl or sulfonyl group at position 7 of the naphthyridine system.[31,32] For example, heating (120–130 °C) of a mixture of ethyl 2-chloro-5-fluoronicotinate **25** and ethyl 3-(cyclopropylamino)propionate (**26a**) in DMF in the presence of Na_2CO_3 afforded diester **27a** (23%), the conversion of the starting nicotinate being 40%. Cyclisation of diester **27a** under the action of sodium hydride in toluene gave ethyl 1-cyclopropyl-6-fluoro-4-hydroxy-7-(*p*-tolyl)-1,2-dihydro-1,8-naphthyridine-3-carboxylate (**28a**), whose dehydrogenation with chloranil in toluene yielded 1,4-dihydro-4-oxo derivative **29a**. Alkaline hydrolysis of derivative **29a** gave 1-cyclopropyl-6-fluoro-4-oxo-7-(*p*-tolyl)-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**30a**). In the reaction of the latter with an equimolar amount of *m*-chloroperoxybenzoic acid, the sulfide group is readily oxidised to the sulfoxide group. In the presence of a twofold excess of the peroxy acid, the sulfide group is oxidised to the sulfonyl group to form naphthyridonecarboxylic acids **24a**. This approach was used for the synthesis of analogous compound **24b** (R = Et) and the antibacterial drug enoxacin (**1d**).



R = cyclo-C_3H_5 (**a**) Et (**b**); *n* = 1, 2; *p*-Tol is *p*-tolyl.

With the aim of studying the structure–antibacterial activity relationship, a series of new 7-substituted 6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acids **31** containing fluoro-substituted *tert*-butyl groups at the N(1) atom was synthesised.[22,23,33–35] For example, the reaction of intermediate **3** (X = N, Y = Cl) derived from ester **2a** with amines **32** in the presence of triethylamine in ethanol produces enamines **33**, whose

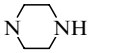
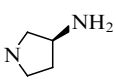
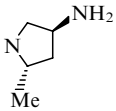
treatment with K_2CO_3 in acetonitrile results in their cyclisation to esters **34**. Condensation of the latter with amines upon refluxing in acetonitrile in the presence of DBU yields esters **35**, whose alkaline hydrolysis gives naphthyridonecarboxylic acids **31**. The latter exhibit high *in vitro* antibacterial activity against four types of Gram-positive bacteria and eight types of Gram-negative bacteria.[23] Examples of naphthyridonecarboxylic acids **31** are given in Table 1.



32: R^1 = Bu^t, FCH_2CMe_2, $(FCH_2)_2CMe$, $(FCH_2)_3C$.

6-Fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid derivatives possess a very broad spectrum of biological activities, in particular, antibacterial action. Many compounds of this class exhibit high activity against various Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538P, CMX 686B, FDA 209P JC-1; *Staphylococcus epidermidis* 3519, IAM 1296; *Streptococcus faecium* ATCC 8043, *Streptococcus pyogenes* 930) and Gram-negative bacteria (*Escherichia coli* Juhl, KC-14, K-12 C600; *Enterobacter aerogenes* ATCC 130048; *Klebsiella pneumoniae* 8045, PCI-602; *Pseudomonas aeruginosa* EZ, 5070, K799/WT; *Acinetobacter* CMX 669, AC54).[19,27]

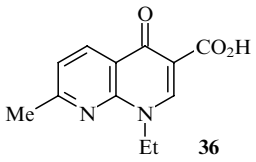
Table 1. Substituted 1,8-naphthyridinecarboxylic acids **31**.

R^2	R^1	Yield (%)	Ref.
	Bu^t	–	31
	FCH_2CMe_2	70	32
	$(FCH_2)_2CMe$	30	32
	$(FCH_2)_3C$	89	32
	Bu^t	–	36, 37
	FCH_2CMe_2	60	32
	$(CH_2F)_2CMe$	50	32
	$(CH_2F)_3C$	84	32
	Bu^t	–	38
	$(FCH_2)CMe_2$	46	32
	$(FCH_2)_2CMe$	76	32
	$(FCH_2)_3C$	79	32
	FCH_2CMe_2	65	32
	$(FCH_2)_3C$	78	32

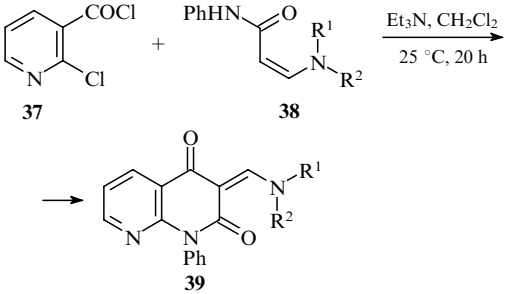
These properties stimulated researchers to modify the 1,8-naphthyridine system by introducing various substituents using standard synthetic approaches. Biological activities of the compounds synthesised were tested, most publications being devoted to problems of analysis of toxicity, synergism of action of these compounds in various mixtures, elucidation of fine details of physiological actions of these compounds, *etc*. These aspects are beyond the scope of the present review, where only a bibliography of recent studies on fluoro-substituted 1,8-naphthyridones is given. Among these publications, numerous papers and patents concerned with the antibacterial drugs enoxacin (**1d**)[36–67] and trovafloxacin (**1e**)[68–187] are noteworthy.

In the literature (particularly, patent), other derivatives of fluorine-containing 1,8-naphthyridines have been described. For example, the review[188] was devoted to the synthesis, pharmacology, pharmokinetics and metabolism of 6-fluoronaphthyridinecarboxylic acids. Antibacterial[189–198] and antimicrobial[199,200] activities of these compounds were studied. These problems were also covered by many recent patents.[201–262]

Voluminous literature on 1,8-naphthyridine derivatives containing no fluorine is available. Explosion of interest in this class of heterocyclic compounds dates back to 1962, when Lesher and co-workers[263,264] synthesised 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**36**) (nalidixic acid) possessing strong antibacterial activity. The pharmacological properties of this compound are still being studied.[265–300]

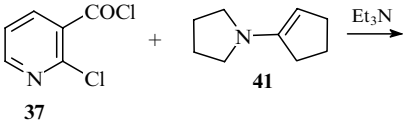


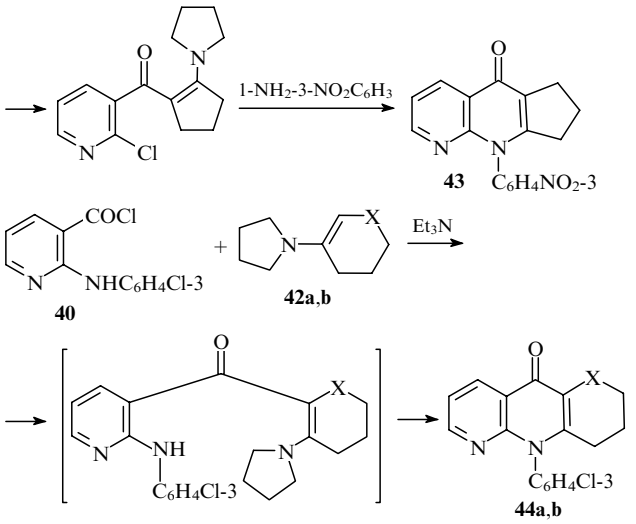
2-Chloronicotinoyl chloride (**37**) is widely used as the starting compound in the synthesis of various 1,8-naphthyridine derivatives. For example, its reactions with substituted 5-aminoacrylic acid anilides **38** produce aminomethylidene-1,8-naphthyridine-2,4-diones **39**.[301]



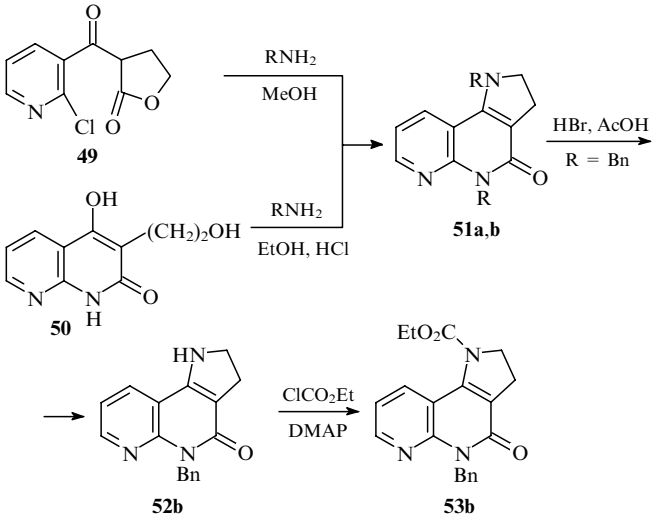
R^1 = H, Me; R^2 = Me, Et, Bn, 2-methyl-6-pyridyl.

The reactions of 2-chloronicotinoyl chloride (**37**) or 2-(3-chloroanilino)nicotinoyl chloride (**40**) with cyclic enamines (**41** and **42a**,**b**) in the presence of triethylamine afforded 1,8-naphthyridones **43** and **44a**,**b** possessing antiallergic, anti-inflammatory, antiulcerative and hypotensive actions.[302–306]





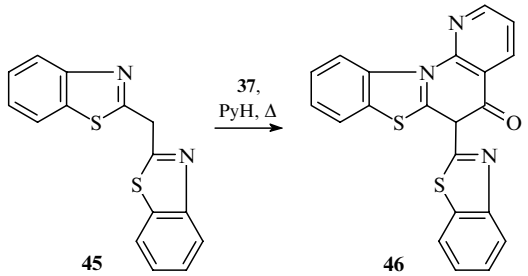
X = CH_2 (**a**), NAc (**b**).



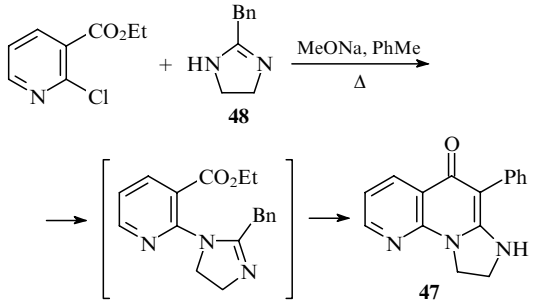
R = Ph (**a**), Bn (**b**); DMAP is 4-dimethylaminopyridine.

According to the ^{1}H NMR spectroscopic data, molecule **44a** is chiral. Naphthyridine **44a** exists as short-lived interconvertable atropoisomeric enantiomers, which form diastereomeric complexes with the shift-reagent [(*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol]. The enantiomers were isolated in the individual form. The racemisation constant is 0.213 min^{-1} at 37 °C. The activation energy is E_a = 21.6 kcal mol^{-1}.[307]

The reaction of 2-chloronicotinoyl chloride **37** with di(benzothiazol-2-yl)methane (**45**) yielded fused naphthyridine system **46**.[308]

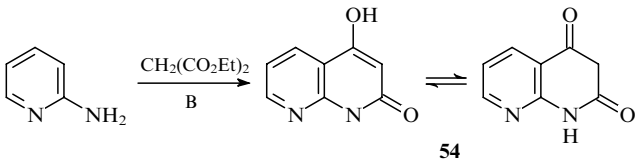


Imidazo[1,2-*a*][1,8]naphthyridine **47** was prepared by refluxing ethyl 2-chloronicotinate with 2-benzyl-4,5-dihydro-1*H*-imidazole (**48**) in toluene in the presence of sodium methoxide.[309]

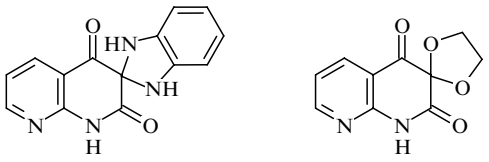


The reactions of 2-(2-chloronicotinoyl)butyrolactone (**49**) or 4-hydroxy-3-(2-hydroxyethyl)-1,8-naphthyridin-2-one (**50**) with amines (aniline or benzylamine) under an inert atmosphere afford pyrrolidinonaphthyridin-2-ones **51a**,**b**. Subsequent transformations of compound **51b** yield pyrrolidinonaphthyridones **52b** and **53b**. Derivatives **51a**,**b**, **52b** and **53b** possess anti-inflammatory and antihyperproliferative actions.[310, 311]

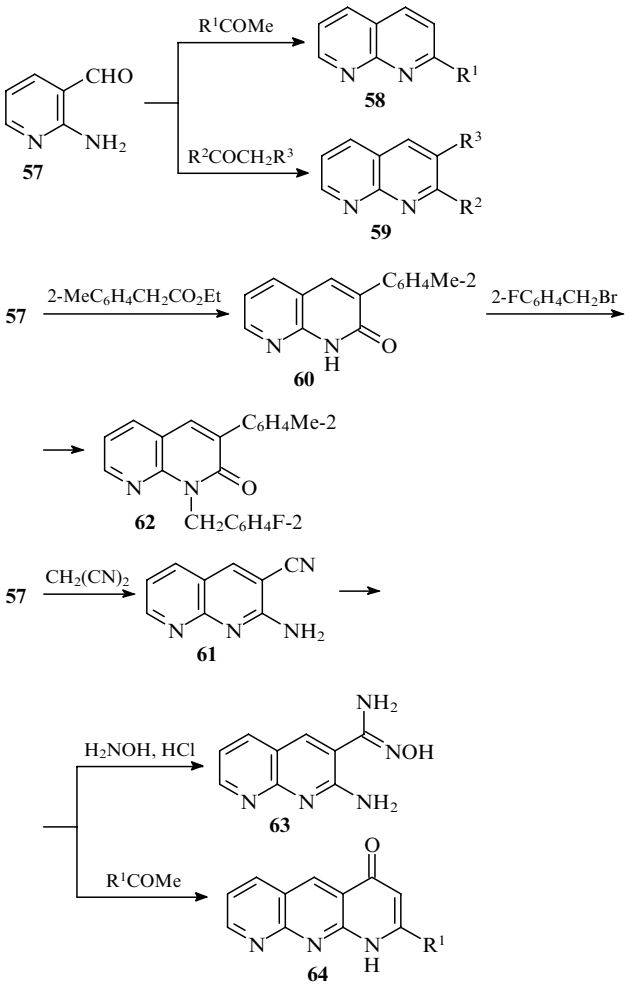
2-Aminopyridine and its derivatives are rather often used as the starting compounds in the synthesis of 1,8-naphthyridine derivatives.[312–353] For instance, the reaction of unsubstituted 2-aminopyridine with diethyl malonate in the presence of bases produces naphthyridinedione **54**, which exists as two tautomeric forms.[312, 313] Halogenation of compound **54** under various conditions (SO_2Cl_2, $POCl_3$, Br_2, I_2) gives rise to both 3-mono- and 3,3-dihalogen derivatives. The reactions of the latter with *o*-phenylenediamine and ethylene glycol form spiro-fused heterocycles **55** and **56**, respectively.[312]



B is a base.

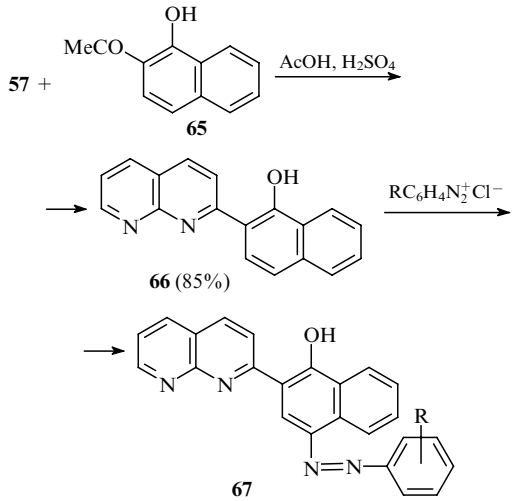


Substituted 2-aminopyridines, in particular, 2-amino-3-formylpyridine (**57**) and its derivatives, possess much higher synthetic potential.[316–319, 322–324, 326, 327, 331–333, 335, 336, 339, 353–356] For example, condensation of pyridine **57** in ethanol in the presence of piperidine as a base with compounds containing the active methylene group as well as with aldehydes, acyclic and cyclic ketones and diketones yielded 1,8-naphthyridines **58**–**61**, which were used as the starting compounds for the synthesis of derivatives **62**–**64**.[316, 318, 322–325, 349, 354] Naphthyridines **58** exhibit antibacterial and antihelmintic activities and are used in the synthesis of fungicides.[318, 323–325, 354] Compounds **59** are intermediates in the synthesis of some hypotensive drugs.[329] Naphthyridine **63** possesses herbicidal properties and is used for selective control of weeds in barley, wheat, maize, sorghum and rice crops.[349] 1,8-Naphthyridin-2-one derivative **62** is used for the treatment of memory disorders, in particular, Alzheimer's disease.[351]



R^1 = Ph, 1-naphthyl, 2-pyridyl, 2-furyl, 2-thienyl, 2-HOC_6H_4, CH=CHPh; R^2 = Me, Ph; R^3 = Ph, COPh, CONHPh, MeCO.

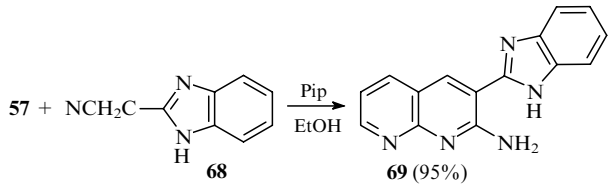
There are numerous examples of the use of 2-amino-3-formylpyridine (**57**) in the synthesis of substituted 1,8-naphthyridines and their fused analogues. For instance, condensation of compound **57** with 2-acetyl-1-naphthol (**65**) in the presence of glacial acetic acid containing catalytic amounts of concentrated



R = H, 2-Me, 4-Me, 3-MeO, 4-MeO, 3-OH, 3-NO_2, 3-Cl, 2-CO_2H, 3-CO_2H, 4-SO_3H, 4-SO_2NH_2.

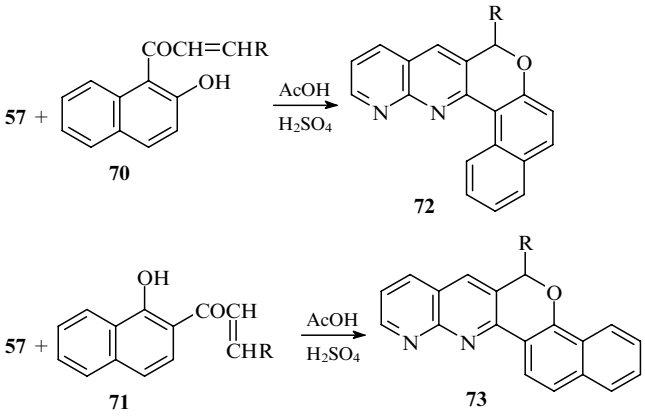
H_2SO_4 afforded 2-(1,8-naphthyridin-2-yl)-1-naphthol (**66**).[323] Treatment of the latter with aryldiazonium salts gave 4-arylazo-2-(1,8-naphthyridin-2-yl)-1-naphthols (**67**) (60%–84% yields) possessing noticeable antibacterial activity.

2-Amino-3-(2-benzimidazolyl)-1,8-naphthyridine (**69**) was synthesised by the reaction of 2-amino-3-formylpyridine (**57**) with 2-cyanomethylbenzimidazole (**68**) in ethanol in the presence of trace amounts of piperidine.[316]



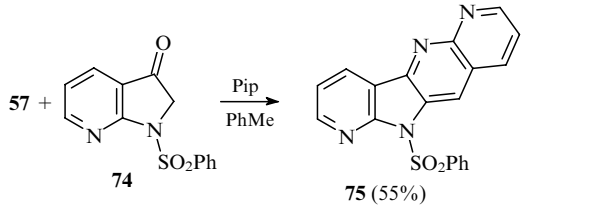
Pip is piperidine.

The reactions of aldehyde **57** with substituted 2-hydroxy-1-naphthyl styryl ketones **70**[318] or 1-hydroxy-2-naphthyl styryl ketones **71**[327] in glacial acetic acid in the presence of catalytic amounts of concentrated H_2SO_4 produce 8-aryl-8*H*-naphtho[1′,2′:5,6]pyrano[4,3-*b*][1,8]naphthyridines **72** or 6-aryl-6*H*-naphtho[2′,1′:5,6]pyrano[4,3-*b*][1,8]naphthyridines **73**, respectively. Compounds **72** and **73** showed no antibacterial activity.

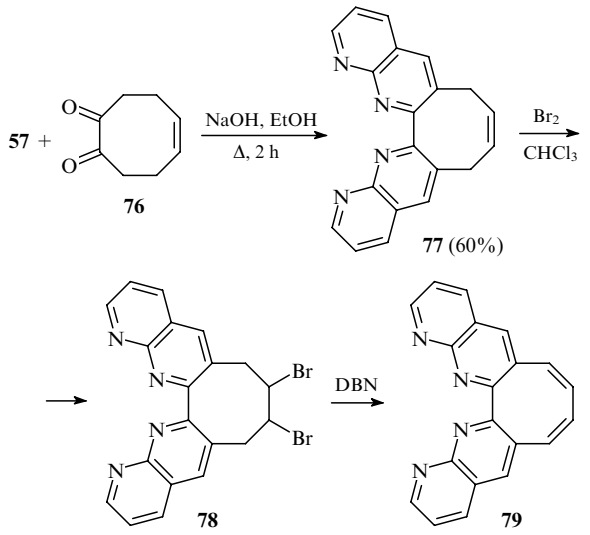


R = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-HOC_6H_4, 4-$Me_2NC_6H_4$, 1-naphthyl, 2-furyl, 2-thienyl.

Treatment of aminopyridinecarbaldehyde **57** with 7-azaindolinone **74** in toluene in the presence of piperidine affords pyrido[3′,2′:4,5]pyrrolo[3,2-*b*][1,8]naphthyridine (**75**).[334]

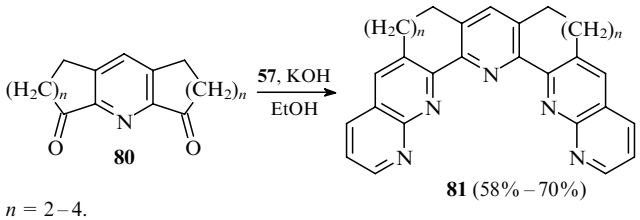


The same aminoaldehyde **57** was successfully used in the synthesis of polyannelated 1,8-naphthyridines. For example, 7,10-dihydrocycloocta[2,1-*b*:3,4-*b*′]di[1,8]naphthyridine (**77**) was prepared by the reaction of compound **57** with cyclooct-5-ene-1,2-dione (**76**) in ethanol in the presence of NaOH. The reaction of compound **77** with bromine in chloroform followed by debromination of adduct **78** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in toluene or DMSO produced cycloocta[2,1-*b*:3,4-*b*′]-di[1,8]naphthyridine (**79**), which is a new promising ligand system.[322, 333] The complex formation of ligand **79** with Cu(II) ions was studied.



DBN is 1,5-diazabicyclo[4.3.0]non-5-ene.

Friedländer condensation of aminoaldehyde **57** with cyclic diketones **80** (anhydrous ethanol, KOH, refluxing under N_2, 4 h) gives rise to heptaannelated heterocyclic systems **81**.[335]

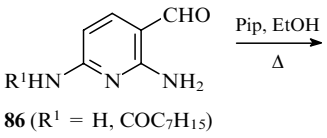


$n = 2-4$.

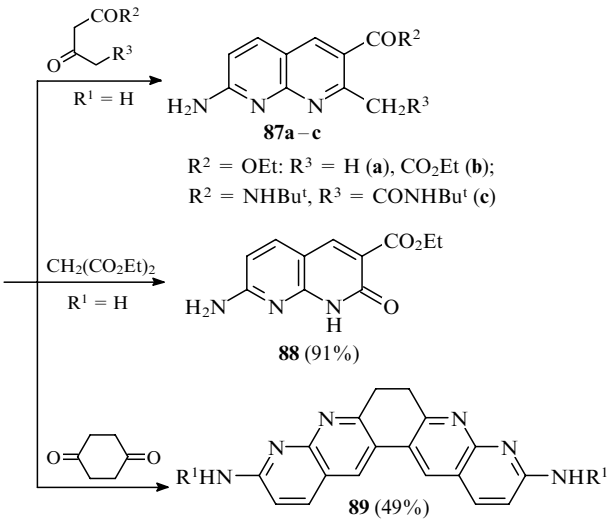
Analogous condensation with dione **82** in ethanol in the presence of piperidine as a base afforded a mixture of polyannelated bisnaphthyridines **83**–**85** in a total yield of 82% (Scheme 1).[336]

Under analogous conditions, α-aminopyridinealdehydes **86** react with activated and nonactivated ketones according to a cascade heterocyclisation scheme to form various 1,8-naphthyridine derivatives in satisfactory yields.

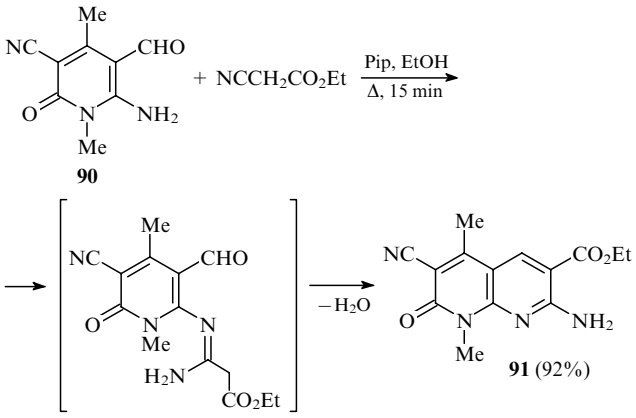
Treatment of compounds **86** with ethyl acetoacetate and piperidine in boiling ethanol affords aminonaphthyridine **87a** in 80% yield. Under the same conditions, the reactions with diethyl 3-oxoglutarate and *N*,*N*′-di-*tert*-butyl-3-oxoglutaramide produce naphthyridines **87b**,**c** in 35% and 40% yields, respectively. Condensation of aminoaldehyde **86** with diethyl malonate and 1,4-hexanedione affords naphthyridinone **88** and bis(aminonaphthyridine) **89**, respectively.[331]



86 (R^1 = H, COC_7H_{15})

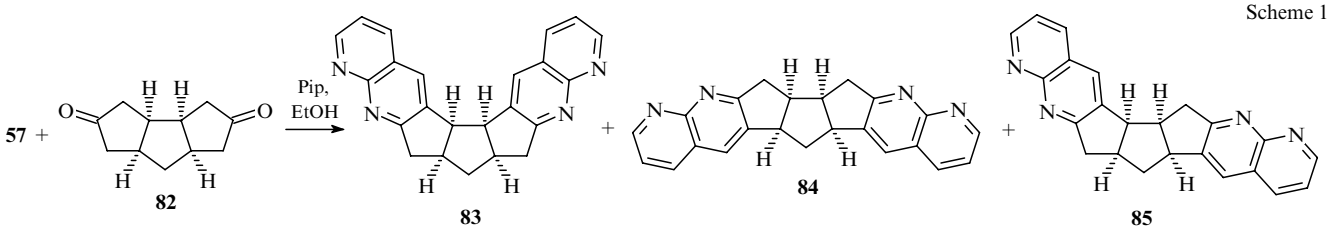


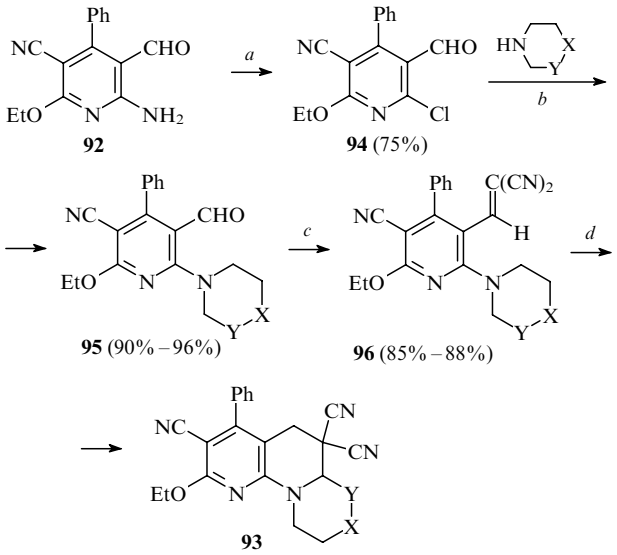
Analogous reactions with substituted 2-amino-3-formylpyridines as the starting substrates provide a promising approach to polyfunctional 1,8-naphthyridines, which are difficult to prepare. For example, refluxing of 6-amino-5-formyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**90**) and ethyl cyanoacetate in EtOH in the presence of piperidine produced the corresponding 1,8-naphthyridin-2-one (**91**).[353]



The use of 2-aminoaldehyde **92** in the synthesis of new polyfunctional heterocyclic systems **93** containing the 1,8-naphthyridine fragment serves as another example of this approach.[339] Deamination of amine **92** (*tert*-butyl nitrite, anhydrous $CuCl_2$, anhydrous MeCN) yields 2-chloro-3-formylpyridine **94**, whose treatment with secondary amine and triethylamine in THF gives rise to 2-dialkylamino-3-formylpyridines **95**. Knoevenagel condensation of compounds **95** with malononitrile in toluene (with the use of butylamine and ammonium acetate as catalysts) produces 2-dialkylamino-3-(2,2-dicyanovinyl)pyridine derivatives **96** in high yields. Thermolysis of the latter by boiling in a polar solvent (butanol or pentanol) or by heating in DMF or DMSO (140 °C) affords heterocyclic compounds **93** in yields from 10% to 100%.

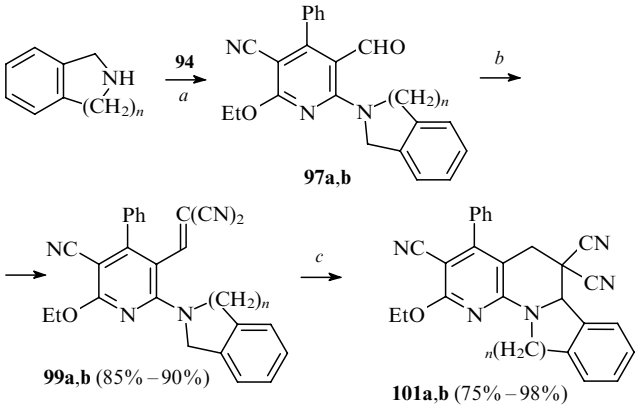
Scheme 1



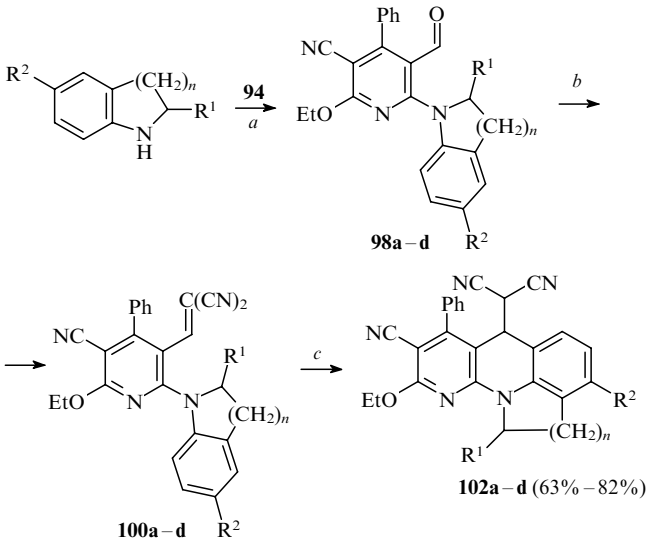


R = Pr^n, Bu^n; X = CH_2, $(CH_2)_2$, O, S; Y = CH_2, S.
(*a*) Bu^tONO, $CuCl_2$, MeCN, Δ, 15 min; (*b*) Et_3N, THF, Δ;
(*c*) 1) $CH_2(CN)_2$, Bu^nNH_2; 2) NH_4OAc, PhMe, Δ;
(*d*) RCH_2OH, Δ, 0.5 h – 7 days.

Substituted chloropyridine **94** was used as the starting compound in the synthesis of other derivatives of naphthyridine systems, such as isoindolo[2,1-*a*]-, isoquino[2,1-*a*]-, indolo[1,8,7-*a*,*b*]- and quino[1,9,8-*a*,*b*][1,8]naphthyridines.[340] The reactions of compound **94** with heterocyclic amines in the presence of triethylamine in THF or DMF produce the corresponding 2-dialkylamino-3-formylpyridine derivatives **97a**,**b** or 2-alkylarylamino-3-formylpyridine derivatives **98a**–**d** in 50%–95% yields. Knoevenagel condensation of the carbonyl groups of compounds **97a**,**b** or **98a**–**d** with malononitrile by refluxing in dichloromethane (2 h) in the presence of butylamine and ammonium acetate affords 2-dialkylamino- (**99a**,**b**) or 2-alkylarylamino-3-(2,2-dicyanovinyl)pyridine derivatives (**100a**–**d**, the yields of products **100a** and **100c** are 91%–95%), respectively. Heating of 2-dialkylamino derivatives **99a**,**b** and 2-alkylarylamino derivatives **100a**–**d** in polar solvents gives rise to tetracyclic compounds **101a**,**b** and **102a**–**d**, respectively.

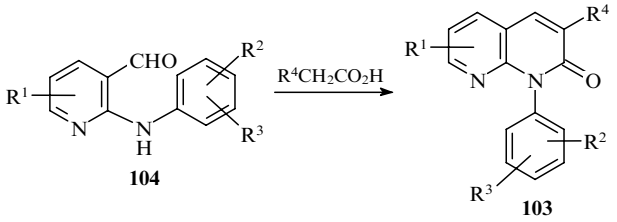


n = 1 (**a**), 2 (**b**);
(*a*) Et_3N, THF or DMF, Δ; (*b*) $CH_2(CN)_2$, $BuNH_2$, NH_4OAc;
(*c*) DMSO, 140 °C, 0.2 – 12 h.



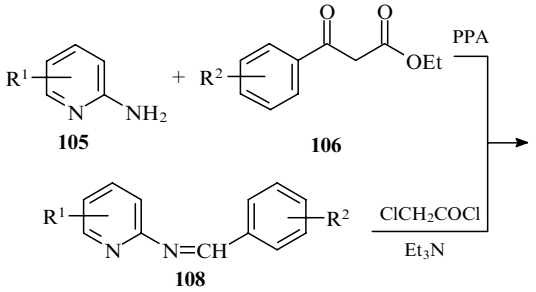
n = 1: R^1 = R^2 = H (**a**); R^1 = Me, R^2 = H (**b**);
n = 2: R^1 = R^2 = H (**c**); R^1 = Me, R^2 = F (**d**);
(*a*) Et_3N, THF or DMF, Δ; (*b*) $CH_2(CN)_2$, Bu^nNH_2, NH_4OAc;
(*c*) MeOH, Δ, 2 h.

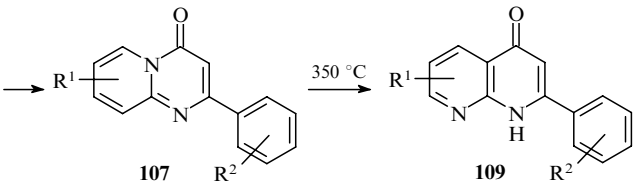
N-Aryl-1,8-naphthyridines **103** possessing antiulcerative action were synthesised by Stobbe, Claisen or Knoevenagel condensations of substituted arylaminopyridinecarbaldehydes **104** with substituted carboxylic acids and their derivatives (esters, anhydrides, sodium salts).[343–347]



R^1 = H, Alk, cyclo-Alk, Hal, MeO, CF_3, NO_2; R^2, R^3 = H, Alk, Hal, CF_3, NO_2, MeO, MeS, $(CH_2)_nCN$, $(CH_2)_nCONH_2$;
R^4 = H, Alk, Alkenyl, NH_2, CO_2H, $HO_2C(CH_2)_n$, Ar, Het; *n* = 0–5.

With the aim of designing new potential antitumour drugs, procedures were developed for the synthesis of substituted 2-aryl-1,8-naphthyridin-4(1*H*)-ones using substituted 2-aminopyridines **105** and ethyl benzoylacetates **106** as the starting compounds.[314, 315] Their condensation in the presence of polyphosphoric acid (PPA) affords the corresponding pyridopyrimidinones **107**. Compounds **107** were also prepared by cyclisation of Schiff bases **108** with monochloroacetyl chloride in the presence of triethylamine. The subsequent thermal rearrangement of pyridopyrimidinones **107** at 350 °C gives rise to 2-phenyl-1,8-naphthyridin-4(1*H*)-ones **109**. An analogous approach was also used for the preparation of the corresponding 2-naphthyl-substituted 1,8-naphthyridinones.[352]

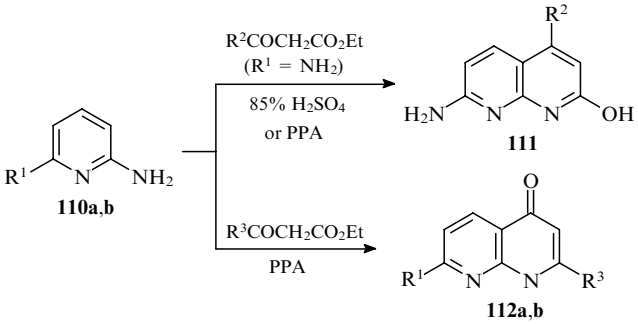




107 **109**

R^1 = H, Me, Cl, Br; R^2 = H, Me, F, Cl;
PPA is polyphosphoric acid.

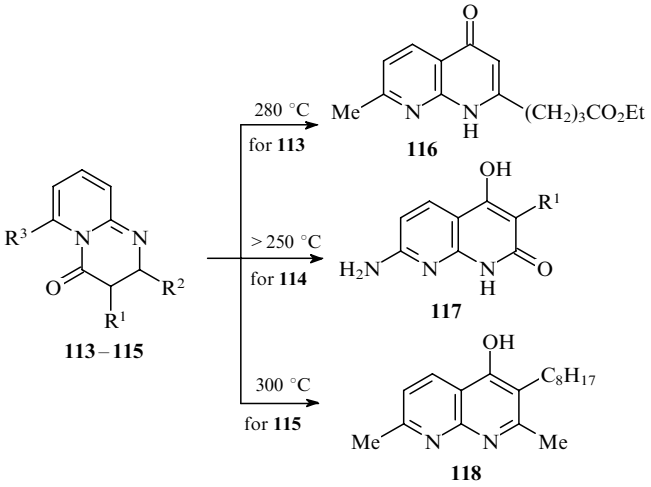
Condensation of 2-aminopyridines **110a**,**b** with β-ketoesters or dicarboxylic esters provides a promising approach to the synthesis of 1,8-naphthyridines. The reaction is carried out at high temperature in polyphosphoric acid or Dowtherm.[357–367] For example, this procedure was used for the synthesis of 7-amino-2-hydroxy-1,8-naphthyridines **111**[357] and naphthyridones **112**.[359, 367]



110a,**b** **111** **112a**,**b**

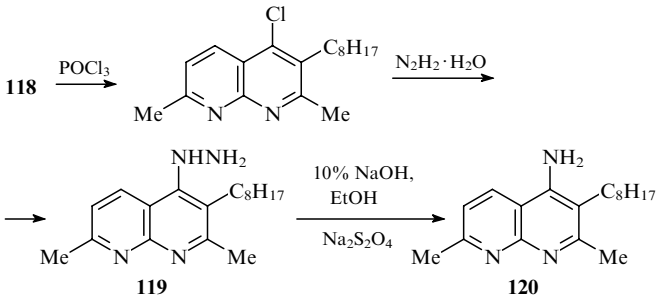
R^1 = Me (**a**), NH_2 (**b**); R^2 = Me, Pr, CF_3, $ClCH_2$, Ph;
R^3 = Me, Ph.

In some cases, pyrido[1,2-*a*]pyrimidines initially formed in analogous condensations (for example, compounds **113**–**115**) are isolated. Thermal isomerisation of these compounds affords oxo (**116**) or hydroxy derivatives (**117**, **118**) of 1,8-naphthyridines. Compounds **116**–**118** were subjected to subsequent transformations. For example, an additional ring was fused to naphthyridines **116** and **117**, and the successive reactions of naphthyridine **118** with $POCl_3$ and $N_2H_4 \cdot H_2O$ produced hydrazine **119**, which was transformed into amine **120**.[365]



113–**115** **116** **117** **118**

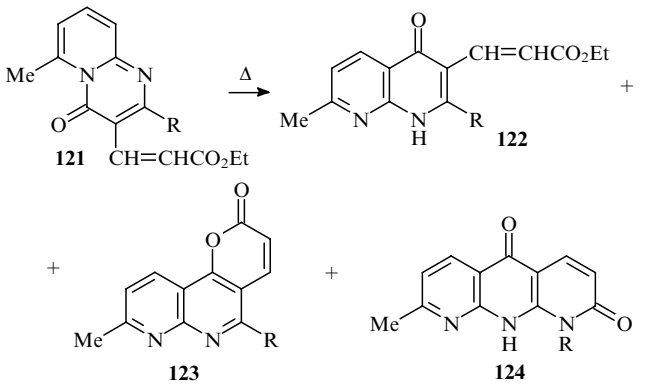
R^1 = H, R^2 = $(CH_2)_3CO_2Et$, R^3 = Me (**113**);
R^1 = H, Alk, Ph; R^2 = OH, R^3 = NH_2 (**114**);
R^1 = *n*-C_8H_{17}, R^2 = Me, R^3 = Me (**115**).



118 **119** **120**

Naphthyridine **111** (R^2 = $ClCH_2$) was covered by a patent as an agent reducing the phytotoxicity of herbicides belonging to cyclohexenones or phenoxyacetic acids.[362] Naphthyridone **112** (R^3 = Me) was used as an intermediate in the synthesis of compounds possessing antimalarial activity against *Plasmodium vinckei vinckei*.[361] Compounds **119** and **120** in doses of 0.1–5 kg hectare^{-1} exhibit fungicidal activity against phytopathogenic fungi (particularly, *Phycomyceten*) and are efficient against *Phytophtora infestans* on tomatoes and potatoes as well as against *Pseudoperonspora cubensis* on cucumbers.[363]

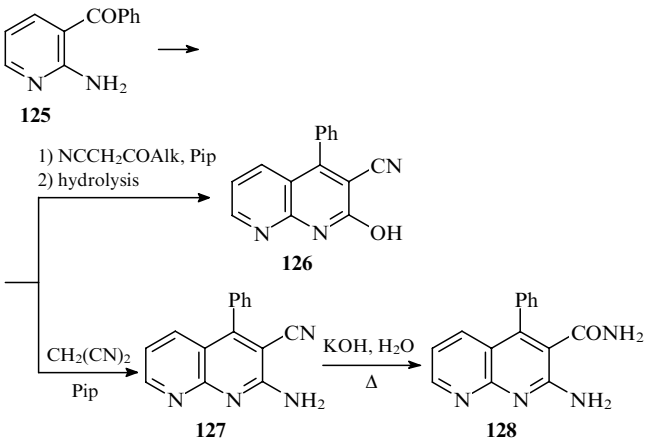
Other substituted pyridopyrimidines can also be used as starting compounds in the synthesis of 1,8-naphthyridine derivatives. For example, thermolysis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl acrylates **121** afforded 2-substituted 1,8-naphthyridin-3-yl acrylates **122**, pyranonaphthyridines **123** or anthyridines **124** depending on the nature of the substituent at position 2 of the starting pyridopyrimidine.[365]



121 **122** **123** **124**

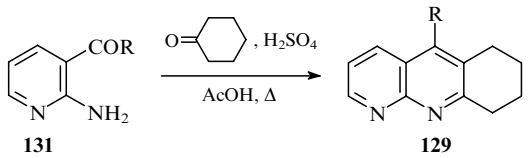
R = NHBu, Ph, Pip.

Other 2-aminopyridines were also successfully used in the synthesis of substituted 1,8-naphthyridines. For example, condensation of 2-amino-3-benzoylpyridine (**125**) with malonic acid derivatives in the presence of piperidine followed by hydrolysis of the reaction mixture affords 4-phenyl-1,8-naphthyridines **126** and **127**. Further hydrolysis of nitrile **127** gives amide **128**. Compounds **126** and **128** possess diuretic action.[330]

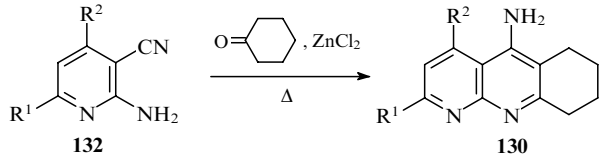


125 **126** **127** **128**

6,7,8,9-Tetrahydrobenzonaphthyridines **129** and **130** were prepared by condensation of 2-amino-3-acylpyridines **131**[366] or 2-amino-3-cyanopyridines **132**[367] with cyclohexanone.

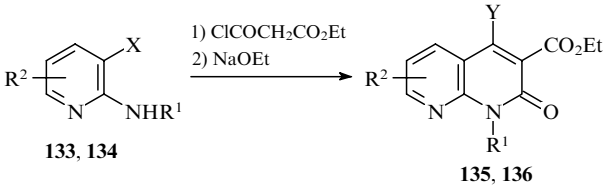


R = Me, Ph.



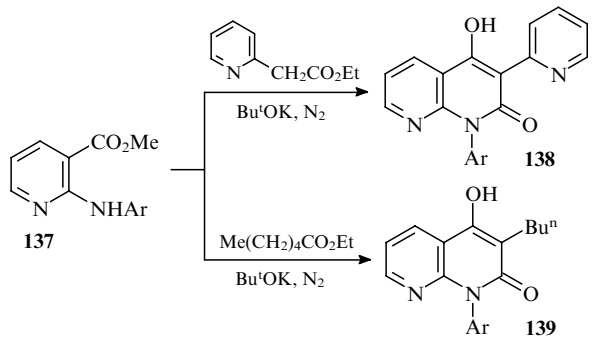
R^1, R^2 = Ph, 4-ClC_6H_4.

1,8-Naphthyridines can also be prepared by the reactions of substituted 2-alkylaminonicotinic acids with malonic acid derivatives. Cyclocondensation of nitriles **133** or esters **134** with $ClCOCH_2CO_2Et$ in anhydrous diethyl ether at 20 °C and then with EtONa in ethanol affords substituted 2-oxo-1,8-naphthyridine-3-carboxylic acids **135** and **136**, respectively. Compounds **135** were also synthesised by the reactions of nitriles **133** with a mixture of two equivalents of $(EtO_2C)_2CH_2$ and Na in anhydrous ethanol. Naphthyridinecarboxylic acids **135** and **136** were used in the synthesis of compounds which inhibit gastric secretion.[368]



X = CN (**133**), CO_2Me (**134**); Y = NH_2 (**135**), OH (**136**);
R^1 = H, Me, Et, All; R^2 = H, Me.

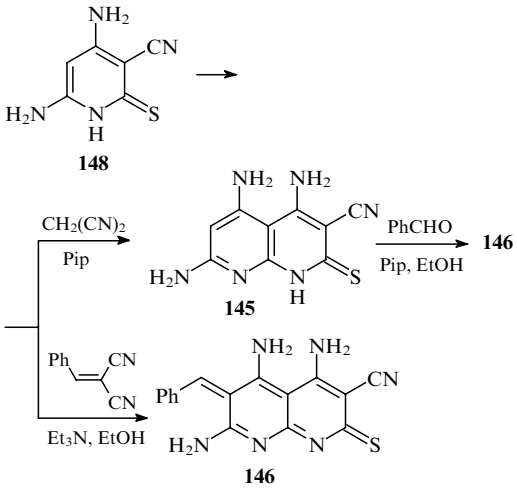
Procedures were developed for the synthesis of various 1,8-naphthyridin-2-one derivatives based on condensation of methyl 2-arylaminonicotinates **137** and carbonyl compounds containing an activated methylene group. This method was used, for example, for the preparation of naphthyridones **138** and **139** exhibiting antiallergic, anti-inflammatory and antiulcerative actions.[369–385]



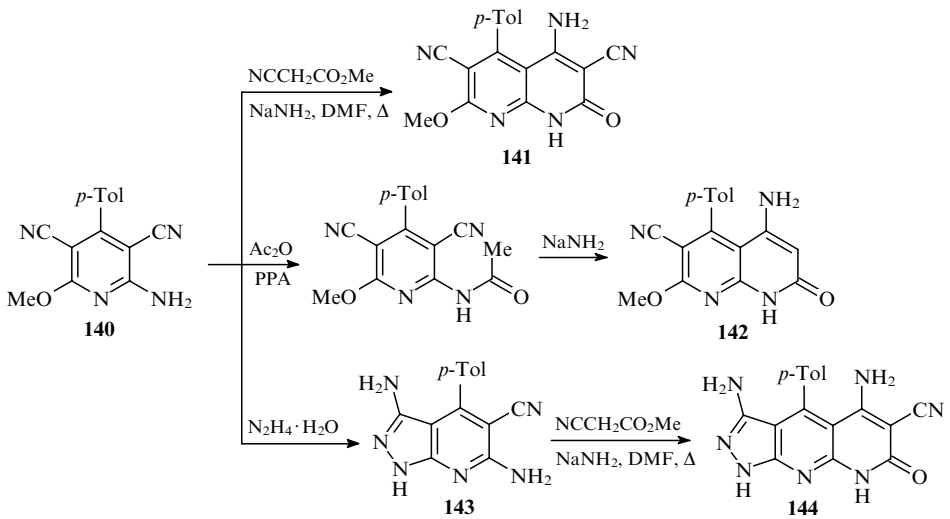
Ar = Ph, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 4-FC_6H_4, 2,4-$F_2C_6H_3$, 2-Me-3-ClC_6H_3, 3-$MeSC_6H_4$.

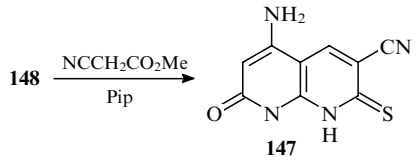
2-Amino-3,5-dicyano-6-methoxy-4-(*p*-tolyl)pyridine (**140**) was used in the synthesis of 4-amino-1,8-naphthyridin-2(1*H*)-ones **141** and **142**. Condensation of compound **140** with methyl cyanoacetate in the presence of sodium amide or acetic anhydride in polyphosphoric acid yields naphthyridones **141** and **142**. Compound **143**, which was prepared by the reaction of aminonitrile **140** with hydrazine hydrate, underwent condensation with methyl cyanoacetate to form naphthyridone **144** (Scheme 2).[385]

4,6-Diaminopyridine-2(1*H*)-thione **148** was used as the starting compound for the synthesis of amino derivatives of 1,8-naphthyridine-2(1*H*)-thiones **145**–**147**.[386, 387] The reactions of **148** with malonic acid derivatives proceed in DMF in the presence of piperidine or in ethanol in the presence of triethylamine.

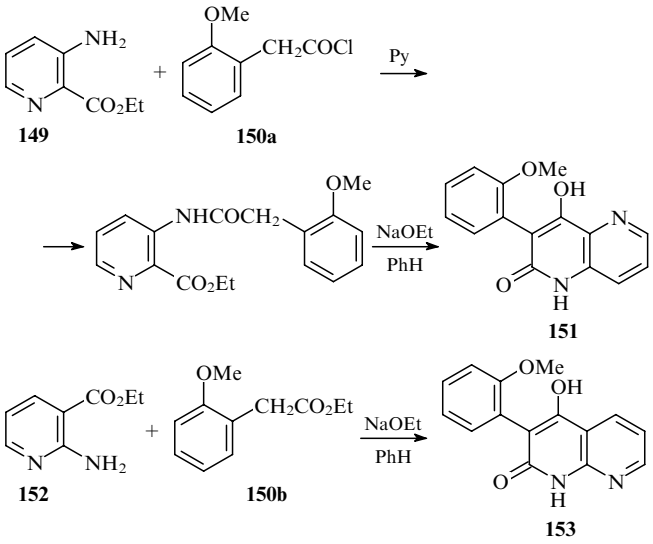


Scheme 2

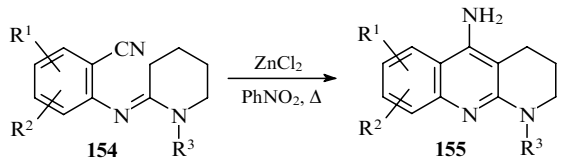




Ethyl 3-aminopyridine-2-carboxylate (**149**) reacts with 2-methoxyphenylacetyl chloride (**150a**) to form 1,5-naphthyridine (**151**). The analogous reaction of ethyl 2-aminopyridine-3-carboxylate (**152**) with ethyl 2-methoxyphenylacetate (**150b**) produces isomeric 1,8-naphthyridine (**153**).[388]



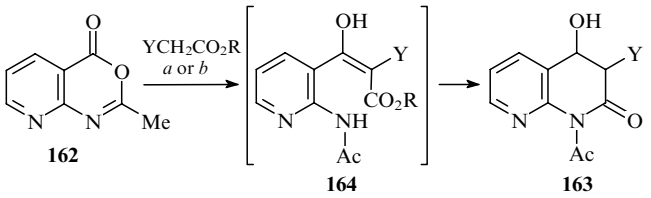
Cyclisation of substituted 2-(2-cyanophenylimino)piperidines **154** by refluxing in nitrobenzene in the presence of $ZnCl_2$ afforded 5-aminobenzonaphthyridines **155**, which were covered by a patent as drugs for the treatment of memory loss, aging and Alzheimer's disease.[389]



R^1 = H, 6-F, 6-Cl, 7-NO_2; R^2 = H, 8-Cl; R^3 = H, Ac, COPh.

A convenient regioselective procedure was developed for the synthesis of new heterocycles, *viz*., 5-phenyl-1*H*- (**156**) and 5-phenyl-3*H*-imidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-ones (**157**), starting from 2-phenylaminonicotinic acid (**158a**) or its methyl ester (**158b**).[390–394] Treatment of ester **158b** with trichloromethyl chloroformate in 1,2-dichloroethane at 80 °C affords *N*-phenyl-3-azaisatinic anhydride (**159**). The reaction of the latter with sodium hydride and ethyl nitroacetate in *N*,*N*-dimethylacetamide produces 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**160**). Chlorination of naphthyridone **160** with phosphorus oxychloride gives rise to chloride **161**, which is transformed into the target naphthyridines by successive amination, reduction and cyclisation. Imidazonaphthyridones **156** and **157** are new non-steroid anti-inflammatory drugs possessing activity analogous to that of glucocorticoids (Scheme 3).

A new efficient procedure was proposed[368,395–398] for the synthesis of 3-substituted 1,8-naphthyridine-2,4-diones, which are of considerable pharmacological interest. The reactions of 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one (**162**) with compounds containing an active methylene group in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol or in the presence of sodium hydride in anhydrous benzene produce 3-substituted 1-acetyl-1,2,3,4-tetrahydro-1,8-naphthyridine-2,4-diones **163** in yields of up to 87%.[399] Evidently, the reactions proceed through intermediates **164**.

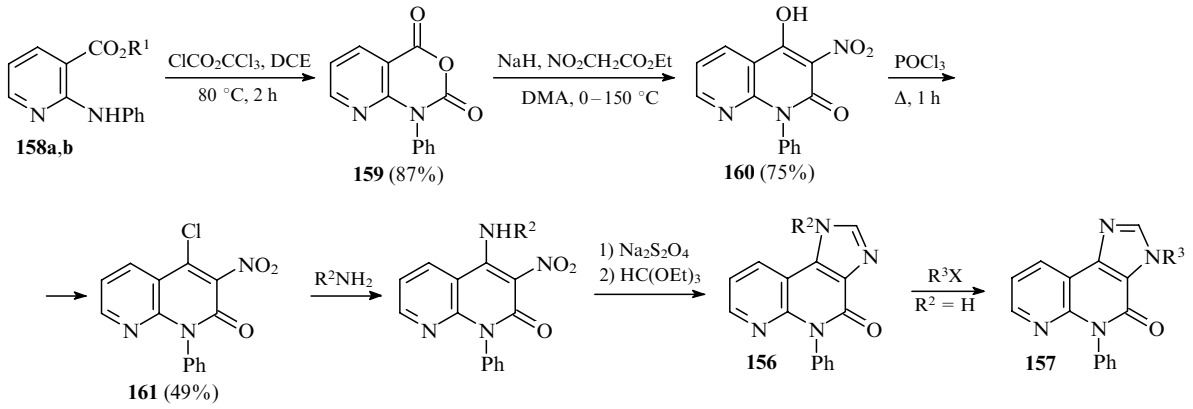


Y = EWG, R = Alk;

(*a*) Bu^tOK, Bu^tOH, 20 °C; (*b*) NaH, PhH, 20 °C

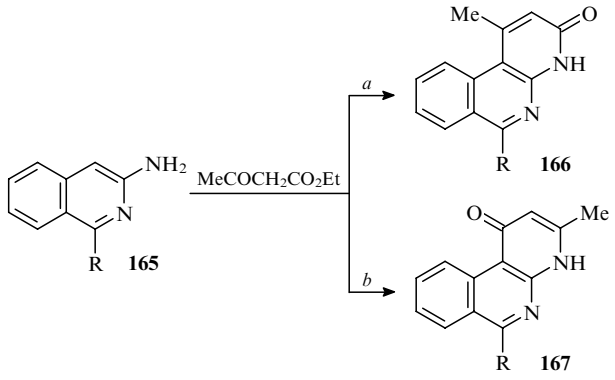
Amines of the isoquinoline series can be used as the starting compounds for the preparation of benzoannelated 1,8-naphthyridines. The reactions of 3-aminoisoquinolines **165** with ethyl acetoacetate form 4-methylbenzo[*c*][1,8]naphthyridin-2(1*H*)-ones **166** or their isomers **167** depending on the reaction conditions.[400–402]

Scheme 3



R^1 = H (**a**), Me (**b**); R^2 = H, Et, Pr^i, Bn; R^3 = Me, Et, Pr^n, Pr^i, Bu^n, Bu^t, C_6H_{13}, Bn, $CH(Me)C_6H_5$;

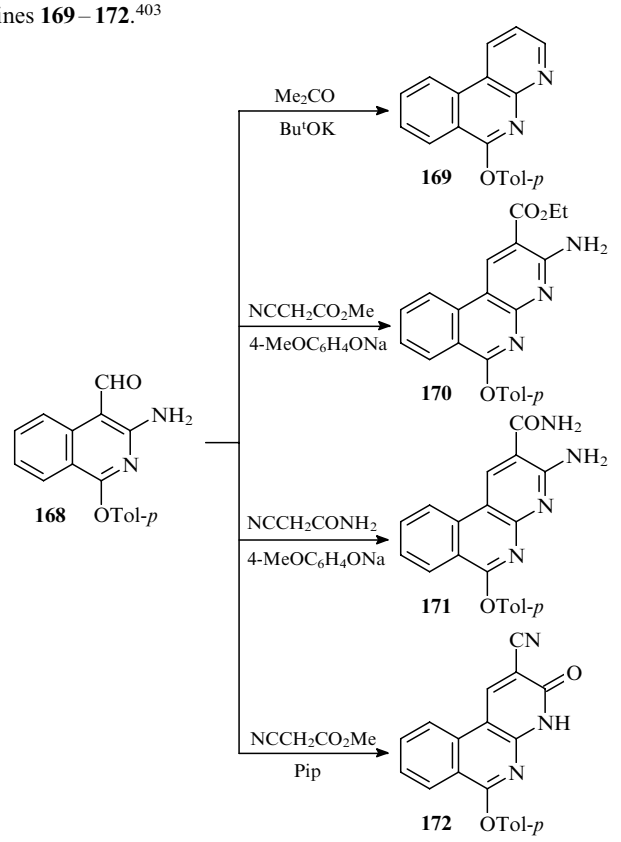
X = I, Cl, Br; DCE is 1,2-dichloroethane; DMA is *N*,*N*-dimethylacetamide.



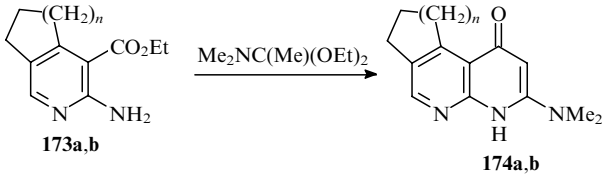
R = MeO, 4-MeC$_6$H$_4$O;

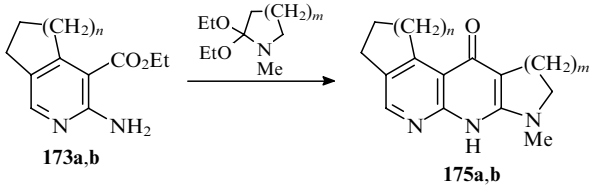
(*a*) AcOH, 150 °C; (*b*) $CaSO_4$, AcOH, EtOH.

Cyclocondensation of 3-amino-1-(*p*-tolyloxy)isoquinoline-4-carbaldehyde **168** with acetone or cyanoacetic acid derivatives in the presence of bases yields substituted benzo[*c*][1,8]naphthyridines **169**–**172**.[403]



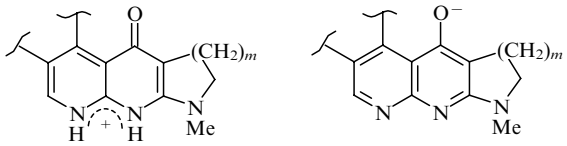
The reaction of ethyl 2-amino-5,6-dihydro-4*H*-cyclopenta[*c*]-nicotinate (**173a**, $n = 1$) with *N*,*N*-dimethylacetamide diethyl acetal produces 1,4-dihydro-4-oxo-1,8-naphthyridine derivative **174a**. Reactions with methylbutyro-, -valero- and -caprolactam diethyl acetals afford tetracyclic compounds **175a**. Similar reactions giving rise to naphthyridone **174b** ($n = 2$) and tetracyclic compounds **175b** were also performed using the cyclohexane analogue of compound **173**.[404]





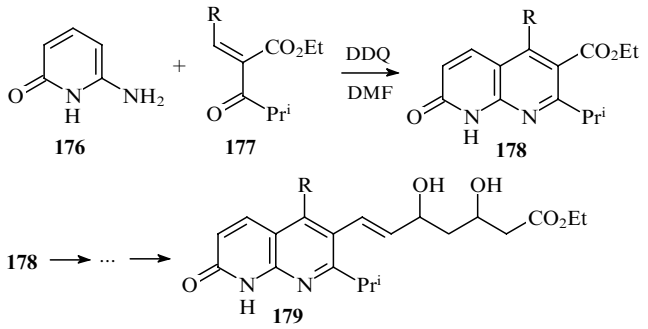
n = 1 (**a**), 2 (**b**); m = 1–3.

Protonation of naphthyridones **175a**,**b** was studied by UV and ^{1}H and ^{13}C NMR spectroscopy.[404] It was found that protonation occurs at the carbonyl group to give the cationic form **A**. In 70% DMF, the ionisation constants of naphthyridones **175a**,**b** depend on the size of the saturated cyclic fragments of the molecules, which is associated with steric factors, such as a change in steric accessibility of the polar groups of the cationic (**A**) and anionic (**B**) forms to solvation.[404]



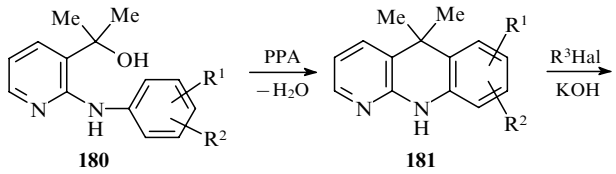
m = 1–3.

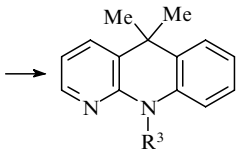
1,8-Naphthyridinones were also synthesised starting from 6-aminopyridin-2-one (**176**).[405] Its condensation with enones **177** in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in DMF afforded ethyl 2-oxo-1,8-naphthyridine-6-carboxylate (**178**). This naphthyridine was transformed into compound **179** in five steps. This compound was covered by a patent as a drug for the treatment of hyperlipoproteinemia, atherosclerosis and lowering of blood cholesterol levels.[405]



R = Ar, Het.

5,5-Dimethyl-5,10-dihydrobenzo[*b*][1,8]naphthyridines **181** were prepared in yields of up to 87% by intramolecular cyclisation of 2-arylamino-3-(1-hydroxy-1-methylethyl)pyridines **180** in polyphosphoric acid. Alkylation of benzonaphthyridines **181** with dialkylaminoalkyl halides in the presence of KOH in toluene gives rise to 10-substituted benzonaphthyridines **182** (yields of up to 88%), which are analogues of the corresponding acridines possessing a broad spectrum of biological activities.[406]

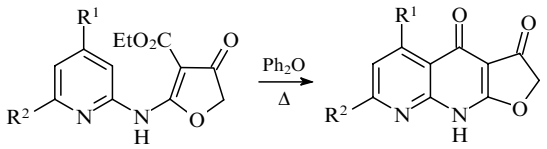




182

R^1 = H, 7-MeO, 7-EtO, 7-Cl, 8-Cl, 9-Cl; R^2 = H, 9-Me, 9-Cl; R^3 = $CH_2CR^4(CH_2)_nNR^5R^6$, n = 0, 1; R^4 = H, Me; R^5, R^6 = Me, Et, Pr^i, Bu^n, Bn; R^5-R^6 = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2NMe(CH_2)_2$, $(CH_2)_2N(CH_2CH_2OH)(CH_2)_2$, $(CH_2)_3CO(CH_2)_2$; Hal = Cl, Br.

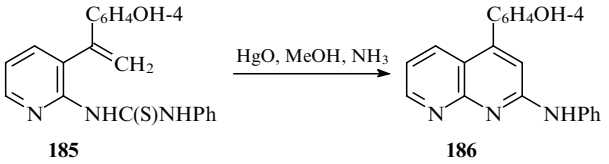
Refluxing of 2-(3-ethoxycarbonyl-4-oxo-4,5-dihydrofur-2-yl)aminopyridines **183** in diphenyl ether leads to their cyclisation to furo[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-diones **184**, which exhibit antiallergic activity.[407]



183 **184** (78%–85%)

R^1, R^2 = H, Me.

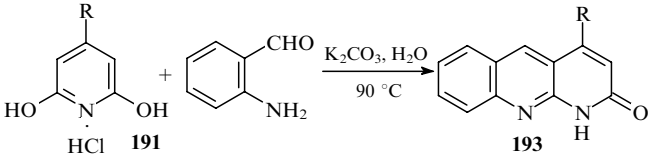
Cyclisation of substituted thiourea **185** occurs under the action of mercury oxide in methanol saturated with ammonia to give 1,8-naphthyridine derivative **186**.[408]



185 **186**

Photochemical cyclisation (DRL-400 mercury lamp, 60% *tert*-butyl alcohol, 20 °C, 10 h) of 8-chloro-1-(2-pyridylamino)naphthalene (**187**) was studied. The reaction proceeds non-selectively to form C–C and C–N bonds and produces new polyannelated heterocyclic systems, *viz*., 7*H*-7,8-diazabenzo[*de*]anthracene (**188**) containing the 1,8-naphthyridine fragment, dimer **189** and pyrido[1,2-*a*]perimidine (**190**). Compounds **188**–**190** were separated by chromatography on silica gel (Scheme 4).[409,410]

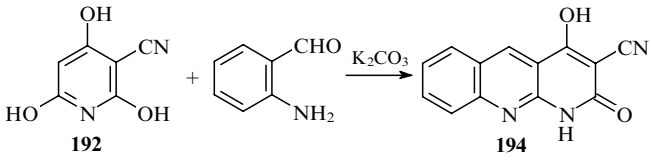
Hydroxy derivatives of the pyridine series were used as the starting compounds in the synthesis of annelated 1,8-naphthyridines. Benzo[*b*][1,8]naphthyridines **193** and **194** were synthesised



191 **193**

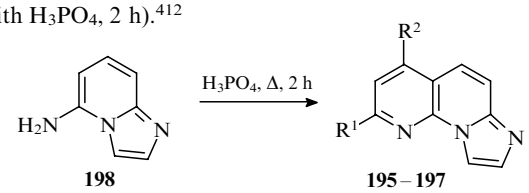
R = H, Me.

by Friedländer condensation of hydroxypyridines **191** and **192**, respectively, with 2-aminobenzaldehyde.[411]



192 **194**

Imidazo[1,2-*a*]naphthyridines **195**–**197** were prepared by the reaction of 5-aminoimidazo[1,2-*a*]pyridine (**198**) with 1,1,3,3-tetramethoxypropane, acetoacetaldehyde dimethyl acetal or acetylacetone under the conditions of the Combes reaction (reaction with H_3PO_4, 2 h).[412]

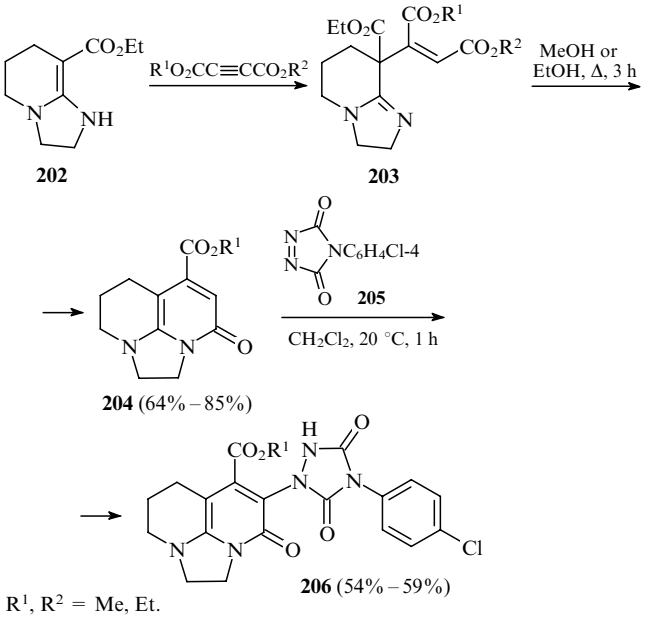


198 **195**–**197**

Reagent	Compound	R^1	R^2
$(MeO)_2CHCH_2CH(OMe)_2$	**195**	H	H
$MeCOCH_2CH(OMe)_2$	**196**	Me	H
$MeCOCH_2COMe$	**197**	Me	Me

Triazolonaphthyridines **199** and **200** were synthesised by condensation of Schiff base (**201**) of the 1,2,4-triazolo[4,3-*a*]pyridine series with malononitrile or its benzylidene derivative in the presence of organic bases (Scheme 5).[413]

The enamino fragment of hexahydroimidazo[1,2-*a*]pyridine-8-carboxylic acid **202** reacts with the triple bond of acetylenedicarboxylates to form compounds **203** in quantitative yields. Their

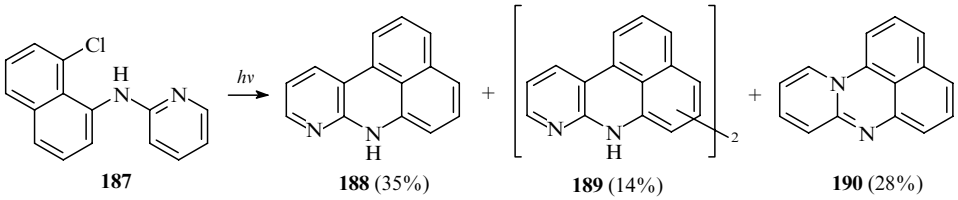


202 **203** **204** (64%–85%) **205** **206** (54%–59%)

R^1, R^2 = Me, Et.

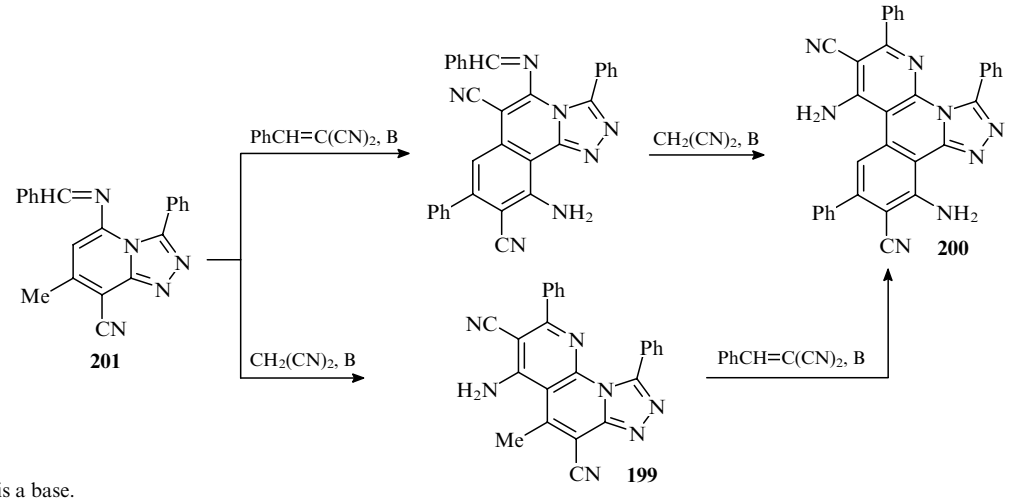
cyclisation (20 °C, 2 days, then refluxing in MeOH or EtOH, 3 h) gives rise to partially hydrogenated imidazonaphthyridines **204**, which react with dione (**205**) to give 6-(1,2,4-triazolidin-1-yl)imidazo[1,2,3-*ij*][1,8]naphthyridines (**206**).[414]

Scheme 4



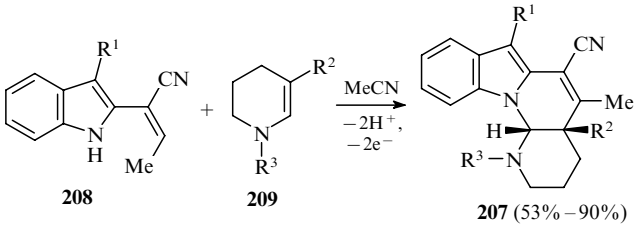
187 **188** (35%) **189** (14%) **190** (28%)

Scheme 5



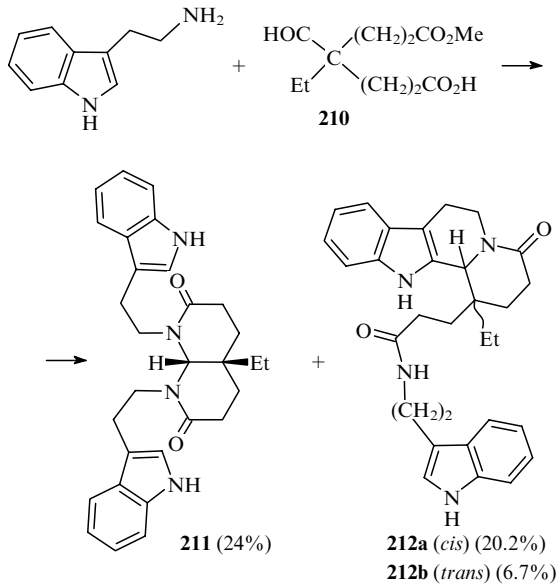
B is a base.

Hexahydroindolo[1,2-*a*]-1,8-naphthyridines **207** containing *cis*-fused rings were synthesised with high stereoselectivity by the electrochemical [4 + 2]-cycloaddition of 2-vinylindoles **208** and β-substituted enamines (**209**) of the tetrahydropyridine series in acetonitrile.[415]

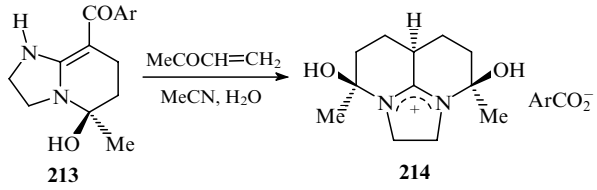


R^1 = Me, $(CH_2)_2OEt$; R^2 = CN, CO_2Me; R^3 = H, Me.

The Pictet–Spengler reaction of tryptamine with aldehyde **210** produces the bisindole derivative of decahydronaphthyridine-2,7-dione **211** along with two isomeric tryptamides **212a** (*cis*-1-Et) and **212b** (*trans*-1-Et).[416]

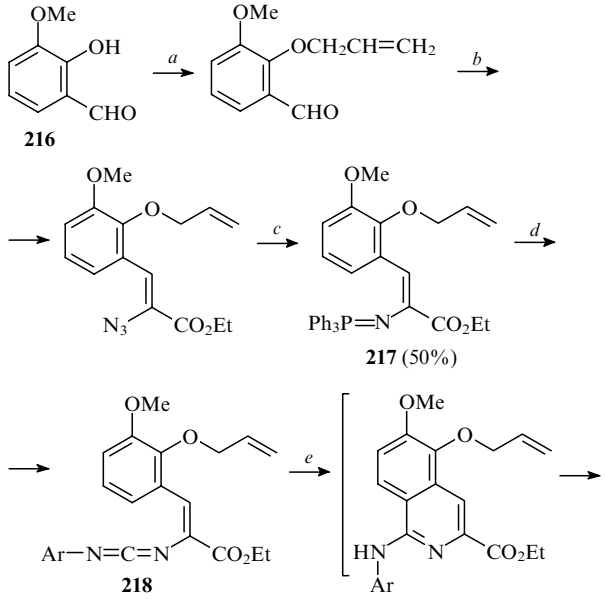


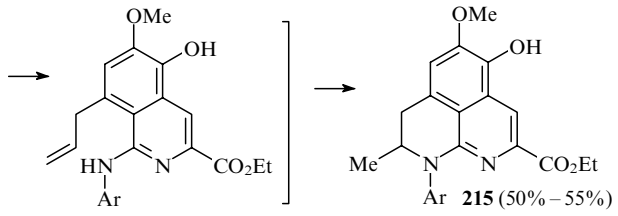
The reaction of imidazo[1,2-*a*]pyridine derivative **213** with a twofold excess of methyl vinyl ketone in acetonitrile proceeds with high stereoselectivity to form exclusively *cis*-dihydroxyimidazo[1,2,3-*ij*][1,8]naphthyridine **214**.[417]



Ar = Ph, 2-furyl, 2-thienyl.

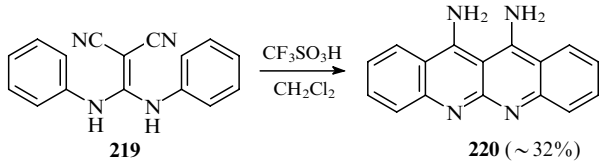
A one-step procedure was developed for the synthesis of the previously unknown dihydro-*1H*-1,9-diazaphenalene **215**, which also contains the 1,8-naphthyridine fragment.[418] The synthesis scheme involves O-allylation, condensation of the reaction product with ethyl azidoacetate and the Staudinger reaction with triphenylphosphine. This procedure was used for the preparation of iminophosphorane **217** from commercially available 2-hydroxy-3-methoxybenzaldehyde (**216**). The reactions of compound **217** with aromatic isocyanates produce carbodiimides **218**, whose thermolysis yields diazaphenalenes **215**.



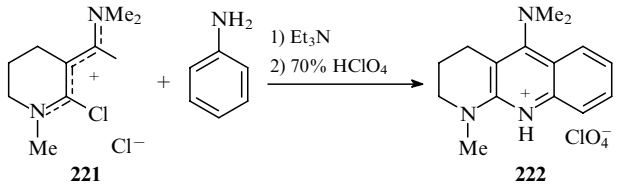


Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4;
(*a*) $BrCH_2CH=CH_2$, K_2CO_3, Me_2CO, Δ; (*b*) $N_3CH_2CO_2Et$, NaOEt, EtOH, −15 °C; (*c*) PPh_3, Et_2O, 20 °C; (*d*) ArNCO, PhMe, 20 °C, 1 h; (*e*) sealed tube, PhMe, 150–160 °C, 12 h.

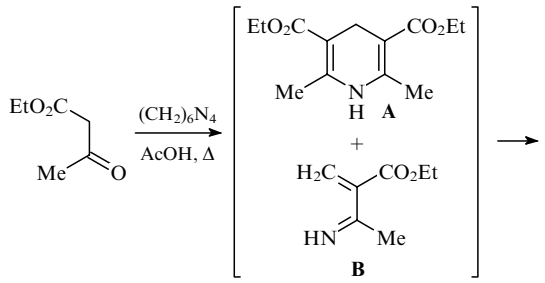
Cyclisation of 1,1-bisanilino-2,2-dicyanoethylene (**219**) under the action of trifluoromethanesulfonic acid in dichloromethane giving rise to 11,12-diaminodibenzo[*b*,*g*][1,8]naphthyridine (**220**) provides an example of the synthesis of annelated 1,8-naphthyridines.[419]

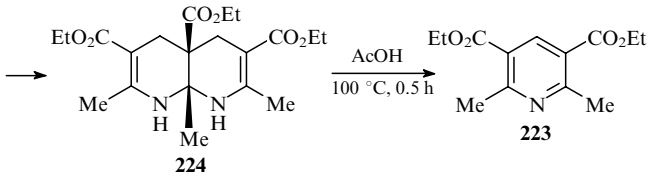


Condensation of iminium salt **221** with aniline in the presence of triethylamine occurs regioselectively. The subsequent replacement of the anion in the presence of 70% $HClO_4$ affords linearly annelated cycloadduct **222**.[420]

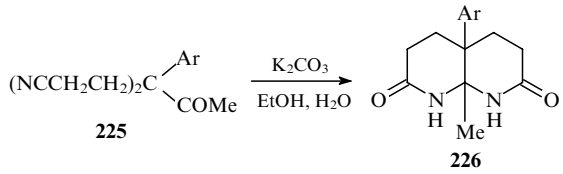


In the study,[421] diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**223**) was synthesised by the Hantzsch reaction of ethyl acetoacetate with hexamethylenetetramine (AcOH, 100 °C). In the course of the reaction, symmetrical bicyclic naphthyridine derivative **224** was detected. According to the X-ray diffraction data, the rings in compound **224** are *cis*-fused and adopt an envelope conformation. It was hypothesised that compound **224** is generated as a result of diene condensation of the intermediates, *viz*., 1,4-dihydropyridine **A** and heterodiene **B**, derived *in situ* from ethyl 2-methyleneacetoacetate and ammonia. The low yield of naphthyridine derivative **224** (2.3%) is attributable to its instability in AcOH. At 100 °C, the transformation of this derivative into pyridine **223** is completed in 0.5 h, although compound **224** is rather stable in EtOH, Pr^iOH and DMF.





Hydrogenated 1,8-naphthyridines were synthesised by the reaction of dinitriles **225** with K_2CO_3 in aqueous alcohol. Intramolecular cyclisation affords 4*a*-aryl-8*a*-methyl-2,7-dioxo-1,8-naphthyridines **226**.[422]



Ar = Ph, 3,4-$(MeO)_2C_6H_3$.

III. Physicochemical properties and reactivities of 1,8-naphthyridine derivatives

Data on the structures, physicochemical properties and reactivities of pyridopyridines, including 1,8-naphthyridine, published up to 1984 inclusive, have been analysed in sufficient detail in the reviews.[1,423–425]

1. Physicochemical properties

Studies on the physicochemical properties of 1,8-naphthyridines are being continued. 1,8-Naphthyridinium 1-tetraphenylborate,[426] 4-oxo-1,4-dihydro-1,8-naphthyridinium methanesulfonate[427] and some other derivatives[428–433] were studied by X-ray diffraction.

The behaviour of bromo-substituted isomeric naphthyridines, which include 2-amino-6-bromo-, 2-amino-3,6-dibromo- and 4-bromo-2-hydroxy-1,8-naphthyridines, was investigated by mass spectrometry.[434] It was demonstrated that fragmentation of aminobromonaphthyridines under electron impact follows three main pathways.

1. Elimination of the $Br^{\bullet}$ radicals followed by successive elimination of two HCN molecules (with high intensity) from the molecular ions.

2. Elimination of the HCN molecule followed by liberation of $Br^{\bullet}$ and HCN (with lower intensity).

3. Elimination of the HCN molecule can also be accompanied by competitive liberation of $Br^{\bullet}$ and HCN.

The fragmentation of bromohydroxynaphthyridines follows two main pathways: liberation of $Br^{\bullet}$ accompanied by elimination of CO and two HCN molecules or liberation of CO accompanied by competitive elimination of $Br^{\bullet}$, HCN and C_2H_2.

Mass spectra of aminonitro derivatives of naphthyridines were also studied.[435] Mass spectrometry was used for investigation of the structures and decomposition of the isomeric $[M-HCN]^{-\bullet}$ and $[M-2\,HCN]^{-\bullet}$ ions formed upon fragmentation of naphthyridines and benzoazines.[436] It was found that the $[M-2\,HCN]^{-\bullet}$ ions can exist as two isomeric forms, one of which is typical of naphthyridines, whereas the other is characteristic of benzoazines.

The absorption and transmission spectra of 1,8-naphthyridines were investigated in the region of 50 000–20 000 cm^{-1} in solutions and various mixed crystals at 4.2 and 300 K.[437] The $\pi^*-\pi$-band system of 1,8-naphthyridines is analogous to the corresponding bands in the spectra of the related naphthalene molecule taking into account perturbations caused by the replacement of the C atoms with N. The position of the long-wavelength

$\pi^* - \pi$ band at 27 000 cm^{-1} corresponds to that predicted based on calculations by the extended Hückel method. The bands at 31 600 – 31 900 cm^{-1} were tentatively assigned to the second $\pi^* - \pi$ transition.

With the aim of elucidating the influence of substituents on the absorption spectra, the UV spectra (in methanol) of 1,8-naphthyridines monosubstituted at positions 2 (Me, Cl, Br, OMe, OEt, SMe, NH_2, OH or SH as the substituent), 3 (Me, Cl, Br, NO_2 or NH_2 as the substituent) or 4 (Me, Cl, Br, OMe, OEt, OH or SH as the substituent) were examined.[438]

The electric dipole moment of 1,8-naphthyridine in benzene was determined (4.10 D).[439] The ESR spectrum of hexahydro-1,8-naphthyridinetetrazole was measured.[440]

Homonuclear 2D *J*-resolved ^1H NMR spectra of 2-(2-pyridyl)-1,8-naphthyridine were measured and a complete assignment of the resonances was made.[441]

The ^1H and ^{13}C NMR spectra of imidazo[1,2-*a*][1,8]naphthyridine were analysed based on the results of quantum-chemical calculations using the CNDO/2 method.[442]

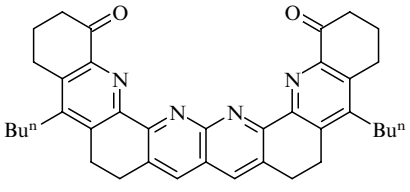
Complexes of the antitumour antibiotics naphthyridinomycins with DNA were investigated by molecular mechanics methods (molecular simulation).[443] It was found that the nature of the substituent at the C(11) atom as well as the stereoconfiguration of the C(7) centre are of importance for biological activity of naphthyridinomycins. The antibacterial activities of various substituted 1,8-naphthyridines,[444] including 2-phenyl-1,8-naphthyridin-4-one derivatives, were calculated using the QSAR method.[445]

The character of deuterium distribution in isotope exchange products of 1,8-naphthyridine and its methyl, hydroxy, amino and nitro derivatives indicates that the rate and pathway of this process depend on the pH of the medium as well as the nature and position of the substituent.[446] In neutral D_2O and a D_2O – DCl mixture, deuterium atoms are replaced with protons exclusively at positions 2 and 7. In D_2O solutions containing NaOD, deuterium atoms are replaced with protons in all positions of the naphthyridine system. In neutral D_2O, the replacement of the protons in monomethyl-substituted 1,8-naphthyridines occurs predominantly in the *ortho* positions with respect to the nitrogen atoms (positions 7 and 2, 7). The high reactivity of these positions is determined by the inductive effect of the substituent.

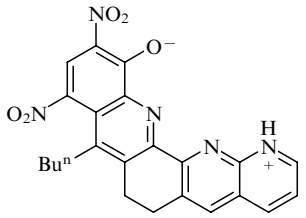
A spectrophotometric procedure [447] and a modified gas-chromatographic method [448] were devised for analysis of nalidixic acid **36**. Drug forms for intramuscular injection [449] and sublimed drugs for parenteral use [450] are available. These drug forms contain the gyrase inhibitor from 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives as the active component.

The complexation properties of naphthyridines are widely used for analytical purposes, primarily, in medicine. A highly sensitive diagnostic was proposed [431] for bacterial infectious diseases based on scanning electron microscopy. Complexes of antibiotics of the 1,8-naphthyridin-4-one series or their salts with ^{99m}Tc, ^{67}Ga, ^{111}In, ^{113m}In and other radionuclides are used for revealing inflammatory focus. These compounds are involved in parenteral drug forms.[451]

Polycyclic compound **227**, which forms stable complexes with urea, guanidine, amidines and their derivatives, is covered by patents.[452, 453] These complexes were used in biological investigations. Receptor betaine molecule **228** was constructed for diagnostic tests for blood (serum) creatinine and renal insufficiency.

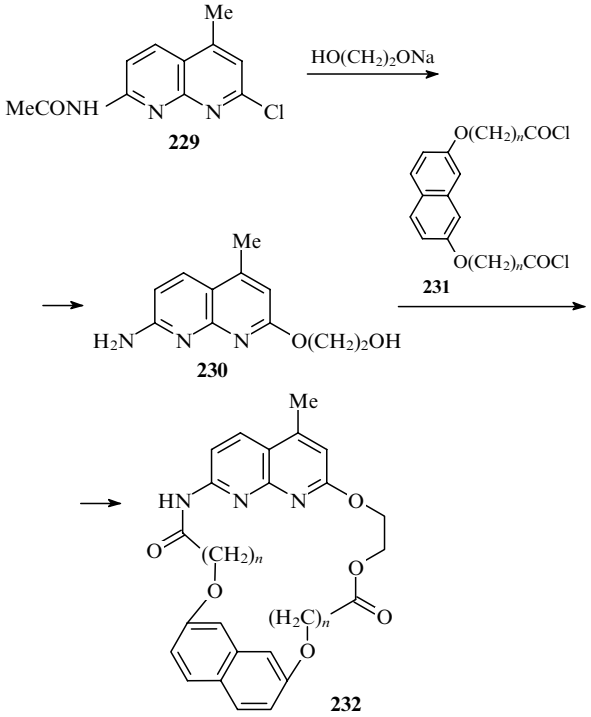


227



228

New guanine receptors were prepared based on 7-acetylamino-2-chloro-4-methyl-1,8-naphthyridine (**229**).[454] Amino alcohol **230** was prepared by the reaction of compound **229** with an excess of sodium 2-hydroxyethoxide. Compound **230** reacts with dicarboxylic acid chlorides **231** under high dilution conditions to form naphthyridine macrocycles **232**.



229

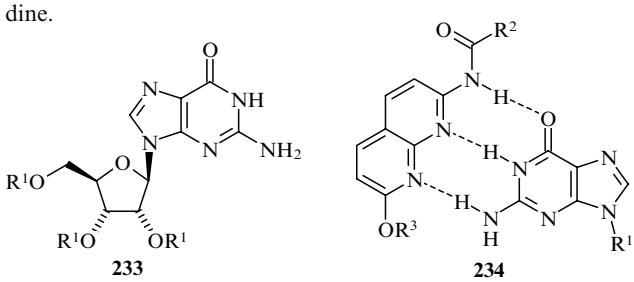
230

231

232

$n = 2, 3$.

It was demonstrated that the addition of 2′,3′,5′-tri-*O*-pentanoylguanosine (**233**) to a solution of macrocyclic compound **232** in $CDCl_3$ causes pronounced changes in the ^1H NMR spectra of both compounds: the resonances of the NH and NH_2 groups are shifted downfield, whereas all six resonances of the naphthalene system are shifted upfield. The assumed [454] structure of the complex consists of two molecules linked *via* three hydrogen bonds (analogous to the structure of complex **234**), and the naphthalene system forms a complex with guanine. The constant of association of compounds **232** and **233** is four times as high as that of the guanine complex with unsubstituted 1,8-naphthyridine.

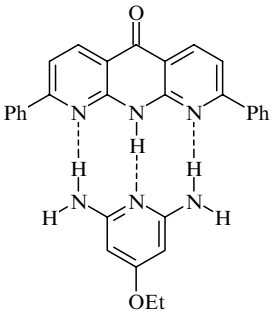


233 **234**

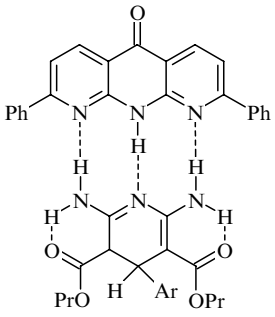
R^1 = C(O)Bu^n; R^2 = H, MeCO, Pr^{n}CO; R^3 = Cl, OEt, O(CH$_2$)$_2$OH.

The structures of other complexes based on 1,8-naphthyridine and pyrido[2,3-*b*][1,8]naphthyridine (1,9,10-anthyridine) derivatives containing three hydrogen bonds each were established.[331, 359, 362, 454–459]

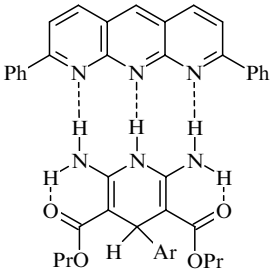
1,9,10-Anthyridine was used for the synthesis of analogous stable complexes **235**–**237**.[456]



235



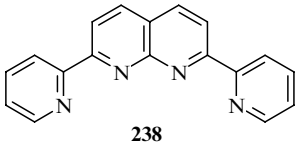
236



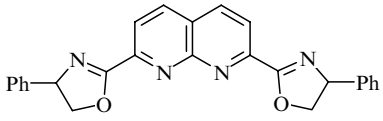
237

Ar = 2-$NO_2C_6H_4$ (**236**), 3-$NO_2C_6H_4$ (**237**).

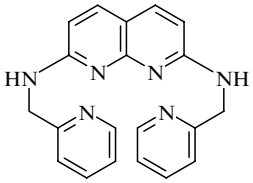
In recent years, 1,8-naphthyridine derivatives have attracted growing interest as promising ligand systems, which coordinate metal ions of different groups of the Periodic table, such as Cu,[460–462] Au,[463, 464] Zn,[465–467] Hg,[468] Mo,[469, 470] Fe,[471] Co,[472] Ni,[473] Ru,[474–477] Rh,[478, 479] Pd,[480] Pt,[480, 481] Eu and Tr.[482] The crystal structures of some complexes were studied by X-ray diffraction analysis.



238



239



240

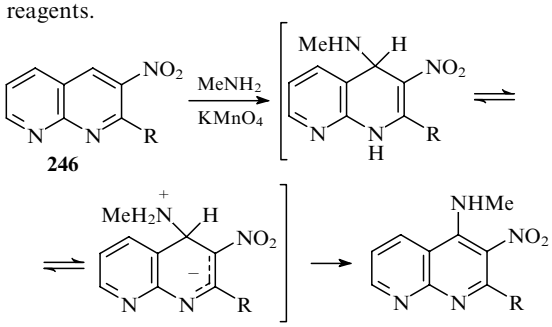
Various ligands based on 1,8-naphthyridines, including polydentate binuclear (compounds **238**,[460] **239**,[483] **240**[484]) and other compounds,[485, 486] were used for complexation with these metal ions.

2. Reactions of 1,8-naphthyridine derivatives

Among nitrogen-containing heterocyclic systems containing the 1,8-naphthyridine fragment, the above-mentioned 1,9,10-anthyridines, which are triaza analogues of anthracene, have attracted considerable attention. Earlier, these compounds have been synthesised according to multistep procedures starting from pyridine derivatives, such as 2,6-diaminopyridine,[487–491] 2,6-diamino-3,5-diformylpyridine,[492] *etc*.[493, 494] Later on, 1,8-naphthyridine derivatives became easily accessible,[316, 322, 358] which made it possible to simplify procedures.

Some transformations of 1,9,10-anthyridines were also described. 7-Nitroanthyridine-2,6-dione (**242**) or 3,7-dinitroanthyridine-2,6-dione (**243**) can be prepared by nitration of anthyridine-2,6-dione (**241**) with various amounts of a mixture of concentrated sulfuric and nitric acids (100 °C, 0.5–3 h). Treatment of nitro derivative **242** with sodium dithionite (in a 5% NaOH solution) gives rise to 7-aminoanthyridine-2,6-dione (**244**) in quantitative yield. The reaction with phosphorus pentasulfide in anhydrous pyridine produces 7-aminoanthyridine-2,6-dithione (**245**) (Scheme 6).[495]

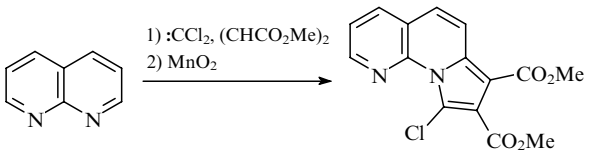
3-Nitro-1,8-naphthyridines (**246**) and their derivatives were subjected to amination at position 4 using liquid ammonia and potassium permanganate[496] or liquid methylamine and potassium permanganate[497–499] as aminating systems. Amination of naphthyridines **246** (−7 °C, 0.5 h) affords 4-methylamino-3-nitro-1,8-naphthyridines (**247**) in 50%–90% yields.[497, 498] Quantum-chemical calculations demonstrated that the reaction is controlled by interactions of frontal molecular orbitals of the reagents.



246 **247**

R = H, OH, OMe, Cl, NH_2, NHMe, NHPh.

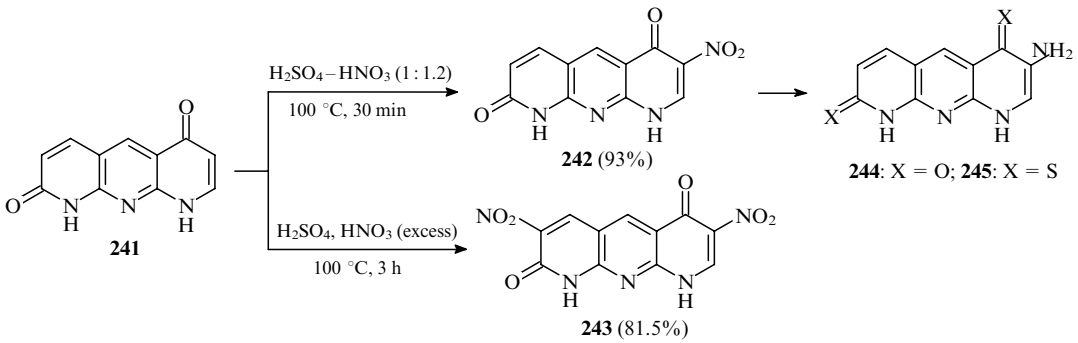
The reaction of 1,8-naphthyridine with dichlorocarbene and dimethyl maleate followed by oxidation of the reaction mixture containing the intermediate cycloadduct with manganese dioxide



248

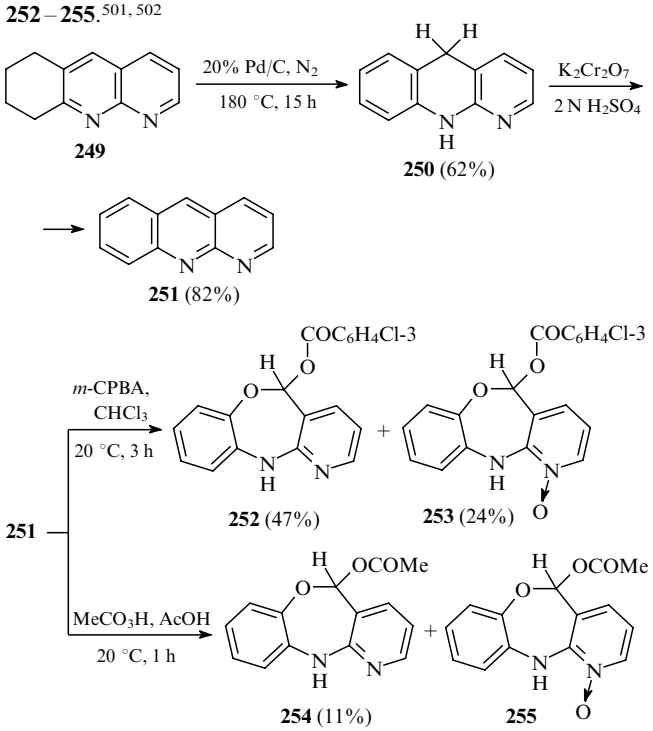
produced dimethyl 1-chloropyrrolo[1,2-*a*][1,8]naphthyridine-2,3-dicarboxylate (**248**) in 11% yield.[500]

Scheme 6

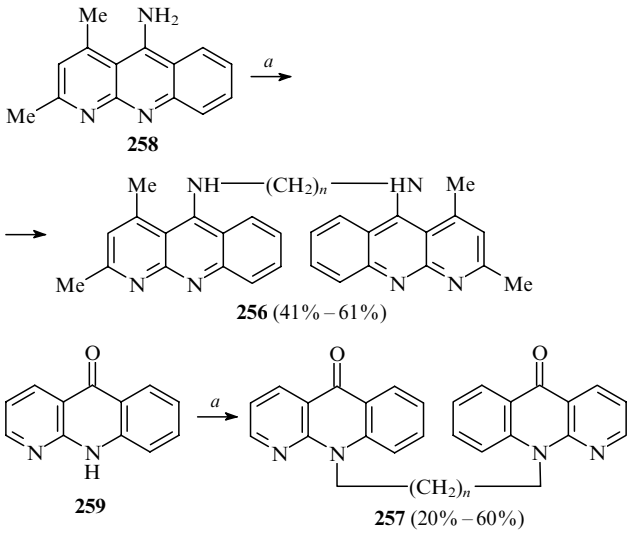


241 **242** (93%) **243** (81.5%) **244**: X = O; **245**: X = S

Dehydrogenation of 5,6,7,8-tetrahydro-1,9-diazaanthracene (**249**) over 20% Pd/C in diphenyl ether or *p*-cymene (250 °C, 3 h) affords 9,1-dihydro-1,9-diazaanthracene (**250**), whose oxidation with potassium dichromate in dilute H_2SO_4 (60 °C, 10 min) gives rise to benzo[*b*][1,8]naphthyridines (**251**). Oxidation of benzonaphthyridine **251** with peroxy acids yields 1,4-oxazepines **252** – **255**.[501, 502]

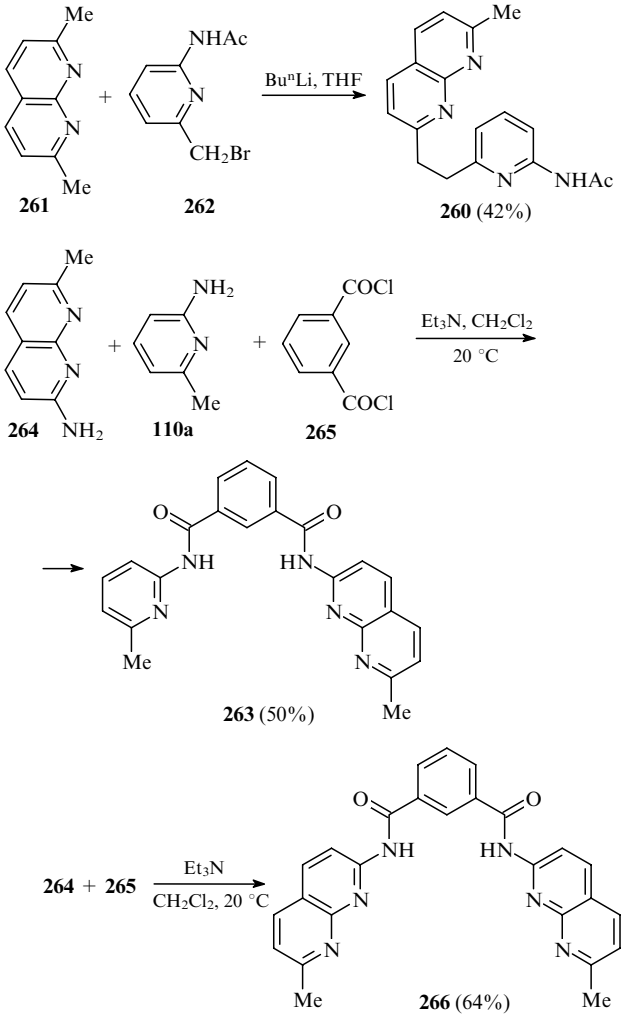


New bisnaphthyridines **256** and **257** containing the 5-amino-2,4-dimethylbenzo[*b*][1,8]naphthyridine or benzo[*b*][1,8]naphthyridone chromophores were synthesised in a phase-transfer system by the reaction of aminobenzonaphthyridine **258** or dihydrobenzonaphthyridone **259** with alkylene dibromides.[503] Such bisintercalates are of interest as potential antitumour drugs.

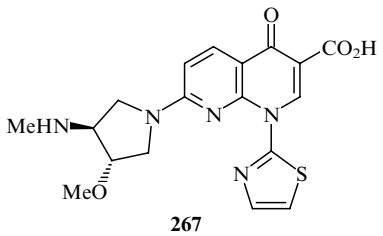


n = 3, 6, 8, 10; *a*) $Br(CH_2)_nBr$, TBAB, PhMe, 50% KOH, Δ; TBAB is tetrabutylammonium bromide.

Procedures were developed for the synthesis of new types of simple receptors based on substituted 1,8-naphthyridines. These receptors serve as carriers for transport of biologically important organic substrates (urea, amino acids, hydroxy acids) into cells. *N*-{6-[2-(7-Methyl[1,8]naphthyridin-2-yl)ethyl]pyridin-2-yl}acetamide (**260**) was prepared by the reaction of 2,7-dimethyl-1,8-naphthyridines **261** with n-butyllithium (2 equiv., THF, −78 °C) and 2-*N*-acetylamino-6-bromomethylpyridine (**262**). Another carrier, *viz*., *N*-(7-methyl[1,8]naphthyridin-2-yl)-*N*′-(6-methylpyridin-2-yl)isophthalamide (**263**), was synthesised from 2-amino-7-methyl-1,8-naphthyridine (**264**), 2-amino-6-methylpyridine (**110a**) and isophthaloyl chloride (**265**) in dry dichloromethane in the presence of triethylamine. *N*,*N*′-Bis(7-methyl[1,8]naphthyridin-2-yl)isophthalamide (**266**) was prepared from naphthyridines **264** and chloride **265** under analogous conditions. Isophthalamides **263** and **266** were used for the determination of L-(+)-tartartic acid as complexes (1 : 1) soluble in chloroform.[504, 505]

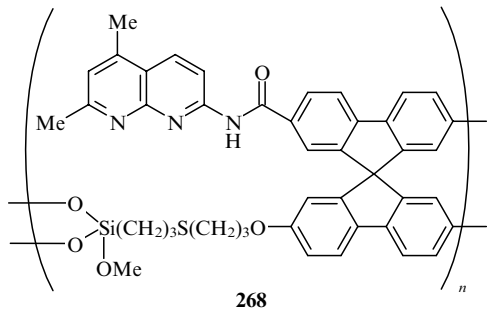


The new antitumour drug Ag-7352 (**267**) was designed based on 1,8-naphthyridin-4-one-3-carboxylic acid.[506, 507] An efficient stereospecific procedure was specially developed for the synthesis of (*S*,*S*)-3-methoxy-4-methylaminopyrrolidine, which is the key reagent in the synthesis of naphthyridine **267**.[508]



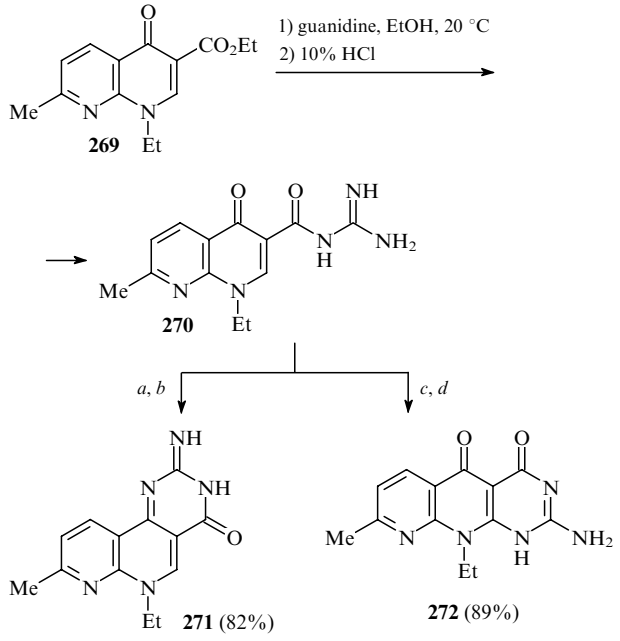
267

1,8-Naphthyridine derivatives were used for the preparation of polysiloxanes. New chiral stationary phase **268** was constructed on the basis of 2-*N*-(5,7-dimethyl-1,8-naphthyridin-2-yl)carboxamide.[509]



268

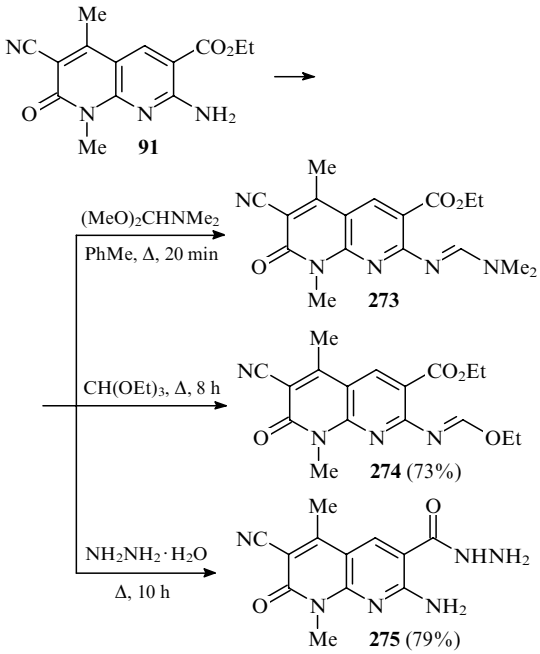
In studies of 1,8-naphthyridine derivatives possessing potential biological activities, a procedure was devised for the synthesis of a new tricyclic system containing the 1,8-naphthyridine fragment, *viz*., pyrimido-1,8-naphthyridines.[510, 511] The synthesis involves condensation of commercially available guanidine carbonate with ethyl nalidixate (**269**) to form *N*-[(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)carbonyl]guanidine hydrochloride (**270**). After pre-neutralisation with 10% NaOH, guanidine **270** readily undergoes cyclisation (EtOH, Δ, 1 h) to form the angularly annelated tricyclic system, *viz*., 6-ethyl-2-imino-8-methyl-2,3,4,6-tetrahydropyrimido[5,4-*c*][1,8]naphthyridin-4-one (**271**), which was isolated as the hydrochloride.[511] Treatment of guanidine **270** with an excess of sodium hydride in dry DMF at 20 °C afforded 2-amino-10-ethyl-8-methyl-1,4,5,10-tetrahydropyrimido[5,4-*b*][1,8]naphthyridine-4,5-dione (**272**), which was also isolated as the hydrochloride.



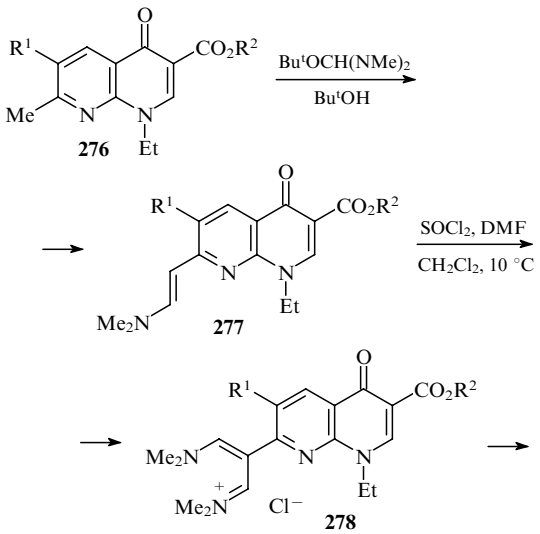
(*a*) EtOH, Δ, 1 h; (*b*) 10% HCl;

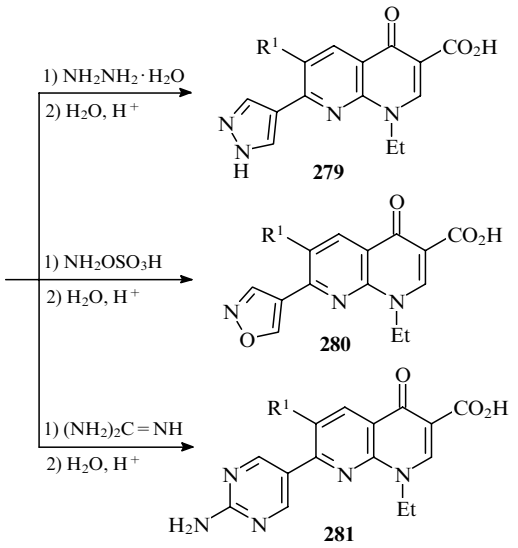
(*c*) NaH, DMF, 20 °C; (*d*) 10% HCl.

With the aim of searching for synthetic approaches to new 1,8-naphthyridin-2-one derivatives, transformations of ethyl 7-amino-1,4-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-6-carboxylate (**91**) were studied. Refluxing of this compound with *N*,*N*-dimethylformamide dimethyl acetal in dry toluene afforded 7-[(*N*,*N*-dimethylaminomethylene)amino]-1,8-naphthyridinone **273**. The reaction of naphthyridone **91** with triethyl orthoformate produced ethoxymethyleneamino derivative **274**. The reaction with hydrazine hydrate gave rise to 7-amino-3-cyano-1,4-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-6-carbohydrazide (**275**).[353]



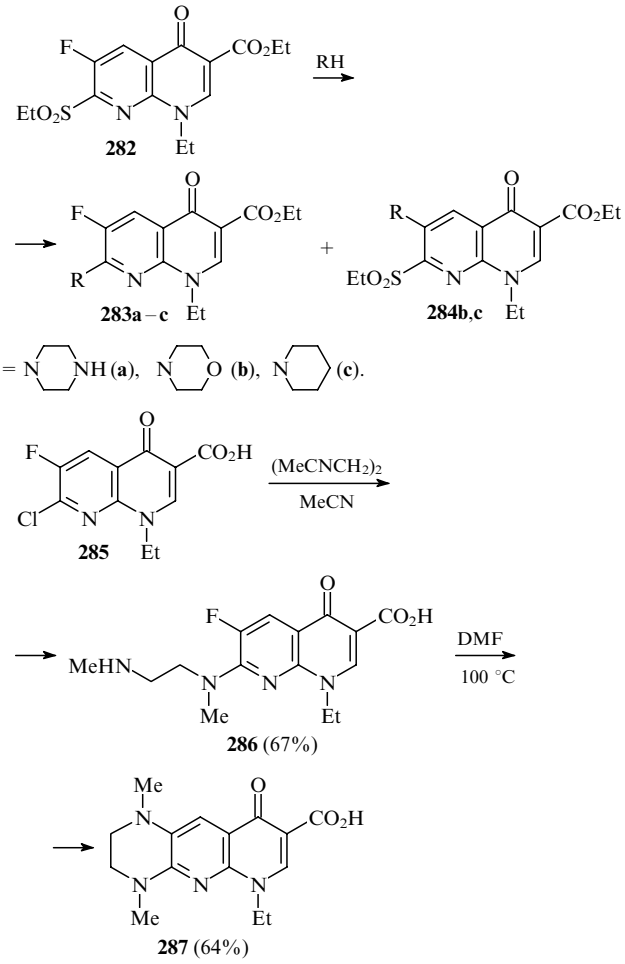
In the last 15 years, considerable attention has been given to variations of substituents in different positions of the molecule (predominantly at position 7), in particular, for the purpose of preparing new active fluoroquinolone and fluoronaphthyridone antibacterial drugs for peroral administration.[512–524] For example, esters of nalidixic acid (**276**) were used for this purpose.[523, 524] The reactions of these esters with *tert*-butoxybisdimethylaminomethane in Bu^{t}OH produce enamines **277**. The addition of the Vilsmeier reagent derived from DMF and thionyl chloride leads to the formation of enamines **278**. Treatment of the reaction mixture with hydrazine hydrate, hydroxylaminosulfonic acid or guanidine followed by hydrolysis of the reaction mixture gives rise to pyrazolyl- (**279**), isoxazolyl- (**280**) and pyrimidinyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid derivatives (**281**).[524]



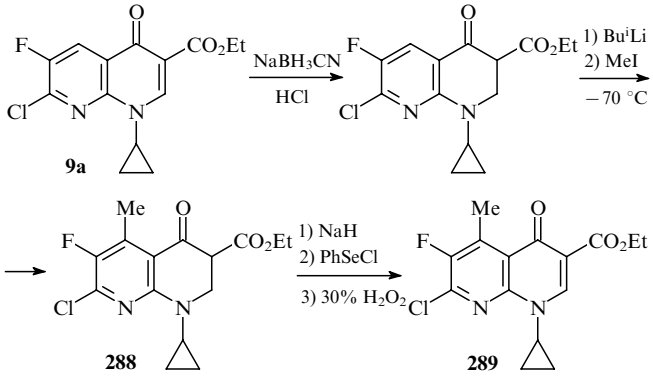


R^1 = H, F; R^2 = Me, Et.

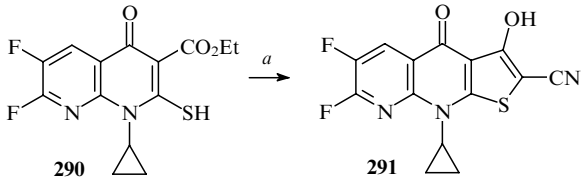
The reaction of ethyl 1-ethyl-7-ethylsulfonyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (**282**) with piperazine is accompanied by the replacement of the ethylsulfonyl group at position 7 to form 7-piperazino derivative **283a** in good yield.[521] Treatment of the starting ester **282** with morpholine and piperidine leads to the replacement of the fluorine atom at position 6 or the ethylsulfonyl group at position 7 to form a mixture of 6- and 7-substituted derivatives **283b**,**c** and **284b**,**c**.[523] The reaction of 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**285**) with *N*,*N*′-dimethylethylenediamine in acetonitrile produces {*N*-methyl-*N*-[2-(methylamino)ethyl]}aminonaphthyridine **286**, which readily undergoes cyclisation upon heating in DMF to give 6-ethyl-1,4-dimethyl-9-oxo-1,2,3,4,6,9-hexahydropyrazino[2,3-*b*][1,8]naphthyridine-8-carboxylic acid (**287**).[523]



Selective reduction of the C(2)=C(3) bond in naphthyridone **9a** followed by treatment with Bu^iLi in THF and methylation affords compound **288**. Subsequent regeneration of the double bond occurs as a result of successive selenation, oxidation and *syn*-elimination to form naphthyridone **289**.[525] Earlier, an analogous scheme has been used for the synthesis of ethyl 7-chloro-1-ethyl-6-fluoro-2-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate.[526]



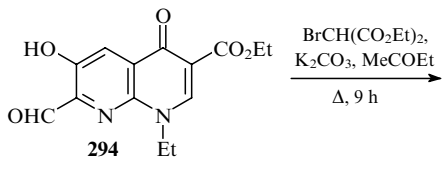
Thieno[2,3-*b*][1,8]naphthyridone **291** exhibiting antimicrobial and antitumour actions was synthesised starting from the 2-mercapto derivative of naphthyridone **290**.[527]

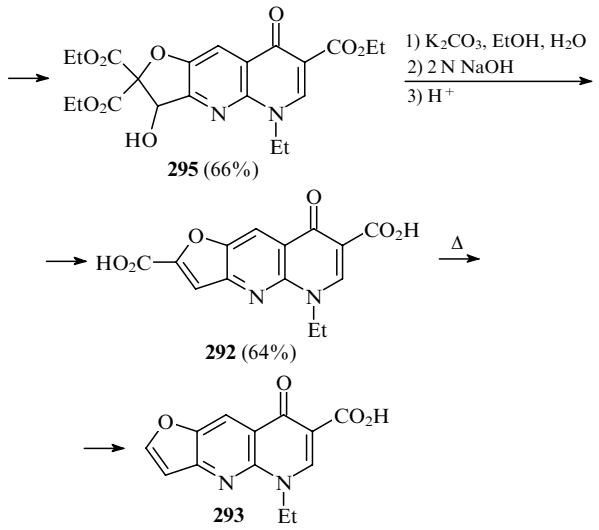


(*a*) 1) $BrCH_2CN$, THF, $NaHCO_3$; 2) $NaHSO_3$, THF, H_2O.

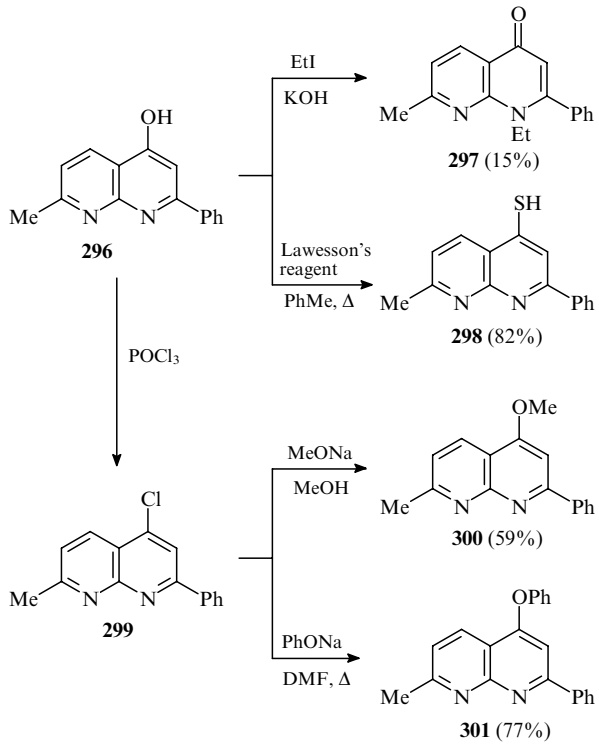
Procedures for the synthesis of compounds containing a five-membered heterocycle with a linearly fused 1,8-naphthyridine fragment (thiazolo[5,4-*b*]-,[528] imidazolo[4,5-*b*]-, triazolo[4,5-*b*]-,[529] oxazolo[5,4-*b*]-, thiadiazolo[5,4-*b*]-, isothiazolo[5,4-*b*]-, pyrazolo[3,4-*b*]-, thieno[2,3-*b*]-, furo[2,3-*b*]-1,8-naphthyridines[530]) were described and the antibacterial activity of these compounds was studied.

5-Ethyl-8-oxo-5,8-dihydrofuro[3,2-*b*][1,8]naphthyridine-2,7-dicarboxylic (**292**) and 5-ethyl-8-oxo-5,8-dihydrofuro[3,2-*b*][1,8]naphthyridine-7-carboxylic acids (**293**) were synthesised in the study.[531] Refluxing of a mixture of ethyl 1-ethyl-7-formyl-6-hydroxy-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**294**), diethyl bromomalonate and K_2CO_3 in ethyl methyl ketone affords compound **295**. Successive treatment of the latter with K_2CO_3 in aqueous ethanol and 2 N NaOH gives dicarboxylic acid **292**. Selective decarboxylation of acid **292** on heating in dimethylformamide, dimethylacetamide or quinoline in the presence of copper compounds yields furonaphthyridinecarboxylic acid **293**.

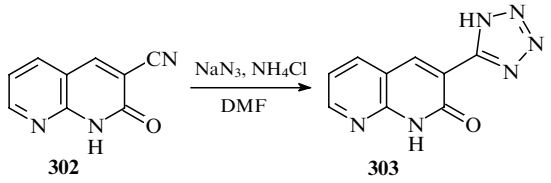




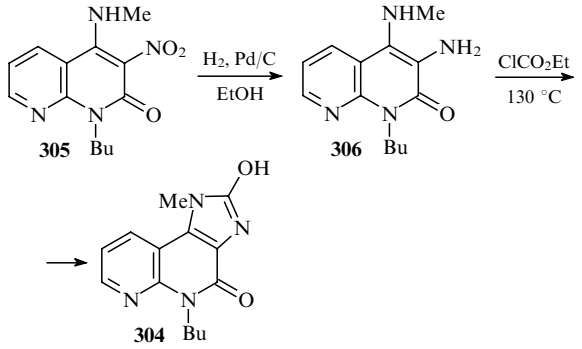
It was found [532] that 1,8-naphthyridine derivatives can react with adenosine receptors of subtypes A_1 and A_{2A}. This stimulated studies on the synthesis and investigation of the biological activities of various functionalised (particularly, at positions 1, 2, 4 and 7) naphthyridines. Alkylation and nucleophilic substitution of these compounds was studied. 7-Methyl-2-phenyl-1,8-naphthyridin-4-ol (**296**) is alkylated at position 1 with EtI and KOH in aqueous ethanol to form 1-ethyl-7-methyl-2-phenyl-1,8-naphthyridin-4(1*H*)-one (**297**).[533, 534] Refluxing of naphthyridone **296** with Lawesson's reagent in toluene affords 7-methyl-2-phenyl-4-thiol-1,8-naphthyridine (**298**). Treatment of 4-chloronaphthyridine **299** (which was prepared by the reaction of naphthyridone **296** with $POCl_3$) with sodium methoxide in methanol gave rise to 4-methoxy-7-methyl-2-phenyl-1,8-naphthyridine (**300**). Refluxing of compound **299** with PhONa in DMF produced 7-methyl-4-phenoxy-2-phenyl-1,8-naphthyridine (**301**). A series of other 1,8-naphthyridine derivatives was also prepared and their properties as A_1, A_{2A} and A_3 adenosine receptors were studied.[534]



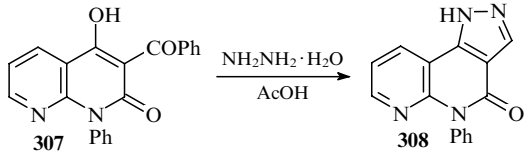
Along with substituted 1,8-naphthyridin-4-ones, derivatives containing the carbonyl group at position 2 were subjected to various transformations. For example, the reaction of 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**302**) with sodium azide and ammonium chloride in DMF produced tetrazolyl-1,8-naphthyridin-2-one **303**, which was covered by a patent as an anti-allergic drug.[535]



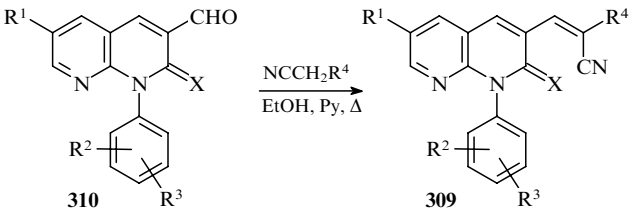
Imidazonaphthyridine **304** possessing anti-inflammatory action was synthesised by hydrogenation of 1-butyl-4-methylamino-3-nitro-1,8-naphthyridin-2(1*H*)-one (**305**) followed by cyclisation of diamino derivative **306** on heating with ethyl chloroformate.[536]



The reaction of 3-benzoyl-4-hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**307**) with hydrazine hydrate produces naphthyridone **308** possessing anti-inflammatory and broncholithic activities.[537]

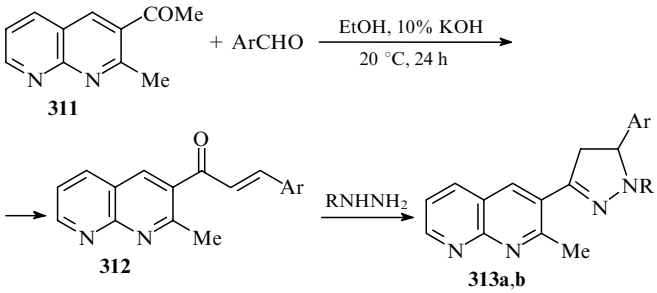


Numerous 3-(2-cyanovinyl)-substituted 1,8-naphthyridines **309** were prepared by refluxing 1,8-naphthyridine-3-carbaldehydes **310** with substituted acetonitriles in alcohol in the presence of catalytic amounts of pyridine. Compounds **309** were covered by a patent as promising starting compounds for the synthesis of new drugs for the treatment of cancer, psoriasis and atherosclerosis.[538]



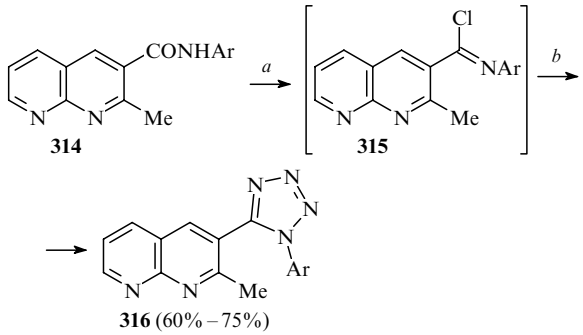
R^1 = H, AlkO, OH, Hal; R^2, R^3 = H, AlkO, AlkS, CF_3, HO, NO_2, CN, Hal; R^4 = Py, $CONH_2$, $CSNH_2$; X = NH, O, S.

Claisen–Schmidt condensation of 3-acetyl-2-methyl-1,8-naphthyridine (**311**) with aromatic aldehydes occurs in ethanol in the presence of KOH to give cinnamoyl-substituted 1,8-naphthyridines **312**. The latter undergo cyclisation under the action of hydrazine hydrate (AcOH, EtOH, Δ, 6 h) or phenylhydrazine (AcOH, Δ, 4 h) to form 3-(5-aryl-2-pyrazolin-3-yl)-1,8-naphthyridines (**313a**) (62%–84% yields) or 3-(5-aryl-1-phenyl-2-pyrazolin-3-yl)-2-methyl-1,8-naphthyridines (**313b**) (64%–86% yields), respectively, which exhibit pronounced antifungicidal activity.[539]



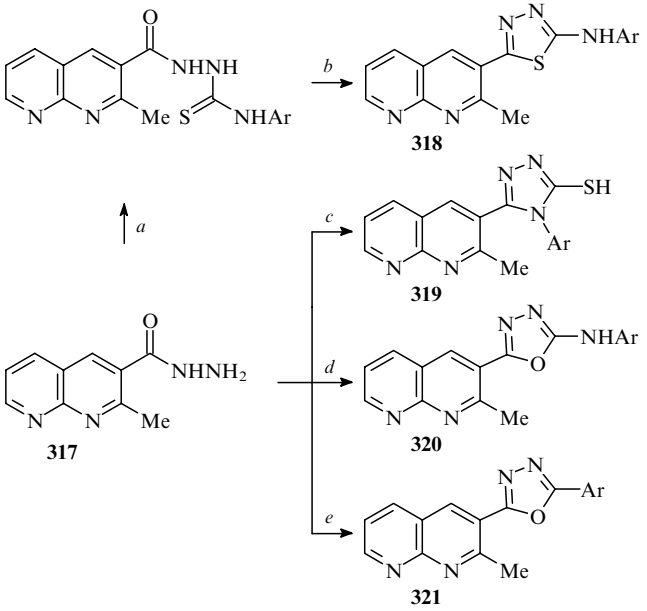
R = H (**a**), Ph (**b**); Ar = Ph, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-HOC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$Me_2NC_6H_4$.

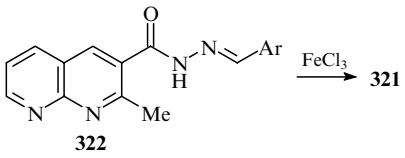
The reaction of *N*-aryl-2-methyl-1,8-naphthyridine-3-carboxamides **314** with $POCl_3$ (120 °C, 3 h) followed by the reaction of the imidoyl chloride **315** that formed with sodium azide afforded 3-(1-aryl-1*H*-tetrazol-5-yl)-1,8-naphthyridines **316**. However, assays of naphthyridines **316** demonstrated that these compounds do not exhibit the expected antibacterial activity.[540]



Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$;
(*a*) $POCl_3$, 120 °C, 3 h; (*b*) NaN_3, AcONa, Me_2CO, H_2O, 20 °C, 24 h.

2-Methyl-1,8-naphthyridine-3-carboxylic acid hydrazide (**317**) served as the starting reagent for the synthesis of numerous 1,8-naphthyridine derivatives, such as 1,3,4-thiadiazol-2-yl- (**318**), 4*H*-1,2,4-triazol-3-yl- (**319**)[541] and 1,3,4-oxadiazol-2-ylnaphthyridines (**320**, **321**).[542] Compounds **321** can also be prepared by oxidative cyclisation of arylmethylidenehydrazides **322** with $FeCl_3$ in AcOH.[542]

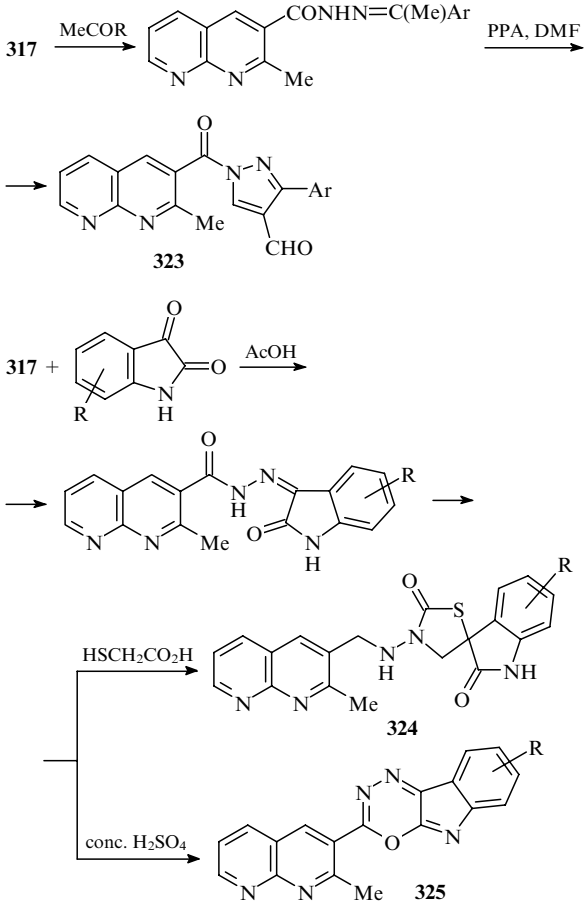




(*a*) ArNCS, EtOH; (*b*) concentrated H_2SO_4; (*c*) ArNCS, 2 N NaOH; (*d*) ArNCO, I_2, KI, 2 N NaOH; (*e*) $ArCO_2H$, 240 °C.

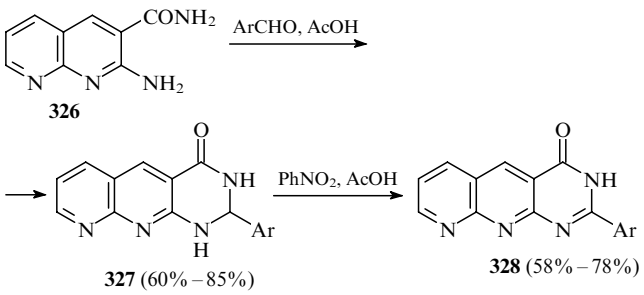
4-Formylpyrazole-1-substituted naphthyridines **323**[543] and compounds **324** and **325** containing complex heterocyclic substituents were synthesised starting from hydrazide **317**.[544]

Naphthyridines **318**–**321** and **323** exhibit bactericidal and fungicidal activities.[542, 543, 545]



R = H, Me, Cl, Br.

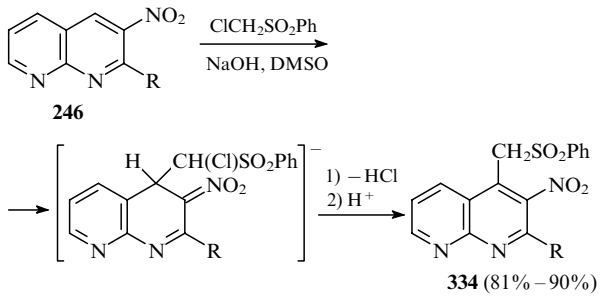
Condensation of 2-amino-1,8-naphthyridine-3-carboxamide (**326**) with aromatic aldehydes in glacial acetic acid affords 2-aryl-1,2,3,4-tetrahydropyrimido[4,5-*b*][1,8]naphthyridin-4-ones **327**, whose oxidation with nitrobenzene in glacial acetic acid gives rise to 2-arylpyrimido[4,5-*b*][1,8]naphthyridin-4(3*H*)-ones **328**. Compounds **328** were also synthesised without intermediate isolation of naphthyridones **327** (condensation of amide **326** with aromatic aldehydes by refluxing in a mixture of nitrobenzene and glacial acetic acid).[546]



Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$Me_2NC_6H_4$.

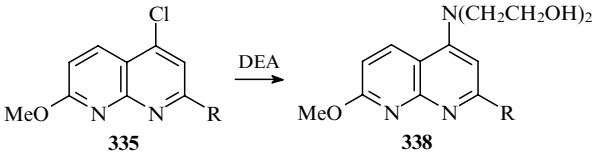
The reaction of 2-amino-5,7-dimethyl-1,8-naphthyridine (**329**) with 2-chlorophenyl sulfochloride produces sulfonamide **330**, which possesses herbicidal and growth-controlling properties.[547] Condensation of amine **329** with trichloroacetone affords a mixture of angular imidazo[1,2-*a*][1,8]naphthyridines **331** – **333** (Scheme 7).[548]

The reactions of substituted 3-nitro-1,8-naphthyridines **246** with chloromethyl phenyl sulfone (DMSO, 20 °C, 2 h) produce 3-nitro-4-(phenylsulfonylmethyl)-1,8-naphthyridines **334** in high yields. Quantum-chemical calculations by the MNDO method demonstrated that the pathway of this reaction, like that of amination (see above), is determined not by charge control but by the interaction between HOMO of the nucleophile and LUMO of the substrate.[549]

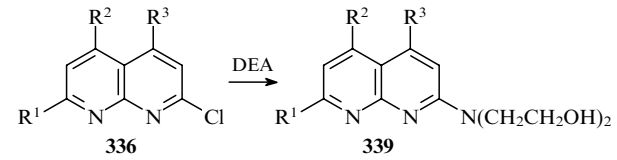


R = H, D, OH, OEt, Cl, NH_2.

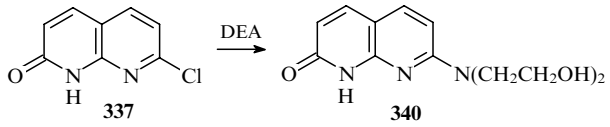
Treatment of chloronaphthyridines **335** – **337** with diethanolamine (DEA) (120 °C) afforded the corresponding bis(2-hydroxyethyl)amino derivatives **338** – **340**. However, the expected antitumour activity of these compounds was not revealed.[550]



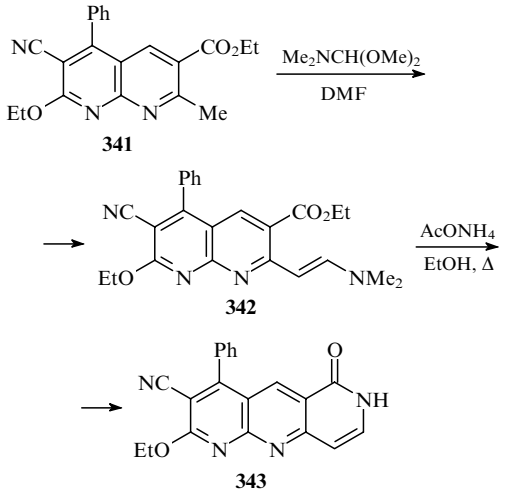
R = Me, Pr^n, Ph, CF_3, 4-$NO_2C_6H_4$.



R^1 = Me, NH_2, OH; R^2 = H, Me; R^3 = H, Ph.

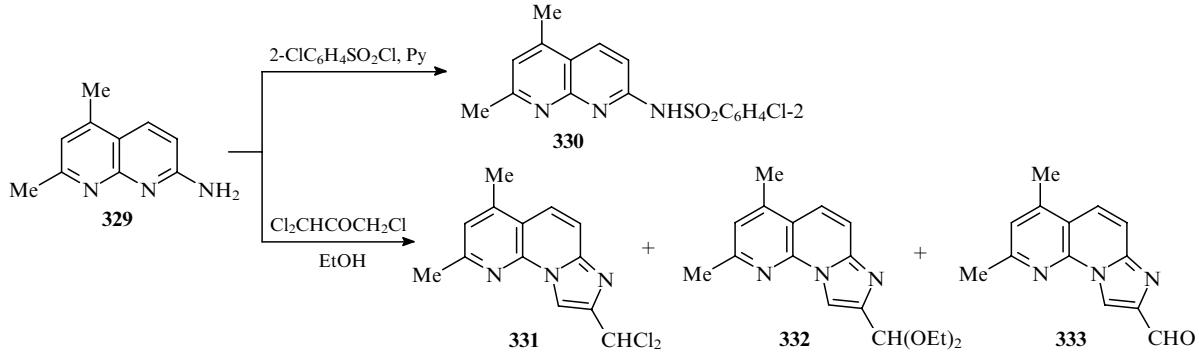


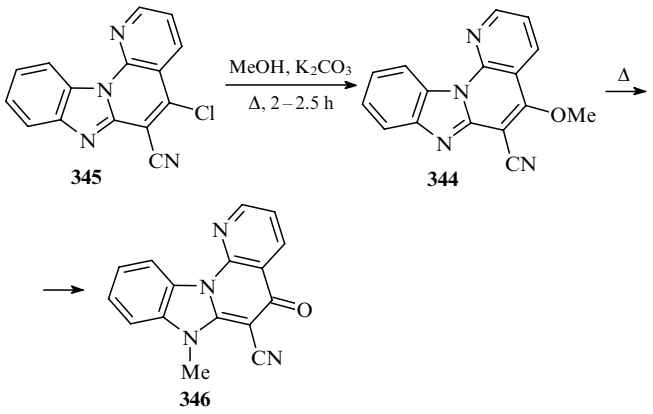
The reaction of ethyl 3-cyano-2-ethoxy-7-methyl-4-phenyl-1,8-naphthyridine-6-carboxamide (**341**) with dimethylformamide dimethyl acetal produces enamine **342**. Subsequent refluxing of the latter with ammonium acetate in ethanol leads to cyclisation to form tricyclic naphthyridine system **343**.[551]



The study [552] was devoted to the transformations in a tetracyclic system containing the fused naphthyridines and benzimidazole ring. 5-Methoxybenzimidazo[1,2-*a*][1,8]naphthyridine-6-carbonitrile (**344**) was prepared by the reaction of 5-chlorobenzimidazo[1,2-*a*][1,8]naphthyridine-6-carbonitrile (**345**) with methanol in the presence of potassium carbonate. Upon heating to its melting point in DMF or in the absence of the solvent, compound **344** undergoes migration of the methyl group from the O atom to the N atom of the benzimidazole fragment to give 7-methyl-5-oxo-6-benzimidazo[1,2-*a*][1,8]naphthyridine-6-carbonitrile (**346**).

Scheme 7





345 344 346

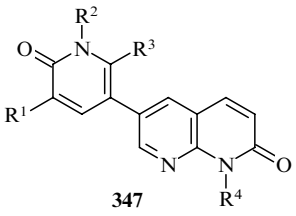
IV. Conclusion

The data surveyed in the present review convincingly demonstrate that the chemistry of pyridopyridines has attracted considerable interest. In the last decade, complex heterocyclic systems containing the 1,8-naphthyridine fragment have been synthesised and their reactions giving rise to functionalised naphthyridines have been investigated. The biological activities of 1,8-naphthyridine derivatives have received the most study. A detailed consideration of these studies is beyond the scope of the present review. For completeness of information, this review contains the bibliography, including patents [553–718] and papers,[719–752] published over the last 15 years, except for those in which 1,8-naphthyridine derivatives are used only in specific biochemical assays.

The activities exhibited by 1,8-naphthyridine derivatives are listed in Table 2. Several examples of the biological properties of this class of compounds are cited below.

With the aim of prolonging the action of nalidixic acid (**36**), which is used, in particular, for the treatment of infectious diseases, acid **36** was subjected to esterification with xanthine using dicyclohexylcarbodiimide in DMSO. The ester proved to be rather efficient against *Staphylococcus aureus* 209P.[753]

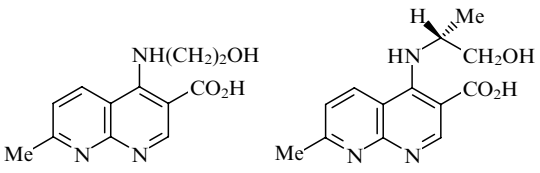
Naphthyridines **347** containing substituted pyridones at position 6 are used as components of cardiotonic drugs.[559]



347

R^1 = H, Alk, AlkO, CHO, CN, NO_2, NH_2; R^2, R^3, R^4 = Alk, Ar.

The inotropic activities of 4-(2-hydroxyethylamino)-7-methyl-1,8-naphthyridine-3-carboxylic acid **348** and its chiral methyl derivative **349** were compared with those of known drugs having an analogous action (isoproterenol, adrenaline, histamine, *etc.*) with the use of isolated samples of guinea-pig myocardium. Biological assays demonstrated that compounds **348** and **349** are similar to heart glycosides in many respects.[754, 755]



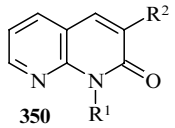
348 **349**

Table 2. Biological activities of 1,8-naphthyridine derivatives.

Activity	Ref.
Antibacterial	25, 137, 194, 195, 197, 215, 234, 236, 237, 241, 245, 247, 248, 253–256, 553, 568, 575, 614, 615, 617, 622, 623, 634, 635, 685, 689, 712, 718, 727, 732, 733, 735, 738–743
Antimicrobial	569, 578, 692, 693, 717, 740, 744, 750
Antiviral	586, 591, 598, 599
Anti-inflammatory	343, 571, 588, 750
Antitumour	583, 588, 712, 715
Antiulcerative	343
Antihypertensive	570, 594, 721, 723
Antidiabetic	588
Anticonvulsive	650
Antithrombotic	574, 580, 724, 725, 727, 750
Antiatherosclerotic	588, 631
Immunostimulating	567, 570, 571, 650
Analgetic	343, 584
Various receptor antagonists	254, 260, 534, 575, 577, 579, 581, 582, 585, 587, 588, 592, 593, 596, 597, 686, 746
Fungicidal [a]	363

[a] This type of activity was found against phytopathogenic fungi *Phytophtora infestans* on tomatoes, *Phytophtora castonuma* on apples and *Pseudoperonospora cubensis* on cucumbers.

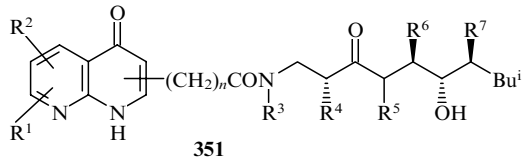
Substituted 1,8-naphthyridin-2(1*H*)-ones **350** were tested as selective phosphodiesterase inhibitors.[756]



350

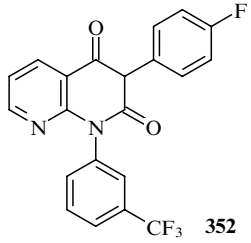
R^1 = Me, $(CH_2)_2Pr^i$, $(CH_2)_3OAc$, n-C_5H_{11}, Allyl, 2-$FC_6H_5CH_2$;
R^2 = H, Me, Ph, 2-Py, $(CH_2)_4OH$, $CH_2CH(OH)Me$.

Numerous substituted naphthyridines were studied and *N*-terminal aminohydroxy derivatives of β-amino acids **351** were demonstrated to inhibit renin.[566, 567] Naphthyridinedione **352** stimulates carotene biosynthesis;[757] (*E*)- and (*Z*)-*O*-(diethylamino)ethyl oximes of the naphthyridine series **353** are potential drugs for local anesthesia.[758] 1,8-Naphthyridine derivatives **354** exhibit high antihypertensive activity.[759]

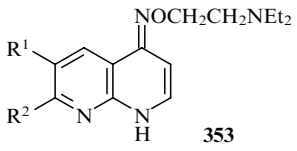


351

R^1, R^2 = H, Alk, OH, OAlk, Ar, CO_2H, NH_2; R^3, R^4 = H, Alk;
R^5 = H, Alk, cyclo-Alk, Bn; R^6 = Alk, cyclo-Alk, Ph;
R^7 = H, OH, OAlk, cyclo-Alk, NH_2.

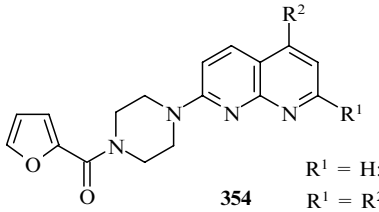


352



353

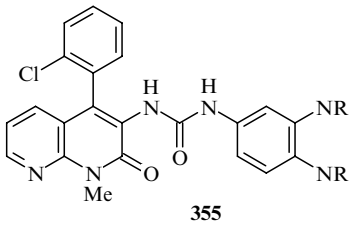
R^1 = H, Br;
R^2 = Me, OMe, OEt, Br.



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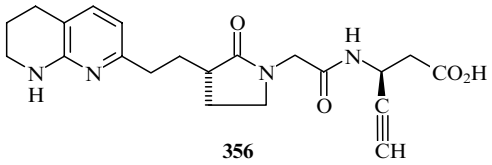
R^1 = H: R^2 = OH, OMe, NH_2;
R^1 = R^2 = Me, CF_3.

Of numerous compounds of the naphthyridine series covered by patents as various receptor inhibitors, cholesterol acyl transferase inhibitors **355**,[574, 580] integrin receptor antagonists **356** and **357**,[579, 581, 587, 588, 592, 593, 595, 596] vitronectin receptor antagonist **358**,[585] *etc*. are worthy of notice.

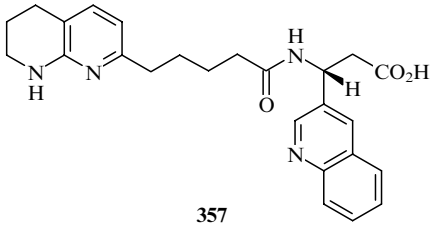


355

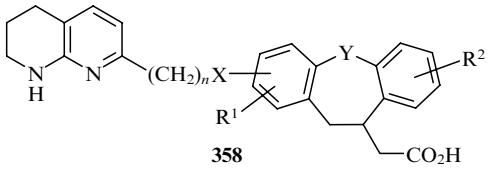
R = H, Alk, cyclo-Alk, Alkenyl.



356



357



358

R^1 = H, Hal, C_1–C_6-Alk; R^2 = H, C_1–C_6-Alk;
X = Y = O, CH_2; n = 2, 3.

The present review, devoted to the chemistry and biological activities of 1,8-naphthyridine derivatives, will hopefully be of interest for organic chemists and biologists. Due to the presence of two geminal endocyclic nitrogen atoms, the 1,8-naphthyridine molecule is more promising for interactions with various biological receptors, coordination to metal ions and other intermolecular contacts compared to other isomeric pyridopyridines and the majority of known nitrogen heterocycles. In the immediate future it is hoped that new regio- and stereoselective procedures will be developed for the introduction of pharmacophoric groups at different positions of the naphthyridine molecule with the use of cascade heterocyclisation and combinatorial chemistry for the design of more efficient medical drugs possessing prolonged action or improved pharmokinetic characteristics. In particular, the design of the so-called dual action antibiotics, *viz*., systems consisting of β-lactam antibiotics of the penicillin and cefalosporin series and fluoroquinolonecarboxylic or fluoronaphthyridonecarboxylic acid derivatives, holds promise.

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