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THE METHODS OF SYNTHESIS, MODIFICATION, AND BIOLOGICAL ACTIVITY OF 4-QUINOLONES (REVIEW)

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Data on methods for the construction of the 4-quinolone skeleton and modification of the substituents around it are reviewed. The "structure–activity" relationships of 4-quinolones are examined with respect to antibacterial and antitumor activity.

Keywords: 4-quinolones, biological activity.

4-Quinolones have been a subject of research for many scientific teams, and this is reflected in the numerous reviews and monographs devoted to various aspects of the subject. One of the early reviews [1] concerns aspects of the synthesis of individual representatives of the group of 4-quinolones and comparative characterization of their antimicrobial activity. Basic approaches to construction of the fluoroquinolone skeleton and also variation of the substituents at various positions of the ring were examined in the review [2]. The relationship between the structure and antibacterial activity is discussed in [3], and methods for the synthesis of polycyclic derivatives of 4-quinolones based on the annelation of rings to the various faces of the quinoline skeleton are discussed in the review [4]. The reviews [5, 6] were devoted to identification of the structural modifications of 4-quinolones responsible for their conversion from antibacterial agents to antitumor agents. The molecular and biological aspects of the antibacterial action of 4-quinolone-3-carboxylic acids are examined in [7], and issues concerned with the clinical application of 4-quinolones are discussed in the reviews [8-12] and in the monograph [13]. The synthesis and the "structure–activity" relationships of the bioisosteres of 4-quinolones – 2-pyridones – are examined in the review [14].

The aim of the present review was to classify existing methods for the synthesis not only of fluoroquinolones but also of any 4-quinolones, to demonstrate the effects of modification of the molecule at all positions, to summarize data on the various types of activity, and to examine the "structure–activity" relationship with respect to antibacterial and antitumor activity.

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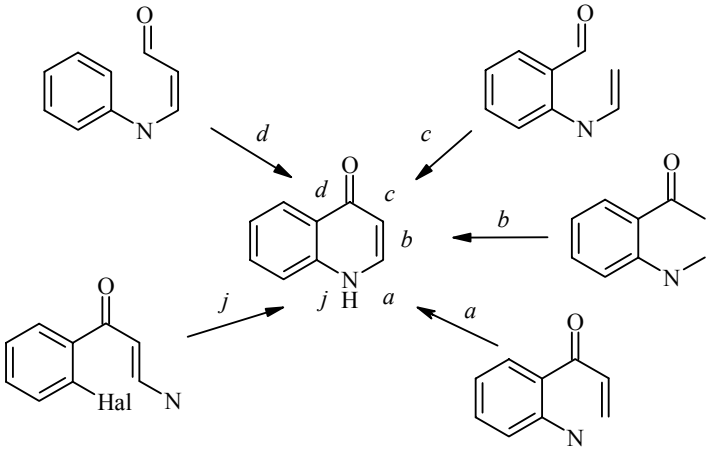
1. METHODS FOR THE SYNTHESIS OF 4-QUINOLONES

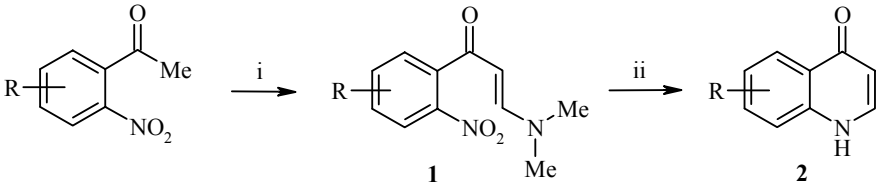
Many methods are currently known for the production of 4-quinolones. All the reactions can be divided provisionally into five groups depending on the formation of which bond (*a*, *b*, *c*, *d*, or *j*) leads to ring closure. It is governed by the fact that the assignment to a specific group in a given case for multistage processes is based on examination of the structure of the compound formed before the 4-quinolone. Its existence is postulated by the authors without regard to the number of stages or the characteristics of the reaction mechanisms.



1.1. Type *a*

Closure of bond *a* is realized by the cyclization of *ortho*-COR-substituted aromatic amines having an electrophilic center at the β-position of substituent R.

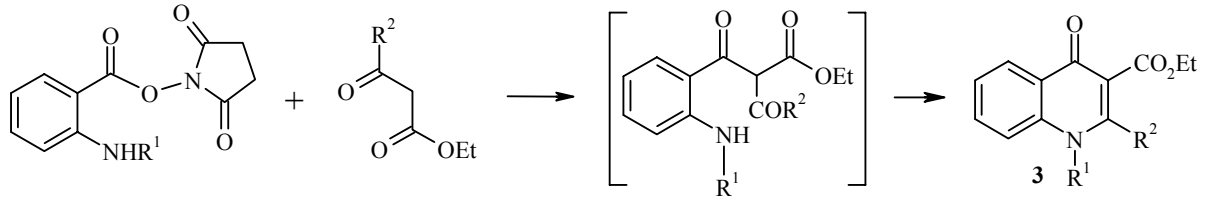
Thus, a method was proposed for the synthesis of 2,3-unsubstituted 4-quinolones by cyclization of the enamine **1** produced by heating *o*-nitroacetophenone with dimethyl formamide dimethyl acetal in DMF at 100°C [15]. The cyclization was conducted under reducing conditions in the presence of cyclohexene with 10% Pd–C as catalyst.



1 **2**

i – $(MeO)_2CHNMe_2$, DMF; ii – 10% Pd–C, cyclohexane, EtOH

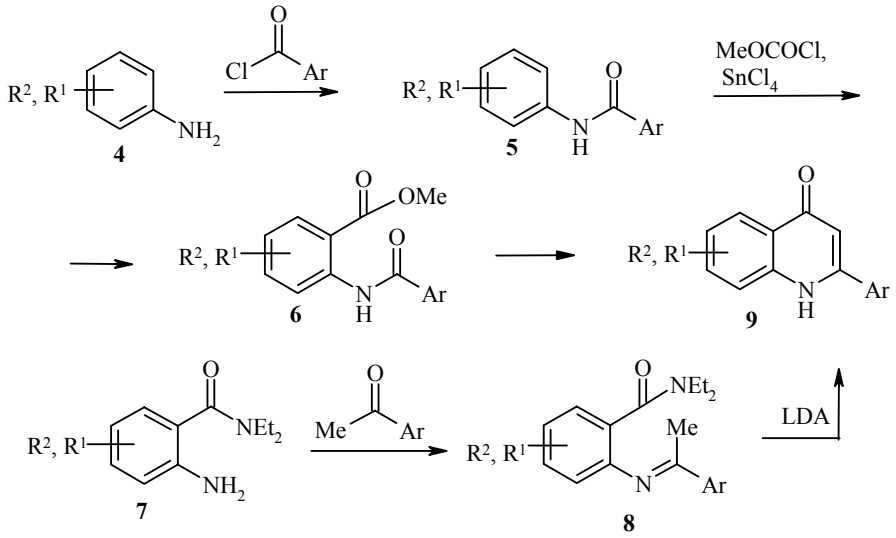
The intermediate product from C-acylation of the anions of β-keto esters with the esters of N-hydroxysuccinimide and anthranilic acids undergoes spontaneous cyclization with the formation of ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylates **3** [16].



3

1.2. Type *b*

This type of reaction amounts to the formation of intermediate derivatives **6** and **8**, whose cyclization with closure of bond *b* leads to the formation of a 4-quinolone ring.



LDA – lithium diisopropylamide

The anilines **4** or the amides of anthranilic acids **7** react with substituted benzoyl chlorides or acetophenones with the formation of compounds **5** or **8** respectively. Compounds **5** are acylated by the Friedel–Crafts method with methyl chloroformate. The obtained derivatives **6** and **8** undergo cyclization with the formation of 4-quinolones **9** [17].

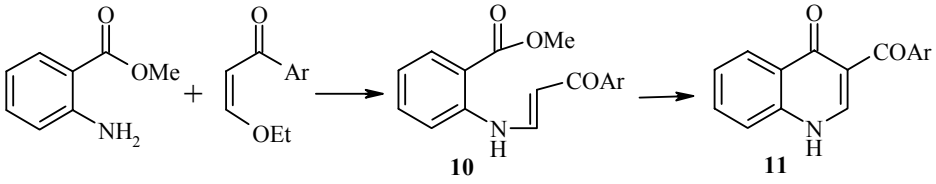
The cyclization of compounds **6** and **8** takes place in the presence of sodium ethoxide (under pressure) [18], under the influence of potassium *tert*-butoxide in *tert*-butyl alcochol [17, 19-23], in absolute dioxane in the presence of sodium hydroxide [24], or in THF in the presence of lithium diisopropylamide (-30°C) [22]. By this method it is possible to obtain N-unsubstituted 2-aryl-4-quinolones containing various substituents in the benzene ring.

The method can be used for the production of [*a*]annelated 4-quinolones [25].

1.3. Type *c*

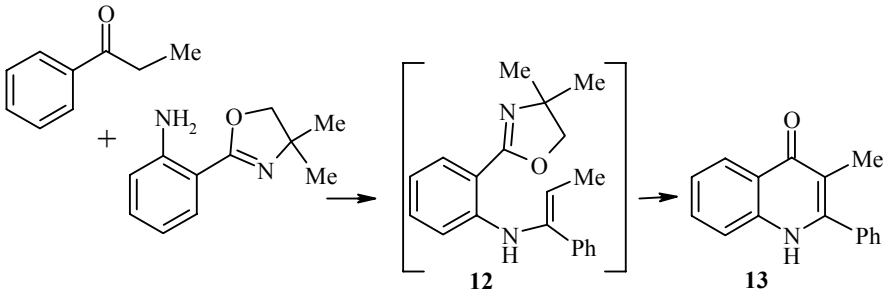
Substituted *ortho*-N-vinylamino derivatives of benzoic acid of type **10** are starting materials for cyclization leading to the formation of bond *c*.

The reaction of methyl anthranilate and aroyl vinyl ethers under various conditions gives 40-84% yields of the enamines **10**, which undergo cyclization to 3-aroyl-4-quinolone **11** in the presence of sodium methoxide in diphenyl oxide (1:8) [26].



Diethyl acetylenedicarboxylate [1] and 2-dimethylamino-3-nitropropene [27] can be used in these transformations in place of the vinyl ether.

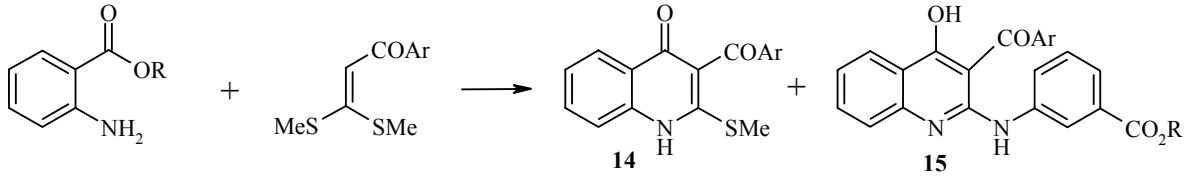
An unusual method was described in [28] for the production of 4-quinolones **13** from various ketones and *o*-oxazoline-substituted aniline, which were kept at boiling point in absolute butanol for 24 h in the presence of catalytic amounts of *p*-toluenesulfonic acid in an atmosphere of nitrogen or argon. The reaction takes place through the formation of structure **12**, which is an analog of the *ortho*-N-vinylamino derivatives of benzoic acid **10** with the only difference that in compound **12** the latent oxazoline form of the carboxyl group is used [29]. (The detailed mechanism was discussed in the original article [28].)



12 **13**

Variously substituted and also [*b*]cyclopentano- and [*b*]cyclohexano-annelated 4-quinolones can be obtained with good yields (70-90%) in different ways depending on the initial ketone.

The authors in [30] propose a method for the construction of a 4-quinolone system involving the reaction of methyl *o*-aminobenzoate with α-aroylketene dithioacetal in toluene or DMF, leading to the formation of the 4-quinolones **14** and 4-hydroxyquinolines **15**. By appropriate choice of conditions it is possible to obtain the 4-quinolones **14** as the main reaction product. The method can be included in the present type of construction of 4-quinolones in so far as the reaction takes place formally with the formation of the same intermediate as described above.

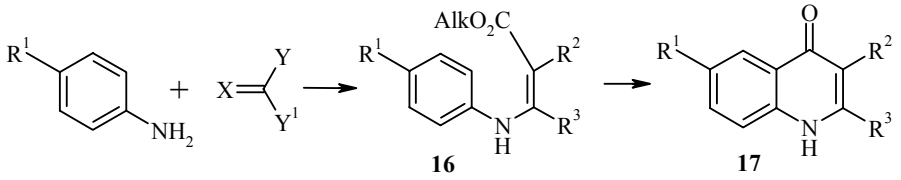


14 **15**

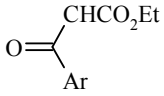
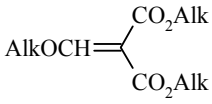
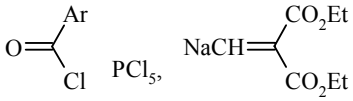
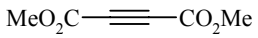
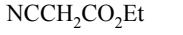
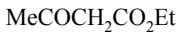
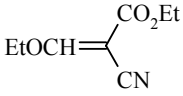
1.4. Type *d*

The group of reactions based on closure of bond *d* includes some of the most numerous methods used for the synthesis of 4-quinolones. The enamines **16**, required for the synthesis of the 4-quinolones **17**, are produced by the condensation of substituted anilines with various reagents.

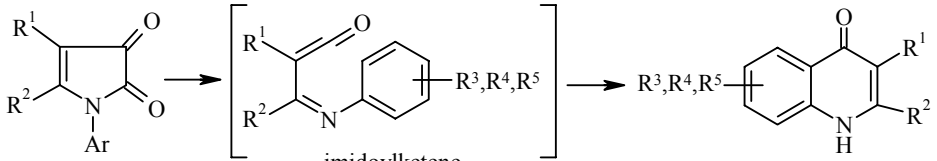
The cyclization of the enamines **16** is realized by the action of heat in high-boiling solvents such as biphenyl [44], biphenyl ether [1, 26, 32, 34, 36, 37, 41, 42, 45-47], Dowtherm A [35, 38, 39, 48, 49], and mineral oil [1] or by using effective cyclization agents such as polyphosphoric acid or its esters [1, 2], the halogen derivatives of phosphorus [1], $ZnCl_2$ [1], conc. sulfuric acid in mixture with acetic anhydride [1], and Eaton's reagent (a mixture of phosphorus(V) oxide and methanesulfonic acid) [37, 40]. With the latter it is possible to reduce the cyclization temperature from 140°C (if polyphosphoric acid is used as cyclization agent) to 50°C (!) while keeping the quantitative yields [39, 40]. The yields of the targeted quinolones are good – 60-97%.



16 **17**

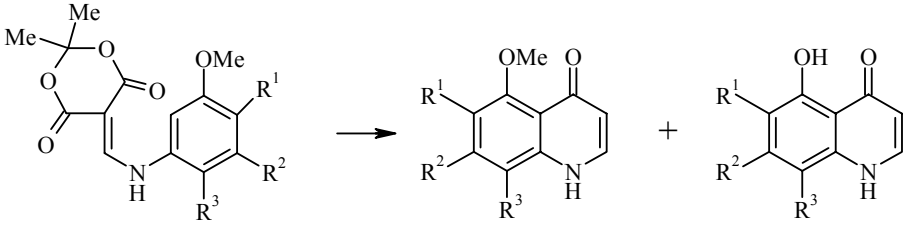
Initial reagents	**16, 17** R^2, R^3
	R^2 = H, R^3 = Ar [31–33]
	R^2 = CO_2Alk, R^3 = H [34–42]
	R^2 = CO_2Et, R^3 = Ar [43]
	R^2 = H, R^3 = CO_2Me [40]
	R^2 = R^3 = H [1]
	R^2 = Me, R^3 = H [1]
	R^2 = CN, R^3 = H [1]

The method for the production of 4-quinolones by the thermolysis of 1-aryl-2,3-dihydro-2,3-pyrroledione **18** can also be ascribed to this type of reaction. The reaction takes place through the formation of imidoylketene, which being an unstable compound undergoes cyclization at the *ortho* position of the benzene ring with the formation of methyl 4-oxo-1,4-dihydroquinoline-2-carboxylates **19** [50, 51].



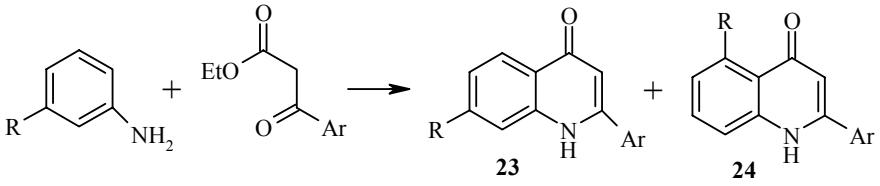
18 imidoylketene **19**

In the case of the arylaminomethylene derivatives of Meldrum's acids **20** the reaction probably also takes place through the formation of imidoylketene and leads to 4-quinolone **21**. In certain cases the formation of the demethylation product **22** is observed. In addition N-methyl-4-quinolone is again isolated, and this can be explained by the fact that the nitrogen atom of the quinolone ring is involved in the demethylation process [52].



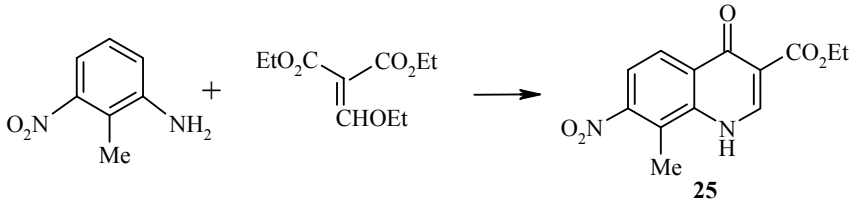
20 **21** **22**

Although the authors in [45, 53, 54] do not postulate the intermediate formation of an enamine these methods were assigned to type ***d*** since they are examples of the known method of construction of the quinoline system by the Conrad–Limpach method. During the reaction of substituted anilines with ethyl aroylacetate in the presence of polyphosphoric acids the substituted 2-aryl-4-quinolones **23** and **24** are formed [53].



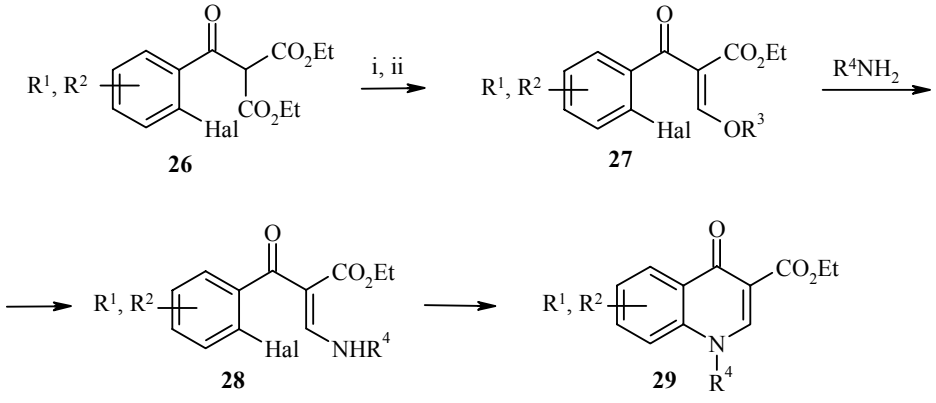
As demonstrated by the authors in [45] this approach can be used in combinatorial chemistry with the aim of producing quinolones variously substituted at all possible positions with methanesulfonic acid as catalyst.

4-Quinolone **25** is formed during the reaction of substituted anilines with diethyl ethoxymethylenemalonate with heat in Dowtherm A [54].



1.5. Type *j*

This type includes multistage reactions in which aminovinyl phenyl ketones are formed. Ring closure at the last stage involves the halogen atom at the *ortho* position of the aryl substituent in the aminovinyl phenyl ketones with the formation of the *j* bond.



i – H_2O; ii – $HC(OEt)_3$ or $CH(OEt)_2NMe_2$, Ac_2O

The derivative **26**, produced by successive transformations from benzoic acids (or acid halides) [55-57] or α-(nitro)acetophenones [58, 59] and DMF acetal [59] or ethyl 3-(dialkylamino)acrylate [55, 60], was hydrolyzed and decarboxylated, and the product was then condensed with ethyl orthoformate or DMF acetal in

acetic anhydride. The obtained compound **27** was transaminated by the action of primary amines, making it possible to introduce various substituents at position 1.

The cyclization of compounds **28** leading to the formation of 4-quinolones **29** can be realized in the presence of various reagents: sodium ethoxide in ethanol [61]; KF in DMF [60]; K_2CO_3 or Li_2CO_3 in DMF [26, 55, 56, 58, 60, 62-64] or acetonitrile or NaH in dioxane [57] or THF [62]; triethylamine in DMF [65], DMSO [59], or toluene [57, 59, 60].

Variously substituted 4-quinolones can be obtained by this type of reaction. The aromatic part may contain various radicals, and there may be alkyl, cycloalkyl, aryl, hetaryl, and hetarylamino groups at position 1. Tricyclic compounds containing a 4-quinolone fragment [61], analogs of ofloxacin [63], and pentacyclic derivatives [66] can also be obtained by this method. At position 3 of the 4-quinolones there is usually a carboxyl or alkoxycarbonyl group [55, 56, 60, 63-67], although there may be a nitro group [59], a CN group [68], or H [58, 69]. Moreover, the scheme can also used to obtain the quite rare 2-substituted 4-quinolones (carboxyl group [69], trifluoromethyl group [58]).

The ease of cyclization depends on the nature of the substituent at the enamino nitrogen atom. As can been seen from the decrease in the reaction time it increases in the transition from alkyl substituents to aromatic substituents [59].

The cyclization of 2-(alkyl)amino-4-oxo-4-polyfluoroalkyl-2-butenoic acids or ethyl 4-amino-2-oxo-3-pentafluorobenzoyl-3-butenoates also belongs to type ***j***. The final 4-quinolone is produced directly in one stage by cyclization in the presence of alkali or triethylamine [69-72].

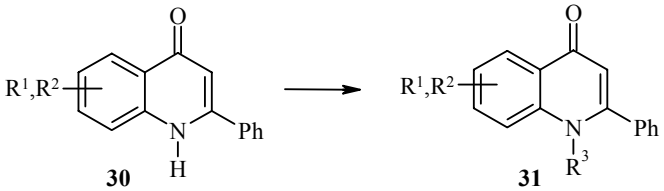
2. MODIFICATION OF 4-QUINOLONES

In this part of the review methods used for the modification of 4-quinolones, i.e., transformations of 4-quinolones synthesized by one of the methods described above and retaining the 4-quinolone fragment, are examined. They have mainly been used during research directed at the production of more active compounds, i.e., the modifications have practical applications.

The methodology used for modification at one or the other position depends on the structure of the initial molecule. For a long time it was considered self-evident that the CO_2H group at position 3 and the fluorine atom at position 6 must be retained in order to synthesize 4-quinolones with biological activity, and most papers were devoted to such quinolones, i.e., the study of 4-quinolone chemistry has been relatively one-sided.

2.1. Modification at Position 1

The modification of N-unsubstituted 4-quinolones involves the introduction of alkyl substituents by reaction with the corresponding alkyl halides in the presence of potassium carbonate, sodium hydride [19, 26, 31, 32, 36, 41, 42, 62], or potassium hydroxide [1], or of aryl substituents by the reaction of the quinolone and 4-fluoronitrobenzene or 3,4-difluoronitrobenzene in DMF in the presence of potassium carbonate [73]. Alkylation can be achieved with methyl and ethyl iodide, *tert*-butyl bromide [36], benzyl bromide [42], or triethyl phosphate [1, 48].

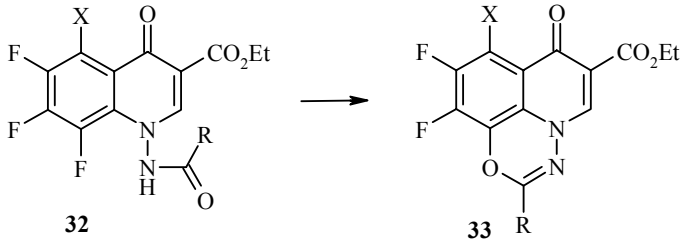


R^3 = Me, Et, *c*-Pr, *t*-Bu, Bn, Ar

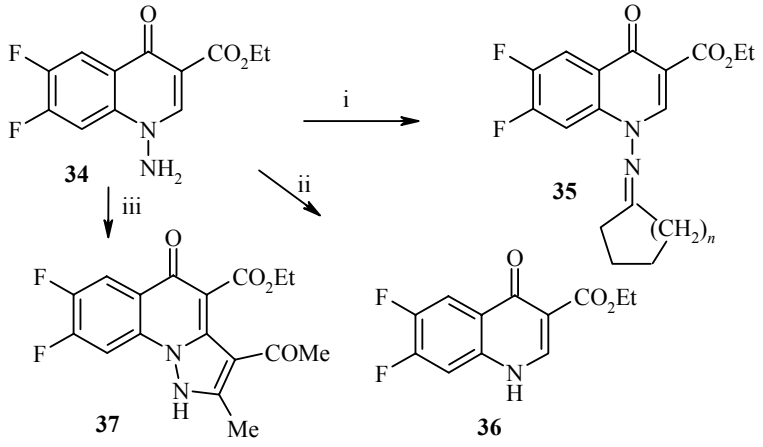
Sometimes the O-alkylated quinolone is isolated as a side product [32].

The range of possible modifications at position 1 is limited by the fact that the appearance of good antibacterial activity in the quinolone requires a relatively small lipophilic group such as cyclopropyl at this position [14].

When heated in toluene in the presence of potassium carbonate 1-acylamino-4-quinolones **32** undergo cyclization to the oxadiazino-annelated analogs **33** [74].



The amino group at position 1 of the 4-quinolone **34** was used to produce the hydrazones **35** by reaction with cyclohexanone or cyclopentanone in acetic acid. In the reaction of the quinolone **34** with α-dicarbonyl compounds (glyoxal, glyoxylic acid, ethyl pyruvate) deamination occurs, and the quinolones **36** are formed. The reaction of the 4-quinolone **34** with acetylacetone in acetic acid leads to the formation of tricyclic pyrazolo-[1,5-*a*]quinolines **37** [75, 76].



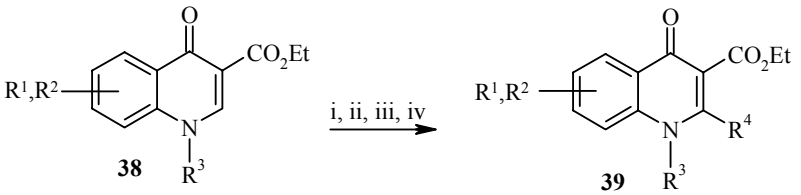
i – cyclopentanone or cyclohexanone, AcOH; ii – R^1COCOR^2, AcOH;
iii – $MeCOCH_2COMe$, AcOH, n = 1, 2

2.2. Modification at Position 2

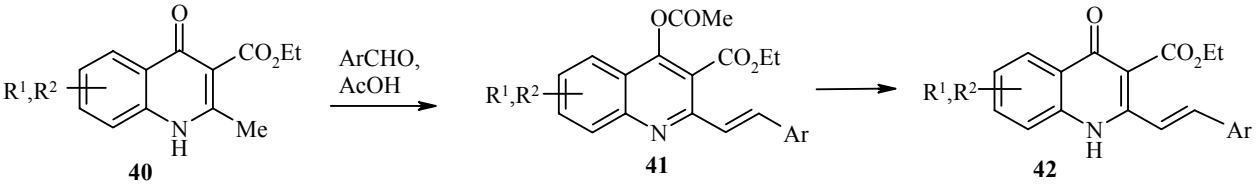
Modifications at position 2 are fairly limited since it was difficult to introduce any substituent at position 2 if there was a carboxyl group at position 3 [6].

In the case of the 2-unsubstituted 4-quinolone **38** the introduction of an alkyl or aryl group at this position can be realized by means of a Grignard reagent and copper iodide with further treatment as follows [56, 62, 77].

The methyl group at position 2 can then be used for modification, for example, by condensation. Thus, the reaction of quinolones **40** with aldehydes in acetic anhydride leads to the formation of the quinolone **42** through a stage involving isolation of the intermediate O-acetyl derivative of 4-hydroxyquinoline **41** [78, 79].



i – R^4MgBr, CuI (R^4 = Me, Ph, C_2H_3); ii – NaH; iii – PhSeCl; iv – H_2O_2



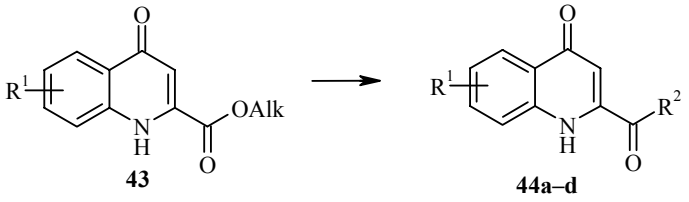
The typical reactions of the ester group in the 4-oxoquinolinecarboxylates **43** can be used to produce the corresponding carboxylic acids and their derivatives.

Hydrolysis of the 2-alkoxycarbonyl group of compounds **43** in an alkaline medium for 5 h at room temperature gives quantitative yields of compounds **44a** (R^2 = OH) [49].

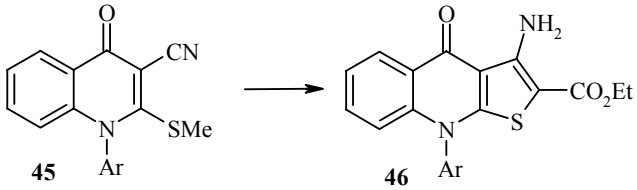
4-Morpholin-4-ylphenylamides **44b** are produced in the reaction of 4-quinolones **43** with morpholinoaniline in the presence of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and hydroxybenzotriazole in DMF for 16 h at room temperature in an atmosphere of nitrogen. The yields are 43-58% [49].

N-[(Quinolinyl)carbonyl]guanidines **44c** are formed as a result of the reaction of guanidine and the ester carbonyl group of the 4-quinolones **43** after holding the components in DMF solution at room temperature for 2-24 h [46].

2-[(2-Quinolinyl)carbonyl]-1-hydrazinecarboximidamides **44d** are formed successively in two stages. The hydrazides of 4-oxo-1,4-dihydro-2-quinolinecarboxylic acids are obtained first, and they then react with 1H-pyrazole-1-carboxamidine hydrochloride in DMF when heated at 100°C for 3 h [46].

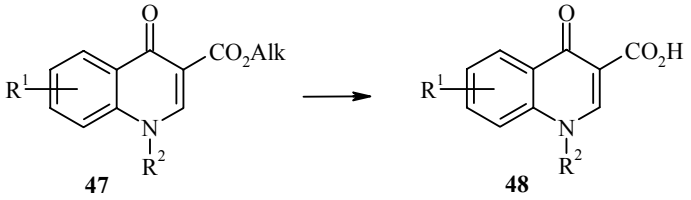


1-Aryl-4-oxo-1,4-dihydro-3-quinolinecarbonitriles **45** react with ethyl 2-mercaptoacetate in the presence of triethylamine in absolute ethanol and in an inert atmosphere with the formation of thieno[2,3-*b*]quinolones **46** [68].

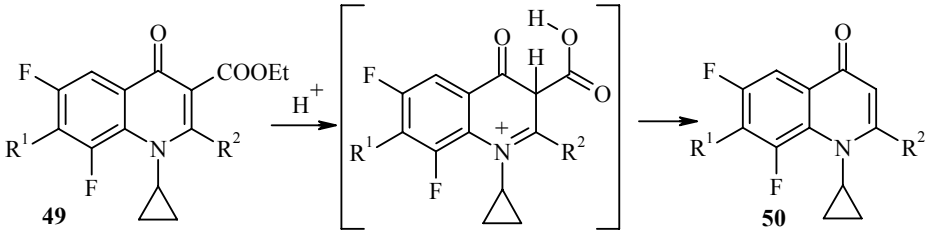


2.3. Modification at Position 3

A large group of reactions use the reactivity of the ester and carboxyl groups at position 3. The hydrolysis of the ester group in compound **47** is realized in hydrochloric acid [62] or in a mixture of acetic and hydrochloric acids [65, 80]. Hydrolysis can also be achieved with 10% NaOH [34] or with sodium hydroxide in ethanol [41, 42, 62].



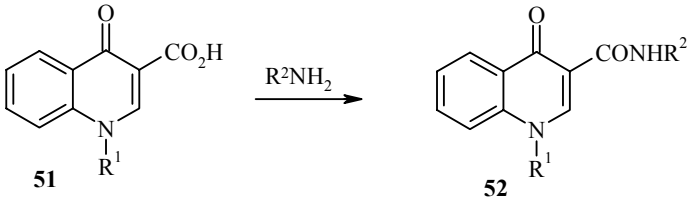
Unexpected results were obtained by the authors in [62] during the usual acid hydrolysis of ethyl 4-oxo-1,4-dihydro-3-quinolinecarboxylates **49** in a mixture of acetic acid, water, and hydrochloric acid. Instead of the expected acids the decarboxylation products **50** were obtained. The authors explain such a surprising result by the higher stability of the ammonium ion with R^2 = Me or Ph compared with R^2 = H under the conditions of acid-catalyzed decarboxylation of the β-keto acids.



Moreover, the treatment of 4-oxoquinolinecarboxylates in biphenyl oxide at 250°C for 10 h also leads to the elimination of CO_2 [27]. The use of sodium cyanide in DMF reduces the reaction time to 30 min and makes it possible to lower the temperature to 150°C [62]. In [81] heating at 230°C in quinoline in the presence of copper was used for the decarboxylation of substituted 4-oxo-1,4-dihydro-3-quinolinecarboxylic acids.

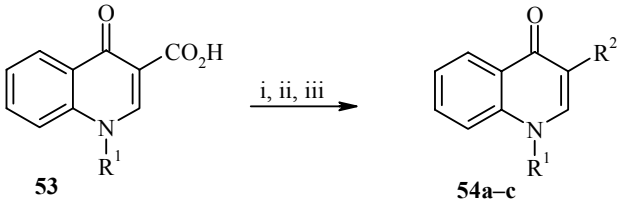
Alkylation of the carboxyl group at position 3 was realized with alkyl halides in N,N-dimethylacetamide in the presence of potassium carbonate or by esterification with 2-morpholino-, 2-piperazino-, or 2-piperidino-ethanol in the presence of triethylamine and ethyl chloroformate in dichloromethane [82]. In the reaction of 4-oxo-1,4-dihydro-3-quinolinecarboxylic acids with amino acids (lysine, arginine) in methanol or in acetone their salts were obtained [82].

1,4-Dihydroquinoline-3-carboxamides **52** are produced from the corresponding acids **51** and amines by a solid-phase synthesis with polystyrene, modified by the insertion of a 1-hydroxy-1H-benzotriazole anchoring group, as support [41, 42]. The analogous reaction of 3-ethoxycarbonyl-4-oxo-1,4-dihydroquinolines with 4-chlorobenzylamine can take place in ethylene glycol [37].



R^2 = Ar, $Ar(CH_2)_n$, Ad

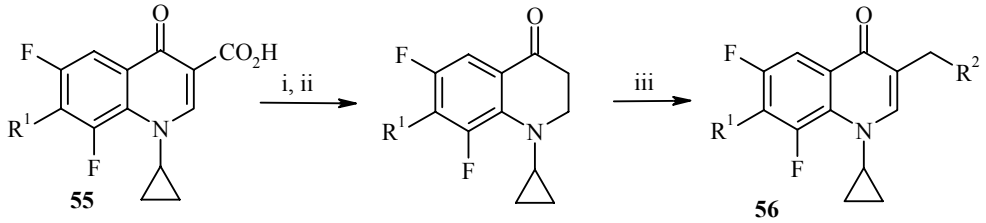
The "retro-amides" **54a** (R^2 = $NHCOR^3$) were obtained from the acids **53** by the Curtius reaction in the presence of diphenylphosphoryl azide (DPPA). The reaction takes place in *tert*-butyl alcohol in the presence of potassium *tert*-butoxide through the formation of intermediate protected amino derivatives, which easily break up under acid conditions and then react with acyl chlorides to form the amides **54**.



54 a R^2 = $NHCOR^3$, i – DPPA; ii – HCl, 6N, iii – R^3COCl; **b** R^2 = CHO; i – $SOCl_2$; ii – $HSnBu_3$; **c** R^2 = CH_2NHR^3, R^3NH_2, i – Et_3N; ii – $NaBH_3CN$, Et_3N

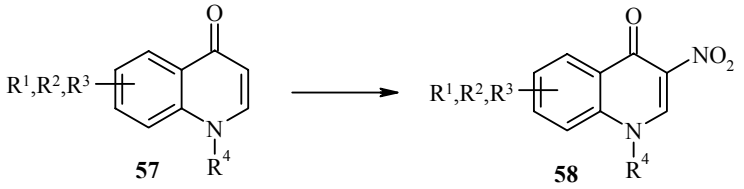
The 4-Oxoquinolinecarbaldehydes **54b** (R^2 = CHO) are synthesized from the acids **53** using tributyltin hydride in the presence of tetrakis(triphenylphosphine)palladium in absolute toluene. The carbaldehydes are then subjected to reductive amination in the presence of sodium cyanoborohydride in absolute methanol with the formation of 3-aminomethyl-4-oxo-1,4-dihydroquinolines **54c** (R^2 = CH_2NHR^3, R^3NH_2) [41, 42].

The authors in [83] used a sequence of reactions (reduction-decarboxylation-condensation) for the introduction of various substituents at position 3 of quinolones **55**.



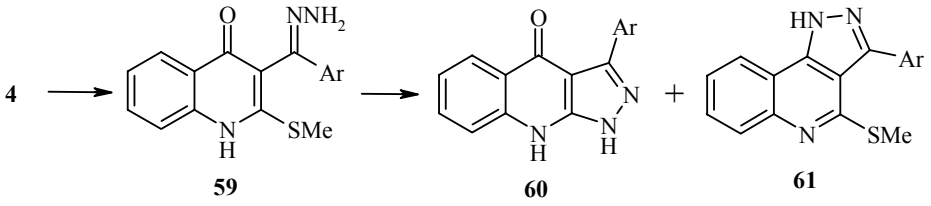
i – $NaBH_4$, ii – TsOH; iii – R^2CHO, NaOH

The nitration of 3-unsubstituted 4-quinolones **57** with the formation of 3-nitro derivatives **58** was realized with conc. HNO_3 [84] or with nitric acid in sulfuric acid [27].

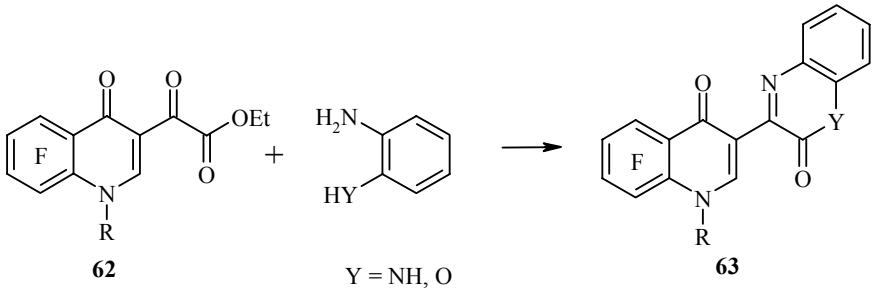


The authors point out that nitration takes place smoothly if there are deactivators of electrophilic substitution processes (a nitro group or three fluorine atoms) in the benzene ring of the 4-quinolone system. This makes it possible to conduct the nitration more selectively, resulting in the isolation of the 3-nitro derivatives as the only reaction products.

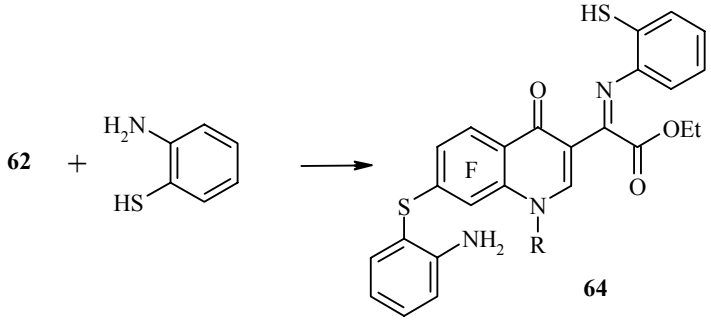
The reaction of 3-aroyl-substituted 4-quinolones **4** with hydrazine takes place with almost quantitative yields with the formation of the corresponding hydrazones **59**, the cyclization of which on heating leads to a mixture of pyrazoloquinolines **60** and **61** [85].



In the reaction of 4-quinolones **62** with aromatic binucleophiles (*o*-phenylenediamine, *o*-aminophenol) the corresponding quinolonylquinoxalones and quinolonylbenzoxazinones **63** are formed [86]. The reaction is conducted in alcohols (MeOH, BuOH) with the reagents in a ratio of 1:2.



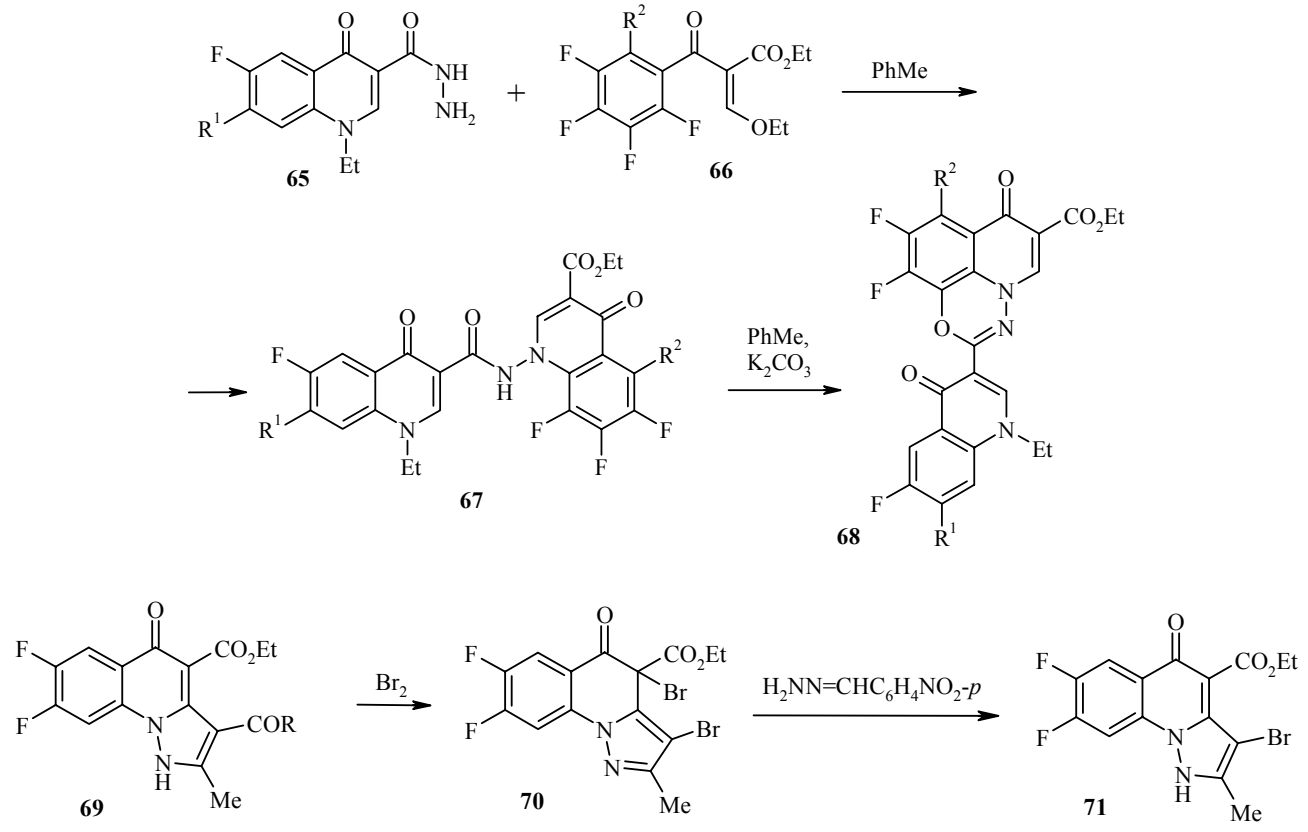
o-Aminothiophenol reacts with compound **62** rather differently; it reacts with the carbonyl group in the ethoxycarbonyl group and substitutes the fluorine atom at position 7 of the aromatic ring. As considered by the authors, nucleophilic substitution in the fluoro aromatic ring is due to the high nucleophilicity of the sulfur atom of the aminothiophenol [86].



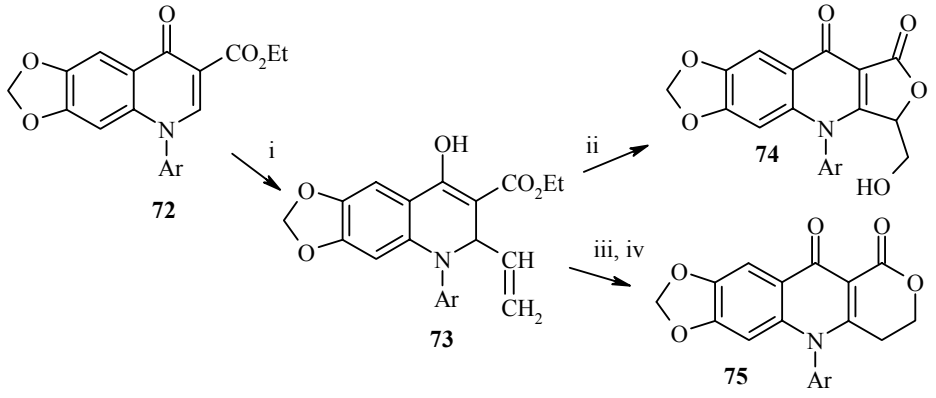
Attempts to bring the quinolone **62** into reaction with phenylhydrazine in ether were unsuccessful, while in alcohol they gave a mixture of unidentified substances [86].

Good yields were obtained during the production of fluoroquinolones **67** containing two quinolone fragments by heating ethyl 3-ethoxy-2-(polyfluorobenzoyl)acrylates **66** with the hydrazides of substituted 4-oxoquinolinecarboxylates **65** in toluene. In toluene in the presence of potassium carbonate compounds **67** undergo intramolecular cyclization with participation of the oxygen atom of the amide group, leading to the formation of an oxadiazine ring in the tricyclic 4-quinolone **68** [87].

The dibromo derivative **70**, in which one bromine atom entered at position 4 while the other bromine atom added at the C-3 atom of the pyrazole ring, was obtained in the reaction of the pyrazoloquinolone **69** with bromine. The dibromo derivative can be easily converted into the monobromo derivative **71** by heating with *p*-nitrobenzaldehyde hydrazone [88, 89].



The ester group at position 3 with a free position 2 makes it possible to complete the formation of the [*b*]-annelated rings. The lactone **74** can be obtained from the quinolone **72** by oxidation of the intermediate 2-vinyl derivative **73**, produced by the reaction of the quinolone **72** and vinyl cuprate [56]. The lactone **75** is produced by the bromination of the 2-vinyl derivative **73** followed by oxidation and cyclization [77].



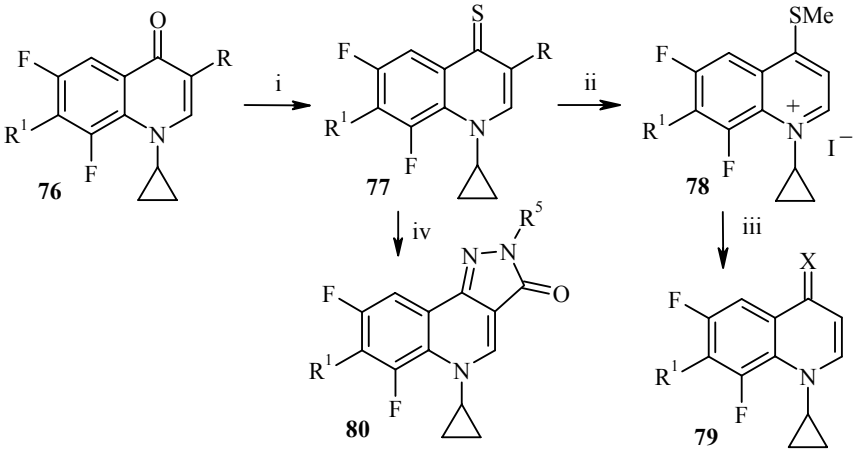
i – CH_2=CHMgBr, CuI; ii – $KMnO_4$, H_2O/Me_2CO; iii – TMSBr; iv – Ag_2O, H_2O/Me_2CO

2.4. Modification at Position 4

Modification at position 4 leads to removal of the carbonyl group, i.e., the products of the respective reactions no longer contain a 4-quinolone fragment as such. However, these transformations are included in this

review since information on the reactivity of a carbonyl group at position 4 is useful for the realization of modifications at other positions. In addition, optimization of a structure from the standpoint of biological activity often presupposes the insertion of bioisosteric substituents, which quite possibly is no exception also for 4-quinolones.

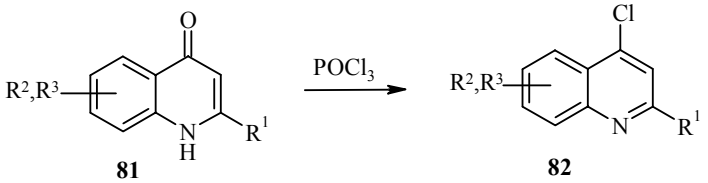
The quinolinethiones **77**, produced by the reaction of 4-quinolones **76** with phosphorus pentasulfide in pyridine [41, 90] or with Lawesson's reagent, can be transformed into hydrazones, imines, oximes, and thiooximes **79** by reaction with hydrazines, amines, hydroxylamine, and its thio analog or cyclized to pyrazoloquinolones **80** [81, 91].



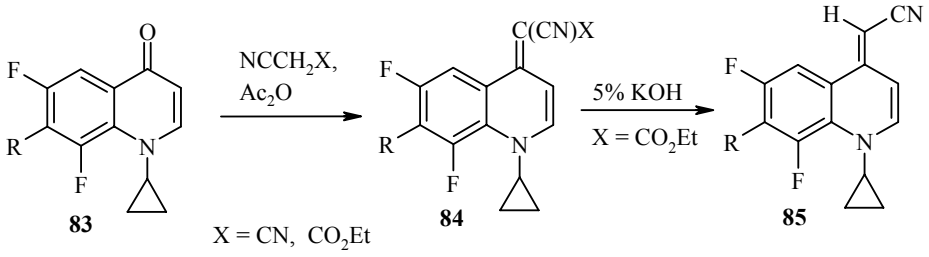
i – P_2S_5, Py, or Lawesson's reagent; ii – R = H, MeI, THF;
iii – $R^2R^3NNH_2$ or R^4NH_2; iv – R = CO_2Et, R^5NHNH_2

The 4-O-alkylation or arylation of 4-quinolones **81** [20, 32, 46] can be realized by using alkyl (aryl) halides in DMF in the presence of sodium hydride. An exception from this is methyl iodide, which methylates the nitrogen atom exclusively [32]. With triethyloxonium fluoroborate $Et_3O^+BF_4^-$ alkylation takes place exclusively at position 4 of the quinolone ring [92]. The introduction of $MeSO_2$ and *p*-$MeC_6H_4SO_2$ groups was realized with methylsulfonyl chloride and *p*-toluenesulfonyl chloride in pyridine [32].

The chlorination of 4-quinolones **81** was realized with phosphorus oxychloride, leading to the formation of 4-chloroquinolines **82** [46, 47].

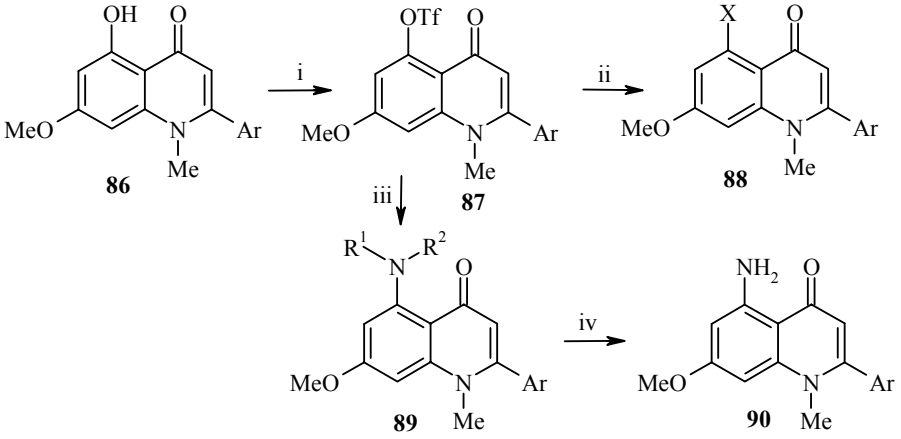


The reaction of the quinolones **83** with malononitrile or ethyl cyanoacetate in acetic anhydride gives the derivatives **84**, which can be used for further modifications [81].



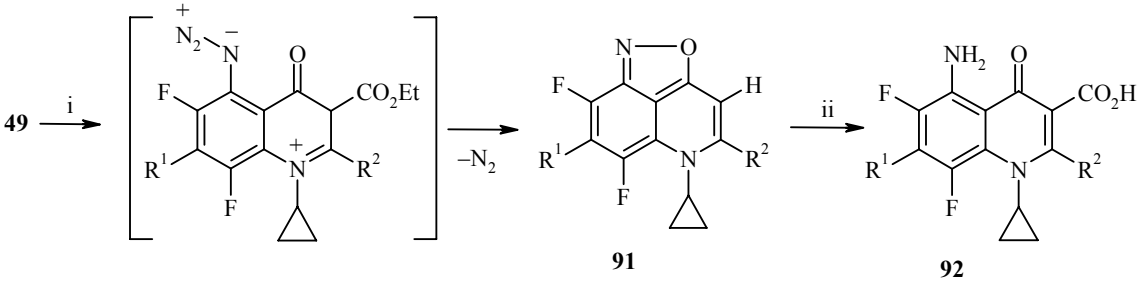
2.5. Modification at Position 5

In [31] the authors describe the production of the 5-vinyl, 5-aryl, and 5-hetaryl derivatives **88**, using the cross-coupling reaction of Stille and Suzuki, and also the 5-amino derivatives **89** and **90** by aromatic nucleophilic substitution of the trifluoromethylsulfonyl group by an amine residue.



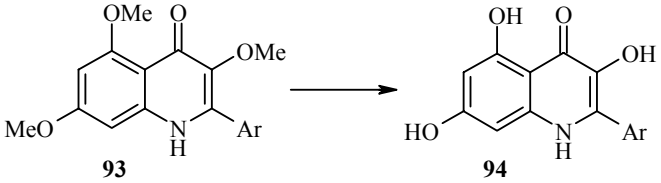
i – Tf_2O, CH_2Cl_2, Py; ii – $XSnBu_3$, LiCl, $Pd(PPh_3)_4$, DMF or $XB(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, X = Vin, Ph, C_4H_3O, C_4H_3S; iii – NHR^1R^2, 1,4-dioxane, 100-120°C; iv – CF_3CO_2H, $NR^1R^2 = NHCH_2C_6H_4OMe$

In [62] an amino group was inserted at position 5 of the 4-quinolone **49** through the synthesis of the intermediate isoxazole derivative **91**.

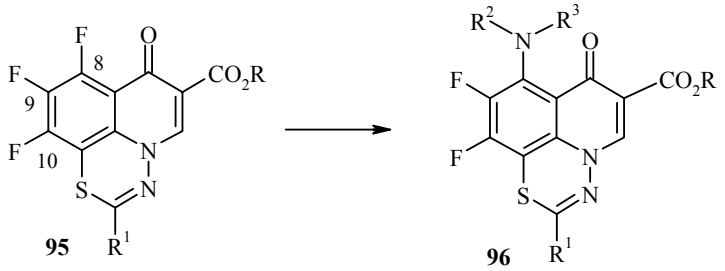


i – NaN_3, DMF; ii – 1) H_2, Pd, DMF, 2) 1N NaOH, 3) 1N HCl

Dealkylation of the 5-methoxy group in compound **93** can be achieved by heating in the presence of hydrobromic acid, pyridine hydrochloride [18, 31], or potassium hydroxide [32].



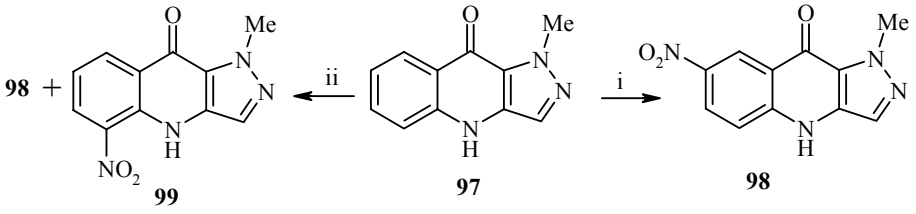
When tricyclic trifluoro-substituted 4-quinolones **95** are heated with morpholine in boiling pyridine or acetonitrile in the presence of catalytic amounts of diazabicycloundec-7-ene the fluorine atom at position 8 is substituted with the formation of compound **96**. Increase in the reaction time and an excess of morpholine lead to the derivative disubstituted at positions 8 and 10 [93].



R = H, Et; NR^2R^3 = morpholino

2.6. Modification at Position 6

During the nitration of pyrazoloquinoline **97** the number, position, and order of entry of the nitro groups depend on the nature of the nitrating agent, the reaction conditions, and the substituents present in the molecule [94]. Thus, during the action of an equimolar amount of nitric acid in sulfuric acid on compound **97** at -5°C 1-methyl-7-nitro-4H-pyrazolo[4,3-*b*]quinolin-9-one (**98**) not containing other isomers is formed with a yield of 87%. During the nitration of compound **97** with nitric acid in acetic anhydride in addition to the nitropyrazoloquinolinone **98** the isomeric 1-methyl-5-nitro-4H-pyrazolo[4,3-*b*]quinolin-9-one (**99**) is formed in a ratio of 2:1.

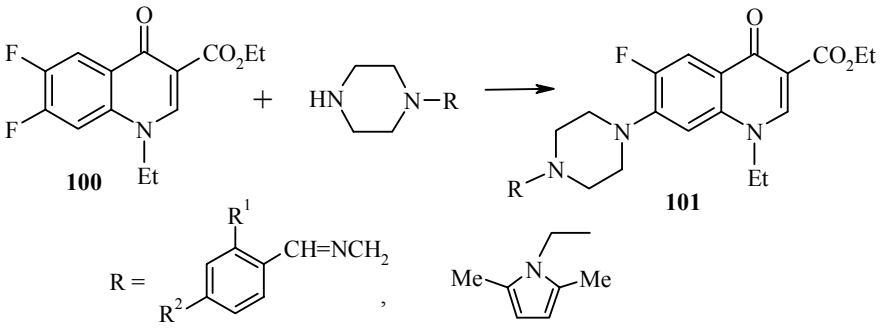


i – HNO_3, H_2SO_4; ii – HNO_3, Ac_2O

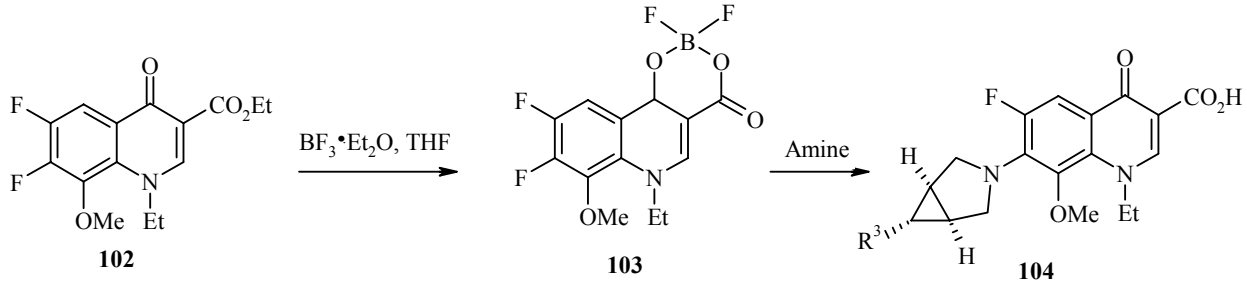
2.7. Modification at Position 7

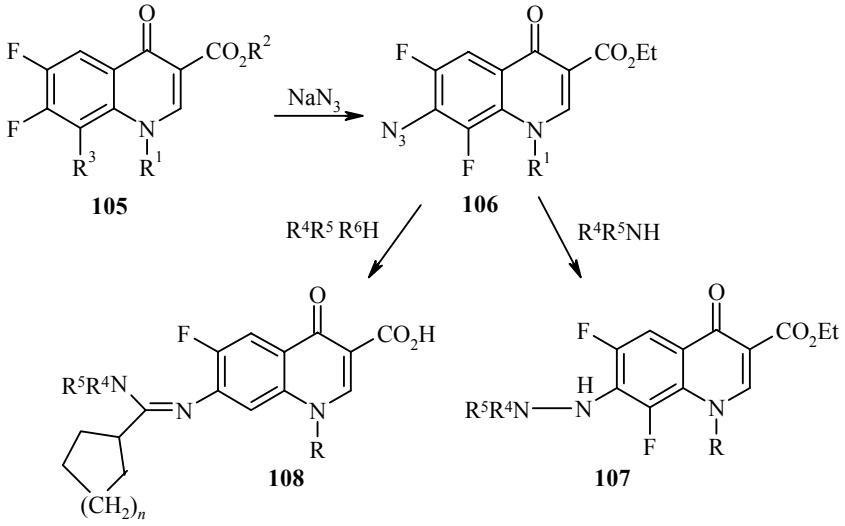
Most of the papers have been devoted to modification at position 7 in so far as the nature of the substituent at this position is responsible for many aspects determining the antibacterial activity of 4-quinolones *in vitro* and *in vivo* [14]. The modifications can be divided into three groups: a) insertion of a nitrogen-containing heterocycle as a result of the formation of a C─N bond; b) modification of an existing nitrogen-containing substituent at position 7; c) insertion of a substituent with the formation of a C─C bond.

2.7.1. Insertion of a Substituent at Position 7 with the Formation of a C─N Bond by Substitution of a Halogen Atom. The fluorine atom at position 7 of 6,7-difluoro-substituted 4-quinolones **100** can be substituted selectively by a piperazine residue while the fluorine atom at position 6 is not affected [95, 96].

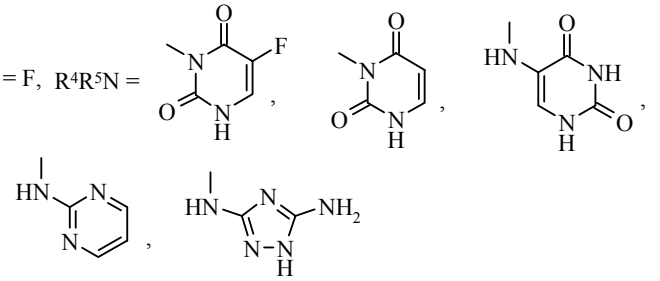


The introduction of a bicyclic heterocycle at position 7 of the 4-oxoquinolonecarboxylate **102** by nucleophilic substitution of a fluorine atom with the intermediate formation of the boron difluoride complex **103** is known [55, 97].





107 R^2 = Et, R^3 = F, R^4R^5N =

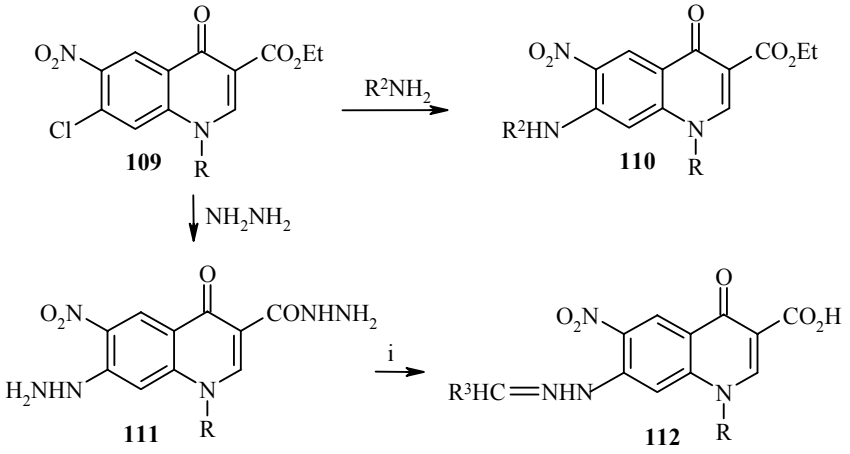


108 $R^2 = R^3 = H$, R^4R^5N = morpholino, 4-methylpiperazino, piperidino, n = 1, 2

If the amine cannot be brought directly into reaction with the 7-fluoro-substituted 4-quinolone, e.g., on account of low nucleophilicity, the approach [98, 99] based on the synthesis of the azide **106** and its subsequent reaction with the heterocyclic amines can be used.

In the case of 5,6,7-trifluoro-substituted 4-quinolones on heating with heterocyclic amines (pyrrolidines, 4-methylpiperazine, 4-ethoxycarbonylpiperazine) disubstitution occurs at positions 5 and 7. (An example with morpholine was described earlier, compound **96** [93].)

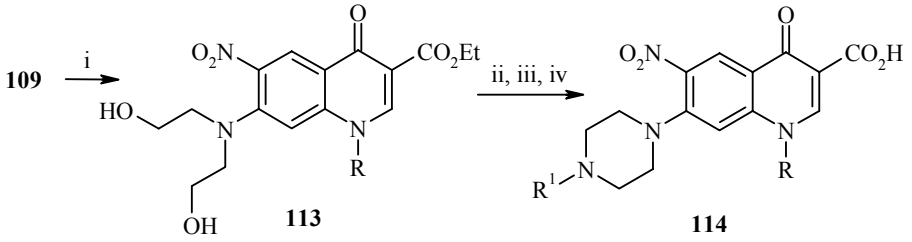
In the presence of an activating group at position 6 the chlorine atom in 7-chloro-6-nitro-4-quinolones **109** can be substituted by an amino, hydrazino, or aryl(hetaryl)oxy group in reaction with ammonia, ethanolamine, or hydrazine hydrate [57, 65]. Ammonia and ethanolamine only react at position 7 while hydrazine hydrate reacts at position 7 and at the ester group, forming the hydrazide **111**, the hydrazine group of which enters into reaction with aldehydes with the formation of compounds **112** [57].



i : 1) H_2O/H^+, 2) R^3CHO, R^3 = *p*-ClC_6H_4, *p*-FC_6H_4, 5-$O_2NC_4H_2O$

Nucleophilic substitution of the chlorine atom was realized in inert aprotic solvents such as DMF, DMSO, N-methyl-2-pyrrolidone, sulfolane, and acetonitrile. Sometimes a water–pyridine solution is used. The released hydrogen chloride is combined with potassium carbonate or an excess of the amine [57, 65].

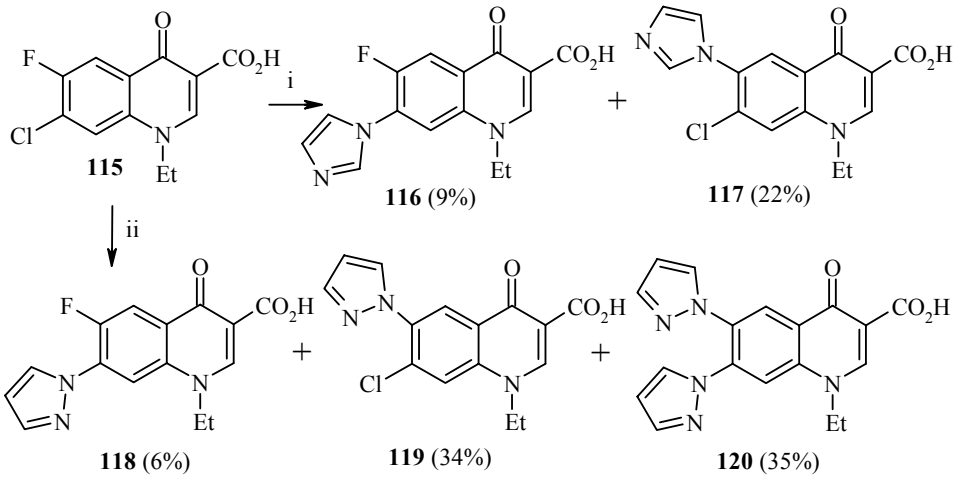
In [100] the authors propose an alternative path to the synthesis of 7-piperazinyl-substituted 4-quinolones **114**. During the reaction of the quinolone **109** with diethanolamine a good yield of the 7-[bis(2-hydroxyethyl)amino]substituted 4-quinolones **113** is obtained. They are then converted by successive treatment with thionyl chloride, conc. HCl, and primary amines into 7-(4-alkyl-1-piperazinyl)quinolonecarboxylic acids **114**.



i – $NH(CH_2CH_2OH)_2$; ii – $SOCl_2$, iii – H_2O, H^+, iv – R^1NH_2

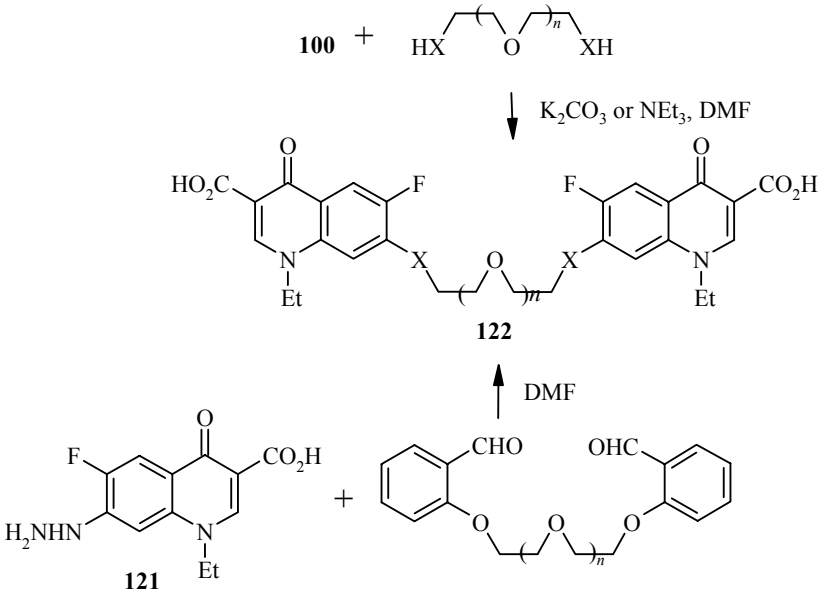
The reactions of 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid (**115**) with imidazole and pyrazole are not selective. If 4-quinolone **115** is heated with imidazole in DMF at 150°C a 1:2.4

mixture of the regioisomeric compounds **116** and **117** is formed; in the reaction with pyrazole, in addition to monosubstitution processes, disubstitution of both halogen atoms leading to 6,7-dipyrazolyl-4-quinolone **120** is observed [2].



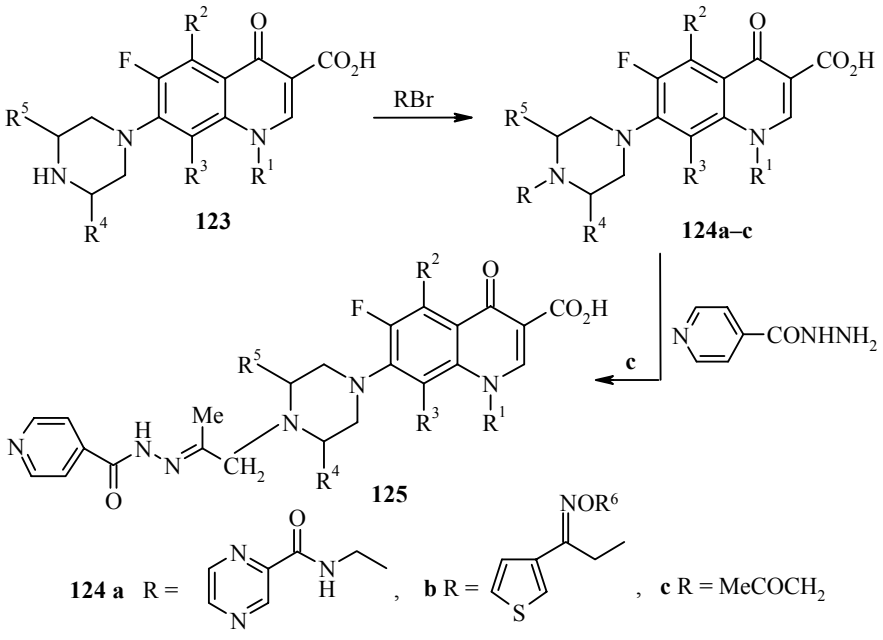
i – 1H-imidazole; ii – 1H-pyrazole

In [101] the authors "stitch" two molecules of 4-quinolone with podands to form compounds **122**.

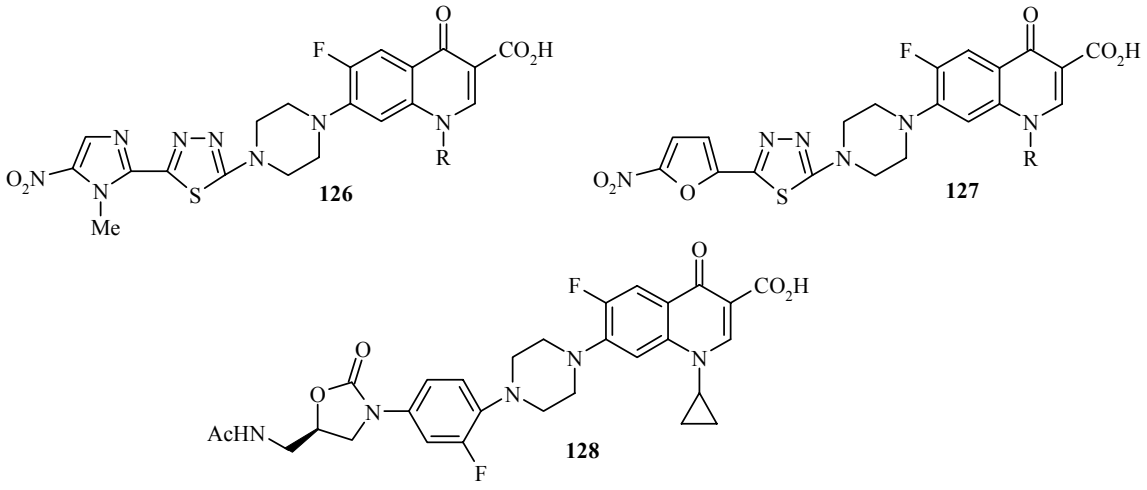


X = O, NH, $OC_6H_4CH{=}NNH$-4; n = 0–4

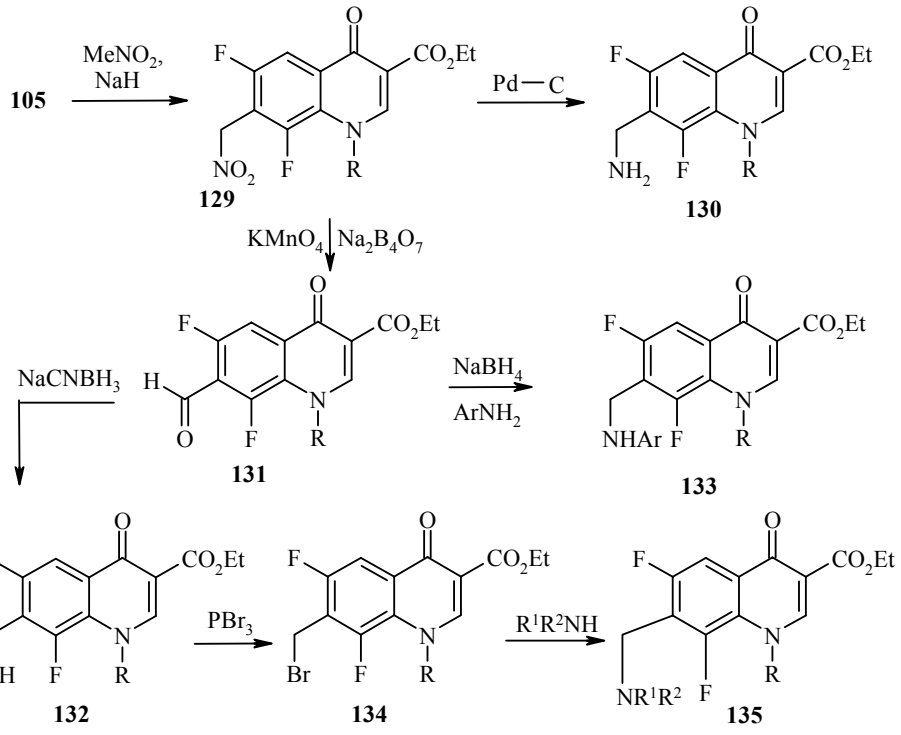
2.7.2. Modifications of an Existing Nitrogen-Containing Substituent at Position 7. The papers belonging to this section mostly relate to the synthesis of derivatives containing a variously substituted piperazine ring at position 7. The required substituent is inserted into the piperazine group by treating the 4-quinolones **123** with the respective bromine derivative in the presence of a base, leading to the derivatives **124a-c** [36, 102, 73]. The 4-quinolone **124c** then reacts with isonicotinohydrazide with the formation of compound **125** [36].



Derivatives of 4-quinolones containing the structural elements of preparations used in medicine, such as metronidazole **126** [103, 104], nitrofurantoin **127** [105], and linezolid **128** [106, 107], are obtained similarly.

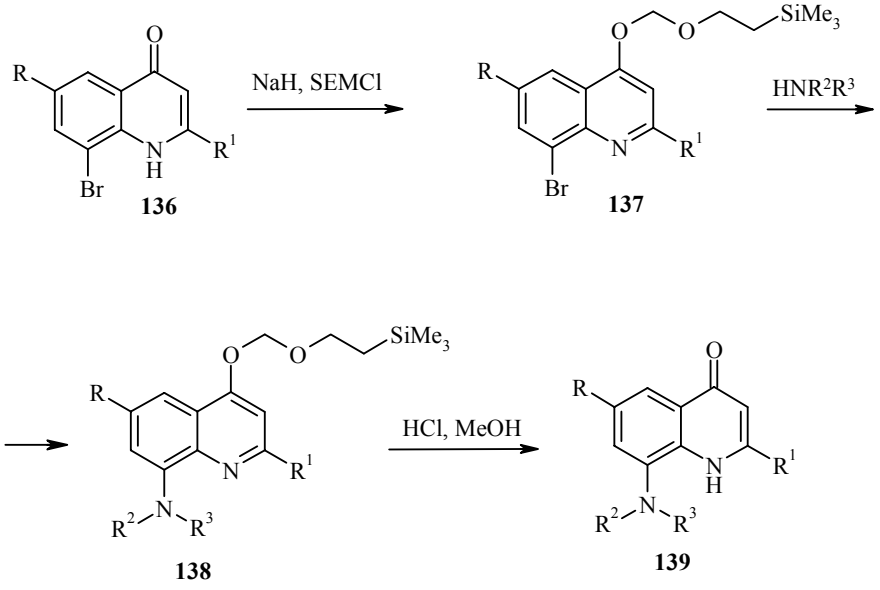


2.7.3. Insertion of a Substituent at Position 7 with the Formation of a C–C Bond. Various substituents can be inserted at position 7 of the 4-quinolones **105** through the initial stage of formation of the 7-nitromethyl derivative **129**, the catalytic reduction of which leads to the 7-aminomethyl derivative **130**. The oxidation of compound **129** with an aqueous solution of potassium permanganate gives the formyl derivative **131**, which has been used for the synthesis of a series of substituted 7-aminomethyl derivatives. Compounds **133** were obtained by its reductive amination. The analogous derivatives **135** are synthesized as a result of a sequence of reactions: reduction to the hydroxymethyl derivative **132**, substitution of the primary alcohol group by bromine by the action of phosphorus(III) bromide with the formation of compound **134**, and reaction of the latter with amines [80].

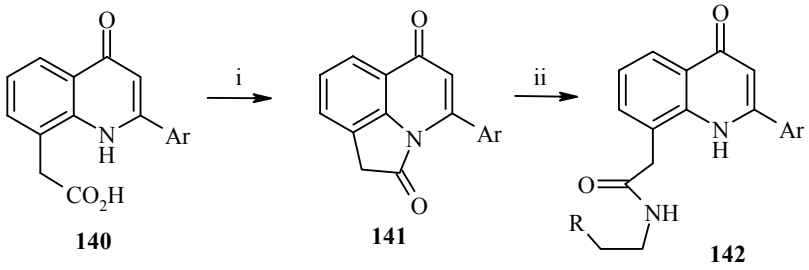


2.8. Modification at Position 8

The introduction of a nitrogen-containing heterocycle at position 8 of the 4-quinolones **136** takes place through a stage involving protection of the 4-oxo group, for which purpose 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) is used. The obtained derivative **137** is brought into reaction with the required amine (morpholine, substituted pyrrolidines, etc.) in the presence of tris(dibenzylideneacetone)dipalladium, ±2,2-bis-(diphenylphosphino)-1,1'-binaphthalene, and cesium carbonate or potassium fluoride. The protection is removed by treating compound **138** with hydrochloric acid [49].



The 4-quinolone **140** undergoes intramolecular cyclization with the formation of compound **141** in dichloromethane in the presence of 3-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride and 4-dimethylaminopyridine. In the reaction of compound **141** with N,N-dimethyl- or N,N-diethylethylenediamine or β-alanine benzyl ester the quinolones **142** are formed [33].



140 **141** **142**

i – EDCl 3-ethyl(1-(3-dimethylaminopropyl)carbodiimide hydrochloride), DMAP (4-dimethylaminopyridine), CH_2Cl_2; ii –amine, MePh; **142** R = NMe_2, NEt_2, CO_2Bn

3. BIOLOGICAL ACTIVITY OF 4-QUINOLONES

The antibacterial characteristics of 4-quinolones were known in 1963 [5, 6, 14] if we start from the introduction of the first example of this series (nalidixic acid) into medical practice. There is now already talk about a fourth generation of 4-quinolones [11], and this group numbers up to 30 members, of which 15 are used in clinical practise in various countries [9]. Ten of them are authorized for use in Russia: *pefloxacin, norfloxacin, ofloxacin, levofloxacin, ciprofloxacin, grepafloxacin, moxifloxacin, lomefloxacin, sparfloxacin, enoxacin* [108].

The product rosoxacin declared by Pfizer in 1978 was the first representative of 7-(4-pyridinyl)-4-quinolones, for which it was found that they react with mammalian type II topoisomerase [5, 6, 62]. This marked the beginning of researches into the antineoplastic activity of 4-quinolones.

In certain cases 4-quinolones are not cytotoxic but exhibit significant antitumor activity [33].

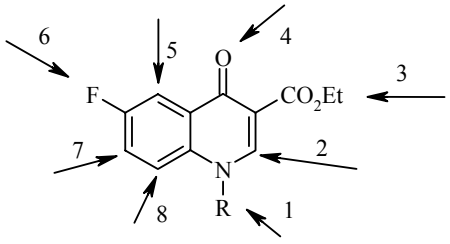
In addition, active researches have been carried out on other types of biological activity in 4-quinolones. The following types of activity have been observed in a series of papers: Antiviral with respect to hepatitis B, C, and HIV viruses [3, 4, 24] and herpes viruses [3, 37], antiallergic [3], antimalarial [68, 109], antitubercular [36, 39, 110], immunomodulating [38], antihypoxic [25], antidiabetic [46]. 4-Quinolones have antithrombocytic [111] and positive cardiotonic activity [24]. The antifungal effect of *fluconazole* is enhanced in combination with 4-quinolones [112]. *Sparfloxacin* can be used in conjunction with ultrasonic therapy for the treatment of cancer [113]. Certain quinolones (e.g., *enoxacin*) are photosensitizers in radiotherapy [114]. There are data to the effect that 4-quinolones serve as antagonists of $5HT_{1B}$ receptor, which is the target during the treatment of depression and other psychiatric disturbances [49], and of the cannabinoid CB_2 receptors that have been actively studied in recent years [41, 42]. 4-Quinolones inhibit protein kinase CK2, which participates in the development of certain types of cancer, virus infections, and inflammatory processes [38], and farnesyl transferase, which takes part in the control of cell division [115].

4. THE "STRUCTURE–ACTIVITY" RELATIONSHIP OF 4-QUINOLONES IN THE CASE OF ANTIBACTERIAL AND ANTITUMOR ACTIVITY

Since the beginning of the nineties conclusions about the dependence of the antibacterial activity on the nature of the substituents have remained fairly constant [13]. At the same time the accumulation of factual material cannot but lead to reexamination of the existing data (scheme 1).

Scheme 1

The "structure–antibacterial activity" relationship for 6-fluoro-4-oxo-1,4-dihydro-2-quinolinecarboxylic esters



1. Replacement of the N atom by an O or C atom deactivates the molecule [4]. The best is an ethyl group at the N atom and also its bioisosteres – cyclopropyl [64, 102-104, 110, 116], *tert*-butyl [64], methylamino, 2,(4)-(di)fluorophenyl, *p*-hydroxyphenyl [3], fluorocyclopropyl [97, 13], 5-amino-2,4-difluorophenyl, 5-fluoro-2-pyridinyl, 2-amino-3,5-difluoro-2-pyridinyl [13], piperidinyl, piperazinyl [110], and 4-amino-2-fluorophenyl [73] substituents. The insertion of phenyl, *p*-nitrophenyl [73], benzyl [13], and morpholinyl [110] substituents has an unfavorable effect.

2. The presence of Me and SMe groups and an F atom at position 2 is unfavorable. [*a*]Thiazolidino and thiazeto annelation are favorable [3, 13].

3. Replacement of the CO_2Et group by H, RCO, NN(R)C(S)NR, and CO_2Me leads to decrease or loss of activity. Esterification with derivatives of cephalosporin and penicillin leads to active compounds with "dual activity". The nitroacetyl derivative [13] and arginine salts [82] have good activity. [*b*]Oxoisothiazolo, pyrido, pyrimido, and pyrazino annelation are favorable [3].

4. Removal or replacement of the C=O group leads to inactivation. The SO and SO_2 groups are not bioisosteres of C=O in quinolones [3].

5. The insertion of Hal, OH, OMe, SH, SMe, CHO, CH_2O [3], Et, NHMe, NMe_2, NHAc [13], NH_2, and Me [3, 13] at position 5 does not lead to an increase of activity. According to data in [97], the insertion of an NH_2 group increases the activity.

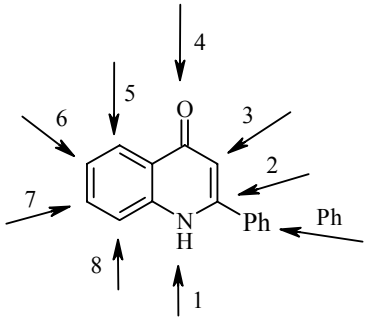
6. The insertion of Hal [13], NO_2 [64], and NH_2 [60] at position 6 is favorable. The substituents can be arranged in the following order of increasing activity: F > H > NH_2 > Me > Br [13]. The introduction of $OCHF_2$, 1-pyrrolidinyl, 4-methyl-1-piperazinyl, 1-piperazinyl, 1-morpholinyl [3], and NH_2 [13, 64] is unfavorable.

7. Compounds containing H, OH, OEt, CO_2H, Me, Cl, NH_2, NHR, $NHNH_2$, $SCH_2CH_2NH_2$ substituents at position 7 have low activity or are inactive. The introduction of the following 4,5,6-membered nitrogen-containing heterocycles is favorable: piperazinyl [3], bicycles [13, 97], pyrrolidinyl, piperidinyl [55, 60, 112], piperazinyl [60]. They, in turn, can contain various bulky substituents (2-(2-furyl)- and 2-(3-thienyl)-2-oxoethyl, hydroxyiminoethyl [102, 116], 1,3,4-thiadiazol-2-yl [103-105]). Compounds with cyclopropyl, 1-amino-cyclopropyl, vinyl, aminomethyl [80], and amino-*tert*-butyl [64] substituents exhibit excellent activity [13]. 1,2,3-Triazolo[4,5-*h*] annelation is favorable [39].

8. The introduction of Me, Cl, F [73], and C=CH_2 at position 8, oxazino[*i*] annelation [3, 14], OMe [55, 60], and H [64] are favorable. The presence of NO_2, NH_2, and SMe groups, benzoxazino and benzothiazino[*i*]annelation [3], and the presence of OH, OEt, OCH_2F, and OCF_3 [13] are unfavorable.

Scheme 2

The "structure–antitumor activity" relationship for 2-phenyl-4-quinolones



1. Replacement of the N atom by S atom leads to inactivation of the molecule [62]. The presence of an unsubstituted N atom is essential [19, 20, 32, 52]. The presence of cyclopropyl, 2-thiazolyl [6], CH_2F_3, $(CH_2)_2F$, NHMe [13], and $(CH_2)_2NEt_2$ [119] at the N atom is favorable. The presence of *p*-fluorophenyl, *t*-Bu, Et, and FC_2H_4 is unfavorable [62, 117, 120].

2. Heteroaromatic substitution at position 2 is admissible [6, 83]. The introduction of CH_2-2-imidazoyl is more favorable than Bn. The pyridinyl and pyrrolidinyl analogs are less active than Bn [83]. The [*b*]-annelated analogs are inactive [22]. The distance between the two aromatic parts is critical. The CH_2 group is best [6].

Position 3 of the phenyl substituent is the most important. The following order of substituents H = F > N > Cl = OMe is preferred [19]. According to data in [21], both electron-accepting (Hal) and electron-donating substituents (NH_2, NHMe, OH, OCF_3, OEt, OBn) can be present at this position without any significant effect on the activity.

Position 4 of the phenyl substituent is not important [19]. According to other data, the substituents can be arranged in the following order of favourability: CO_2H = OH > *n*-Bu > NH_2 = Me = CO_2Et > *t*-Bu [18]. This position must be free [22].

In spite of the fact that the 3-fluoro derivatives have high activity the 3,5-difluoro derivatives are inactive [19].

3. The introduction of Bn at position is favorable. The activity is sensitive to the distance between the phenyl ring and the quinolone fragment. Thus, Bn is better than Ph or CH_2Bn. The introduction of $CH_2C_6H_{11}$ or CH_2-1-naphthyl is unfavorable [82]. The unsubstituted position is more favorable than the position substituted by OH, Et [18], or COOH [62, 81]. In [6] the main requirements are considered to be coplanarity of the substituent and the quinolone ring. Isothiazolo[*b*] annelation is favorable. The CO_2H group is better than the CO_2Et group [12].

4. Replacement of the carbonyl O atom by S [20, 81] or alkylation of the oxygen (Me, Et, *i*-Pr, Bu, *i*-Bu, $C_2H_4NMe_2$, Bn [20, 32]) leads to loss of activity. Replacement of the O atom by a hydrazone, imine, or thioxime group increases the activity by ten times [81]. Pyrazolo[*c*]-annelation leads to an increase of activity [91].

5. The presence of OH, F, NH_2, and H at position 5 is favorable [18, 19, 52, 62]. The presence of SPh, OAlk, and CO_2H groups is unfavorable [15, 21, 45]. However in [47] is shown that the substituent does not have an effect.

6. At position 6 groups with unshared electron pairs OMe, OCH_2O, NRR^1, Cl, and F [22, 32, 118], heterocyclic rings, NMe_2 and AcNH [21] groups and H [52] are favorable. The NH_2, OMe [19, 21], OH, and CO_2H [32, 53] groups are unfavorable.

7. The introduction of 2,(6)-(di)methyl-4-pyridinyl or unsubstituted 4-pyridinyl, 4-hydroxyphenyl [5, 62], pyrrolidinyl, aminoazobicycles [6], and H [52] at position 7 is favorable. The introduction of 3-pyridinyl, 2,6-dimethylpiperidinyl, methylpiperazinyl, and aminopyrrolidinyl is unfavorable [62]. According

to some data, the presence of OMe, OH, and F is favorable [19, 32]. According to data in [18], OH and OMe groups are not favorable. The carboxyl derivative is inactive [53].

8. The introduction of the F atom [6] and other halogens at position 8 [32, 117, 120] is favorable. The introduction of OH and OMe groups is unfavorable [32]. In [52], conversely, OMe was favorable, and Me, H, and Cl were unfavorable.

The effect of substituents at certain positions is unequivocal (3, 4), while at certain positions, e.g., 6, it depends on the substituent at position 8. Thus, an unfavorable substituent at position 6 will be advantageous with the "right" substituents at positions 1, 3, and 8 [5]. In 1997 at the 37th International Conference on Antimicrobial Products and Chemotherapy Hayashi and co-workers demonstrated convincingly that the presence of a fluorine atom at position 6 of 4-quinolone is not essential [14], although it had been accepted as self-evident for almost 20 years.

Data on the antitumor activity of 4-quinolones have been quite uncoordinated and often contradictory (see scheme 2). This indicates, first, that the structure–activity connection has not been fully studied and, second, that the results obtained during investigation of the activity using different testing methods have been examined during the study of antitumor activity, and this hampers analysis of the data. Moreover, no single position in the molecule is evidently key, and it is more likely that activity corresponds to a combination of different substituents.

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