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NEW QUINOLINE CARBOXYLIC ACID DERIVATIVES IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE SUBSTANCES. (Review)

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Data on the synthesis and biological properties of derivatives of quinoline-4-carboxylic acids over the past 10 years have been summarized. The review considers both the derivatives substituted at different positions of the heterocyclic ring and the derivatives of the carboxyl group of quinoline-4-carboxylic acid. Given the importance of quinoline derivatives in the search for new promising compounds of biomedical use [3-8], the review provides information on methods for the preparation and biological activity of the described new derivatives of substituted quinoline-4-carboxylic acids.

References 43.

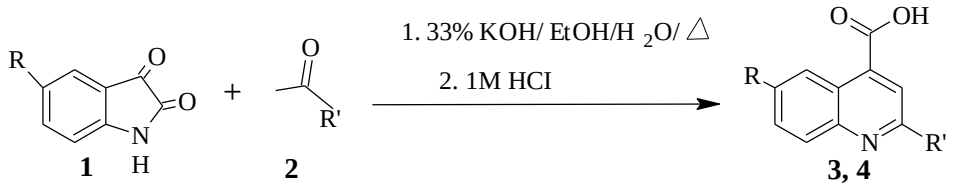
Introduction

Though after the discovery of the antigout and analgesic properties of 2-phenylquinoline-4-carboxylic acid (Cinchophen), undesirable side effects, associated with the use of the drug, were identified limiting its further use, quinoline-4-carboxylic acid continues to be considered as a promising scaffold for the creation of new multidirectional drugs [1]. Prerequisites for this are both a wide range of biological activity of quinoline-4-carboxylic acid derivatives and relatively well-developed methods for the synthesis of various derivatives of this acid [2]. Moreover, quinoline-4-carboxylic acid derivatives, for example 2-chloro, 2-hydrazine derivatives, can be used to synthesize other biologically active compounds based on them, which confirms the relevance of further targeted synthesis and study of new quinoline-4-carboxylic acid derivatives. This review summarizes the data predominantly of the last 10 years on the synthesis and biological properties of new derivatives of quinoline-4-carboxylic acid, including those substituted at different positions of the heterocyclic ring and derivatives of the carboxyl group of the acid.

Synthesis of quinoline-4-carboxylic acid derivatives

Under the conditions of the Pfitzinger reaction using isatins **1** and various substituted acetyl heterocyclic compounds **2**, 2-aryl-(hetaryl)quinoline-4-carboxylic acids **3** (R = H) and **4** (R = F, Cl, Br, NO_2) were synthesized in good yields. Quinolines **3** have pronounced antitumor, antituberculosis and antimalarial activity, and compounds **4** containing the CF_3 group have high antibacterial activity (Scheme 1) [9, 10].

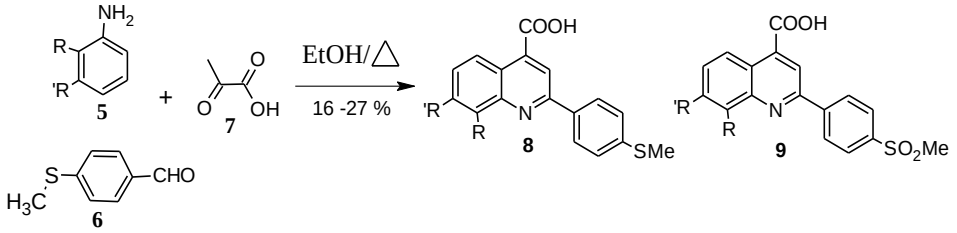
Scheme 1



3: R1 = furan-2-yl, 5-methylfuran-2-yl, 1,5-dimethylpyrrol-2-yl, 4-BrC_6H_4, CH = CHPh, CH = CH (4-ClC_6H_4), 2,4,5 -$Me_3C_6H_2$, naphthalen-2-yl, 1-hydroxynaphthalen-2-yl, anthracene-9-yl; **4:** R1 = 3,5- $(CF_3)2C_6H_3$, imidazol-1-yl, piperazin-1-yl, CH_2(4-$CF_3C_6H_4$).

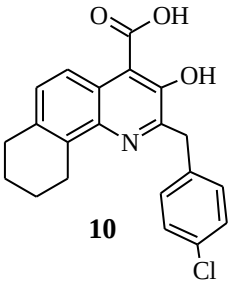
In a study on the search for new active antiinflammatory drugs in the series of **COX-2** enzyme inhibitors, by three-component condensation of substituted anilines **5**, 4-methylthiobenzaldehyde **6** and pyruvic acid **7**, new derivatives of quinoline-4-carboxylic acid **8** were synthesized in low yields, and the interaction of 1-[4-(methylsulfonyl)phenyl]ethanone with unsubstituted isatin **1** (R = H) afforded derivative **9** (Scheme 2) [11].

Scheme 2



Antiinflammatory drugs, derivatives of 2-(4-chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo- [h]quinoline-4-carboxylic acid **10,** obtained by the methodology of convergent synthesis from the starting 3-(4-chlorophenyl)-2-oxopropyl acetate and 1,2,3,4-tetrahydronaphthalene were patented [12] (Scheme 3).

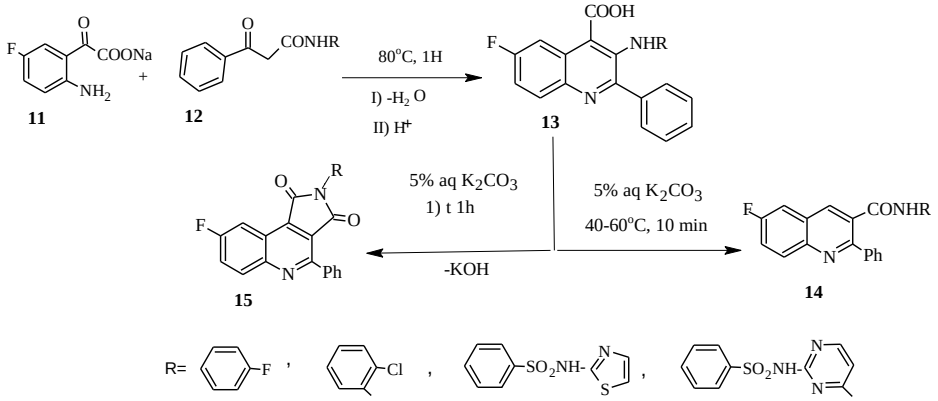
Scheme 3



10

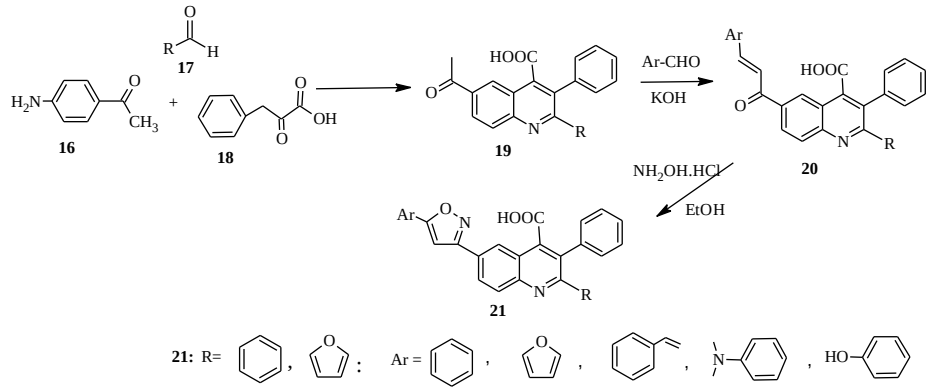
The high-yield synthesis of fluorine-containing quinoline-4-carboxylic acids by cyclo-condensation of the sodium salt of 2-amino-5-fluorophenylglyoxylic acid **11** with benzoylacetanilides **12** when boiling in DMF is described. Decarboxylation of **13** led to 6-fluoro-2-phenyl-3-(substituted amino)ketoquinolines **14**, and boiling - to 7-fluoro-1-(aryl)-3-phenylpyrrolo[3,4-c]quinolin-2,9-dions **15.** The compounds were effectively studied as amylolytic agents (Scheme 4) [13].

Scheme 4



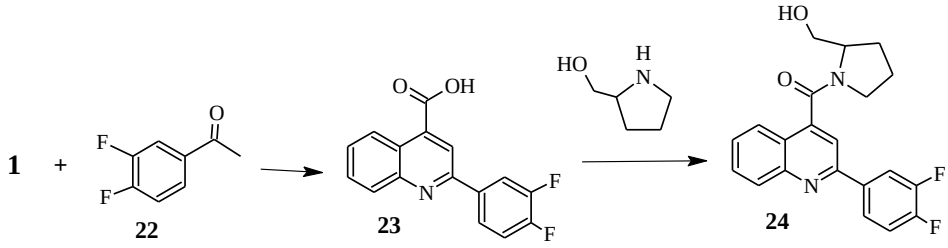
The synthesis of new 2,3-diaryl-6-acetylquinoline-4-carboxylic acids **19a-e** by three-component condensation of 4-aminoacetophenone **16,** benzaldehyde **17** or furan-2-carbaldehydes and phenyl-pyruvic acid **18** by the Doebner reaction is described. Compounds **19a-e** by interaction with various aromatic aldehydes in the basic medium were transformed to the corresponding chalcones **20a-e,** which were condensed with hydroxylamine hydrochloride in ethanol to heterocyclic derivatives of isoxazoles **21a-e.** The latter were tested for antibacterial and antifungal activity (Scheme 5) [14].

Scheme 5



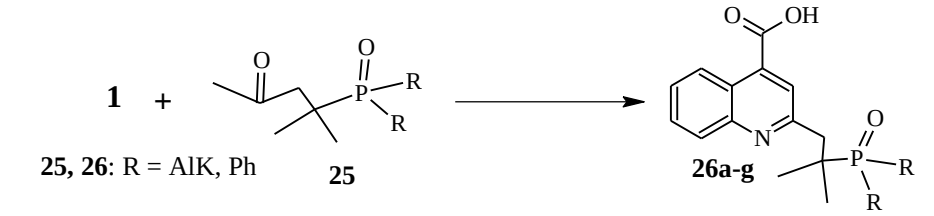
By the interaction of isatin **1** with 3,4-difluoroacetophenone **22** under the conditions of the Pfitzinger reaction, a number of quinolinecarbonylpyrrolidines **24** were synthesized, which were patented as compounds exhibiting high selectivity for GABA benzodiazepine receptors (Scheme **6**) [15].

Scheme 6



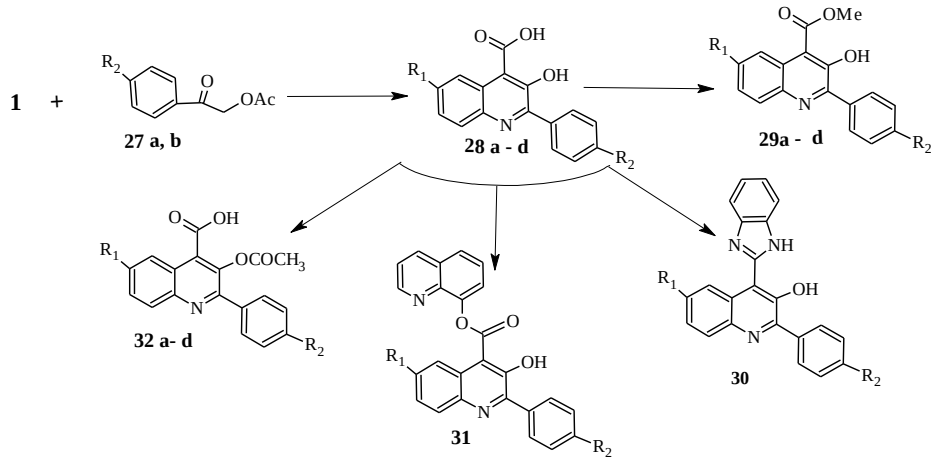
The work presents the synthesis of new derivatives of 2-[2-(dialkyl(diaryl)-phosphoryl)-2-methylpropyl]4-quinolinecarboxylic acids **26a-g** containing a phosphine oxide fragment; the synthesized derivatives were tested for antibacterial activity (Scheme 7) [16].

Scheme 7



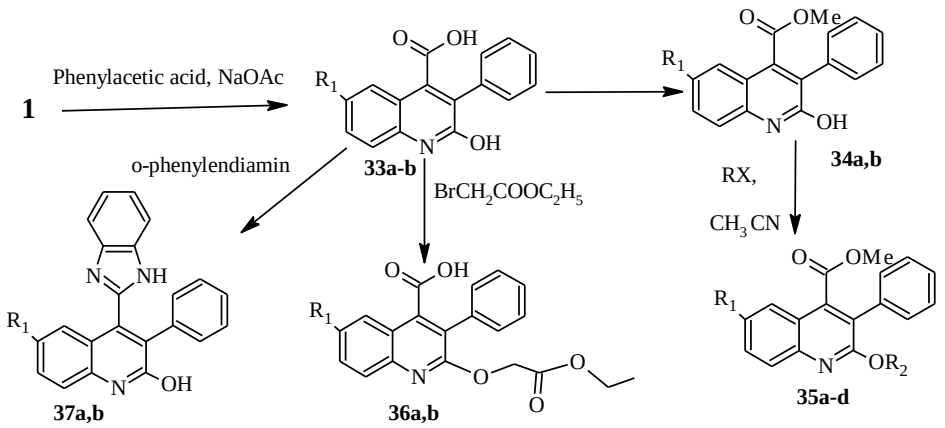
Two new series of 2-aryl-3-hydroxy- and 3-aryl-2-hydroxyquinoline-4-carboxylic acids **28a-d**, **33a, b** and their derivatives **29-32** and **34-37** are presented**.** Antioxidant activity was studied using the **ABTS** method (Scheme 8, 9**)** [17].

Scheme 8



R_1, R_2: CH_3, H (a), CH_3, CH_3(b), Br, H(c), Br, CH_3 (d).

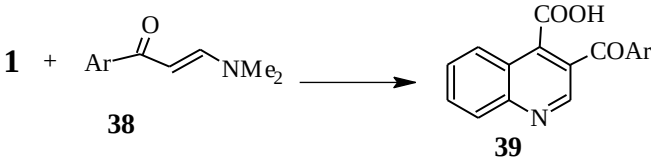
Scheme 9



R_1, R_2 : CH_3, CH_3 (a), Br, CH_3 (b), CH_3, CH_2Ph (c), Br, CH_2Ph(d)

A simple one-step method for the synthesis of quinoline-4-carboxylic acids **39** by the reaction of enaminones **38** and isatin using the conditions of the Pfitzinger reaction has been described (Scheme 10) [18].

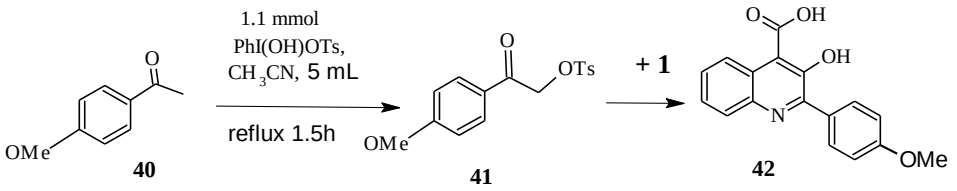
Scheme 10



The synthesis of 2-(4-methoxyphenyl)quinoline salicylic acid **42** from α-tosyloxyaceto-phenone and isatin **1** under the conditions of the Pfitzinger reaction has been developed. α-Tosyl-oxyacetophenone was obtained by boiling

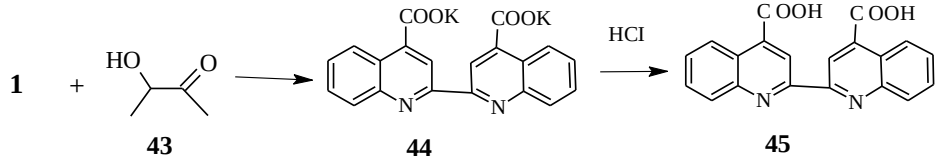
5 *ml* of 4-methoxyacetophenone **40** with Kosser's reagent [hydroxy(tosyloxy) iodo]benzene (HTIB) in acetonitrile (Scheme 11) [19].

Scheme 11



The synthesis of 2,2-biquinolyl-4,4-dicarboxylic acid **45** by the Pfitzinger reaction from isatin **1** and acetoin (2-hydroxy-butanone-3) **43** was registered in the work (Scheme 12) [20].

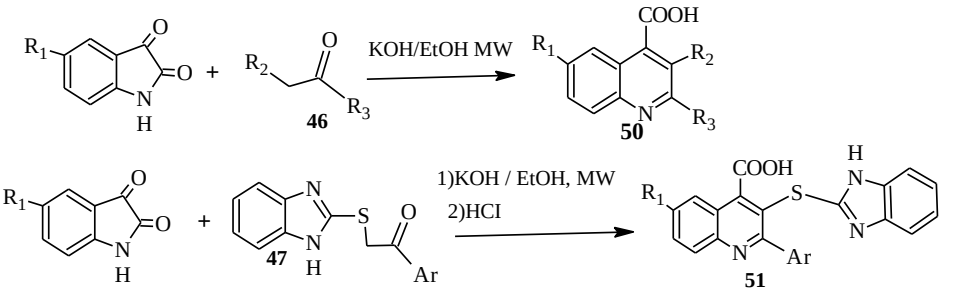
Scheme 12

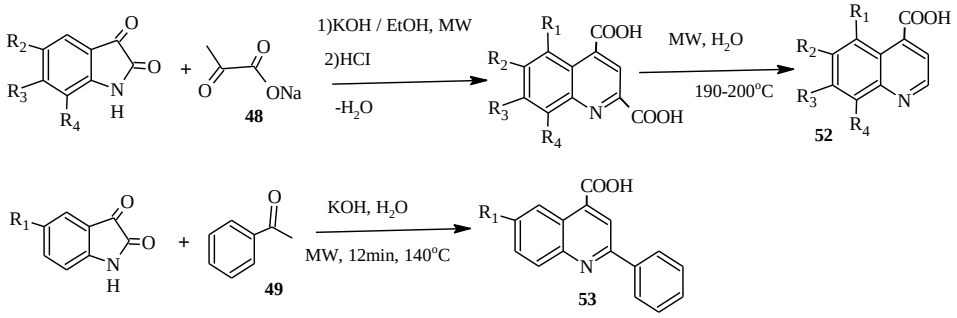


2a. Synthesis of quinoline-4-carboxylic acid derivatives using microwave irradiation and catalysts

Microwave irradiation was used to quickly and efficiently synthesize substituted quinoline-4-carboxylic acids **50a-q, 51a-d, 52a-k,** and **53** by reacting substituted isatines **1** with acyclic and cyclic ketones **46**, 2-(1-benzimidazol-2-ylthio)-1-arylethanones **47**, sodium pyruvate **48** and acetophenone **49** under the conditions of the Pfitzinger reaction (Scheme 13) [21-24].

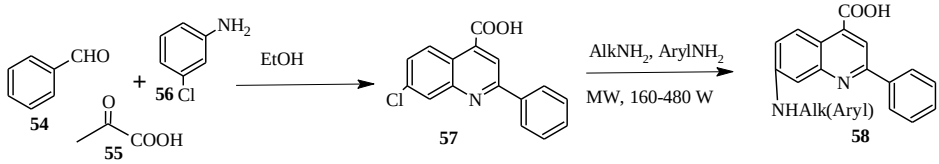
Scheme 13





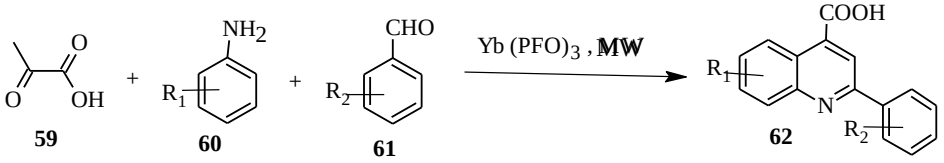
The main attention is paid to the synthesis of derivatives of 2-phenyl-7-substituted quinoline-4-carboxylic acids **58** under the influence of microwave irradiation with an output power of 160 to 480 W, the output varies from 90% to 95% and the reaction time is shorter than with the conventional method. The compounds are active against a wide range of microorganisms (Scheme 14) [25].

Scheme 14



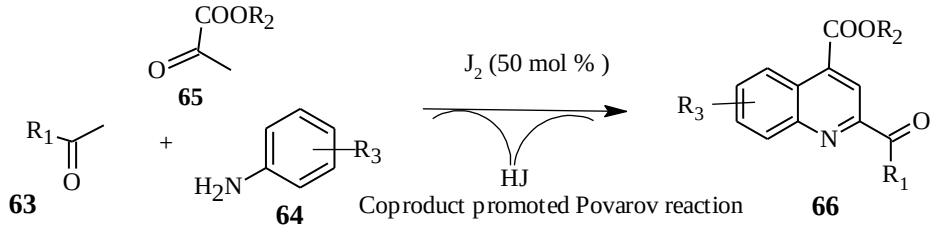
Ytterbium perfluorooctanoate [Yb (PFO) 3] effectively catalyzes the Doebner reaction and is described as a new procedure for the preparation of quinoline-4-carboxylic acid derivatives **62** using the three-component reaction of combining pyruvic acid **59**, amines **60** and aldehydes **61** in water. This process is quick, easy and environmentally friendly, and the catalyst is repeatedly processed with sequential activity (Scheme 15) [26].

Scheme 15



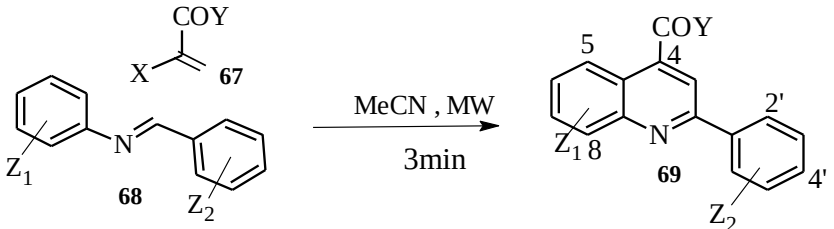
A highly efficient method for the synthesis of substituted quinolones 66 from methylketones 63, arylamines 64 and α-ketoesters 65 has been developed. This reaction uses a catalytic amount of HI-coproduct as a promoter for the synthesis of substituted quinolones (Scheme 16) [27].

Scheme 16



Rapid synthesis of quinoline-4-carboxylic acid derivatives **69** has been achieved by the reaction of 2-methoxyacrylates or acrylamides **67** with *N*-arylbenzaldimines **68** in acetonitrile under $InCl_3$ catalysis and microwave irradiation. The yield of the product was up to 57% within 3 min. The role of indium chloride and ytterbium triflate was specified using ^{13}C NMR data and model theoretical studies (Scheme 17) [28].

Scheme 17



Z_1=H, 6-F, 6-Cl, 6-Br, 8-F.

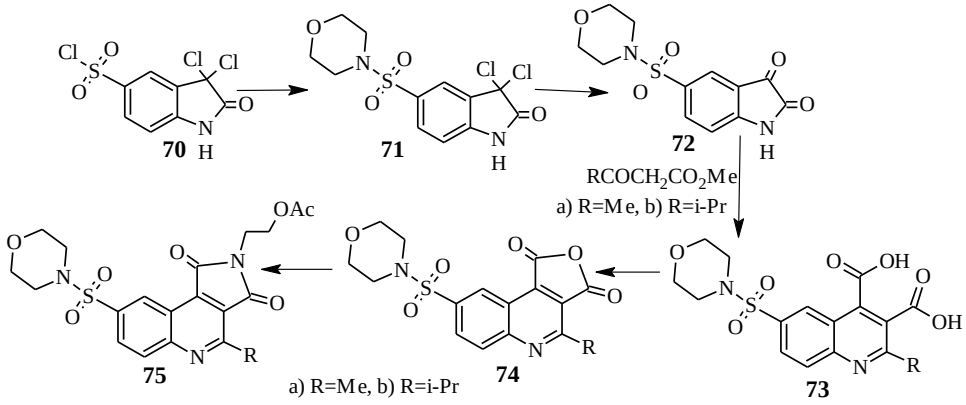
Z_2=2',3' or 4'-F,4'-Br, 3',4'-OMe, NHBr, NH-CH(Ph)Et

X=OMe; Y=OEt,OMe,NHBr,NH-CH(Ph)Et

Multisubstituted Carboxamides of 4-Quinoline Carboxylic Acids

The connection between synthesis, biological assessment and SAR is described for a series of new inhibitors of caspase-3 1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinoline **75**. The inhibitory activity of the synthesized compounds is highly dependent on the nature of the substituent in position 4 in the nucleus frame structure. 4-Methyl and 4-phenyl substituted derivatives are the most active compounds in this series; caspase-3 with an IC50 of 23 and 27 nM, respectively, was inhibited (Scheme 18) [29].

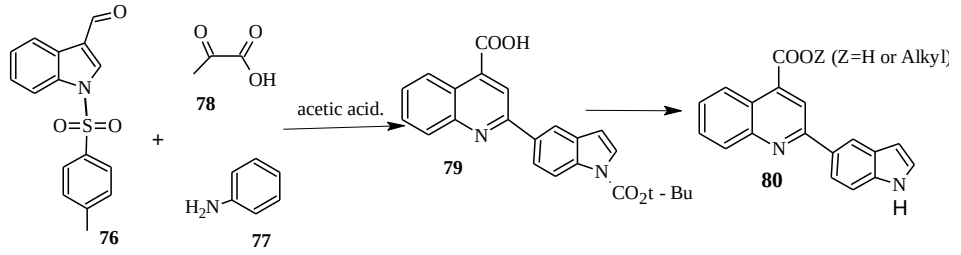
Scheme 18



The patented work relates to a method for producing a pharmaceutical preparation of 2-(N-Boc-3-indolyl)-4-quinolinecarboxylic acid **79** and carboxylate **80,** which inhibits the growth of bacterial microorganisms.

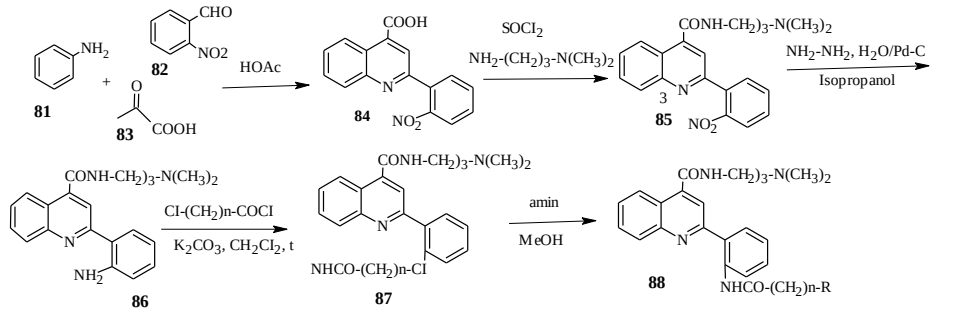
2-(N-Boc-3-indolyl)-4-quinolinecarboxylic acid was obtained under the conditions indicated in Scheme 19) [30].

Scheme 19



A number of new derivatives of 2-phenylquinoline-4-carboxylic acid **84** were synthesized from aniline **81**, 2-nitrobenzaldehyde **82**, pyruvic acid **83** under the conditions of the Doebner reaction, followed by amidation **85**, reduction **86**, acylation **87** and amination **88**. We studied the antibacterial activity of these compounds. Results showed that some compounds exhibited good anti-bacterial activity against *Staphylococcus aureus* (Scheme 20) [31].

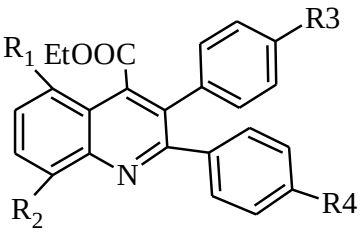
Scheme 20



R=-N(C$_2$CH$_4$)$_2$N-, -NC$_4$H$_8$, -N(Et)$_2$, -NC$_5$H$_{10}$, NH$_2$ (CH$_2$)$_3$ NMe$_2$, - NH (CH$_2$)$_3$ -NEt$_2$, - NC$_4$H$_8$O,

The patent describes the preparation of polysubstituted quinoline-4-carboxylates **89a-h** as anti-microbial agents (Scheme 21) [32].

Scheme 21

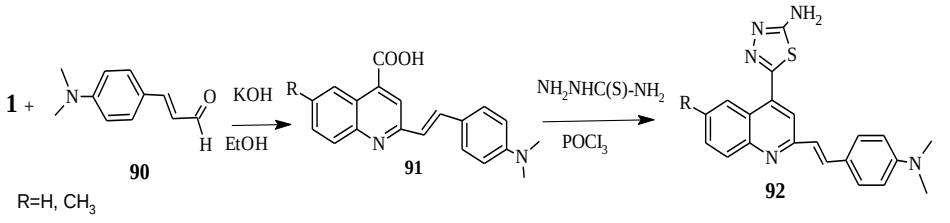


89a-h

89a-h: 5.8-Dichloro-2,3-diphenyl- (a), 5,8-dichloro-2- (4-chlorophenyl) -3-phenyl- (b), 5,8-dichloro-3- phenyl-2-p-tolyl- (c), 5,8-dichloro-4-methoxyphenyl) -2-phenyl- (d), 5,8-dichloro-3- (4-methoxy phenyl) -2- p-tolyl (e), 5,8-dichloro-2-n-pentyl-3-phenyl- (f), 6-chloro-2-n-propyl-3- (3,4-methylenedioxy) - (g) 5,8-dichloro-2-n-propyl-3-phenyl- (h).

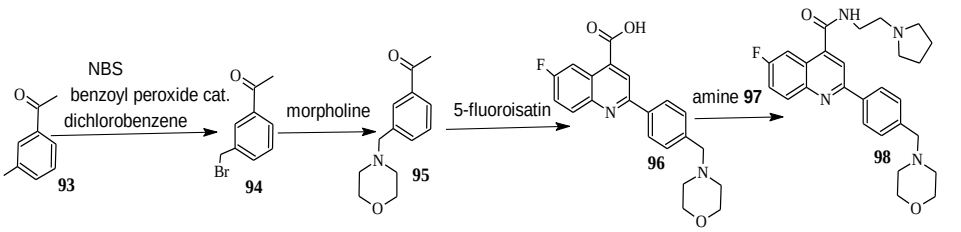
A new series of 4,6-disubstituted-2-(4-(dimethylamino)styryl)quinolines **91**, **92** were synthesized and the antitumor activity of all compounds was studied by MTT analysis against two cancer cell lines. A discussion of the results showed that some derivatives exhibited the highest antitumor activity against the tested cell lines compared to control preparations (Scheme 22) [33].

Scheme 22



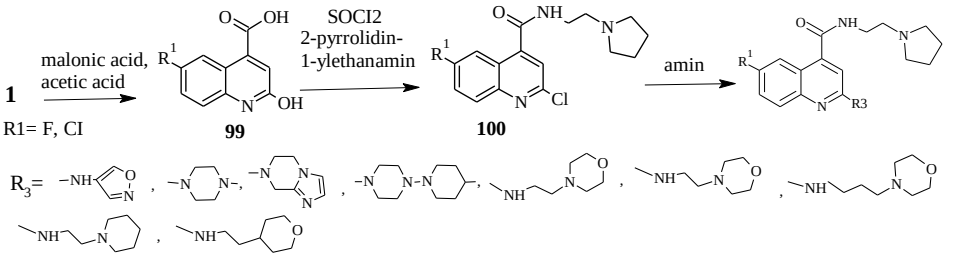
The authors have developed an effective method for the synthesis of a quinoline-4-carboxylic acid derivative from a series of carboxamides with multi-stage antimalarial activity *in vivo*. 6-Fluoro-2-[3-(morpholinomethyl)phenyl]-N-[2-(pyrrolidin-1-yl)ethyl]quinoline-4-carboxamide **98** was obtained from a mixture of 6-fluoro-2-[3-(morpholinomethyl)phenyl]quinoline-4-carboxylic acid **96** and 2-pyrrolidin-1-ylethanamine **97** under the conditions indicated in Scheme 23 [34].

Scheme 23



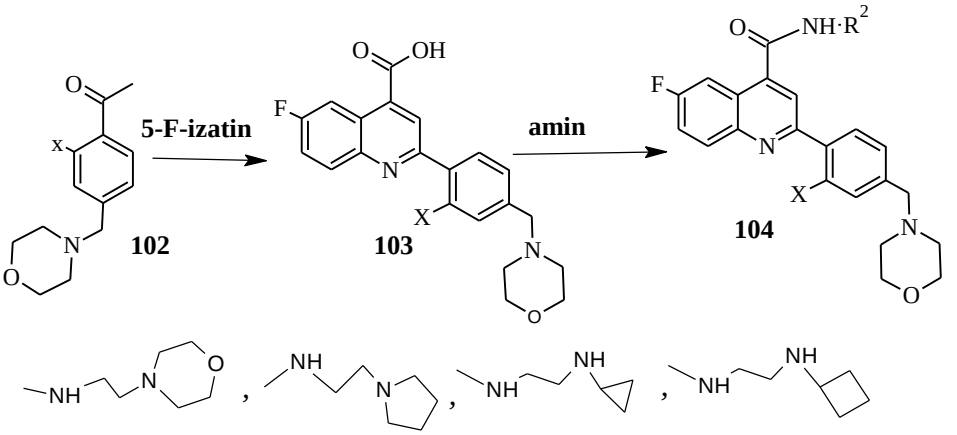
The synthetic pathway for the preparation of a number of carboxamides with aromatic R_3 substituents is presented. The synthesis of compound **101** was achieved by treating 2-hydroxy-quinoline-4-carboxylic acid **99** with thionyl chloride in DMF, followed by reaction with 2-pyrrolidin-1-ylethanamine in THF which resulted in carboxamides **100** treated with a series of amines **101** (Scheme 24) [35].

Scheme 24



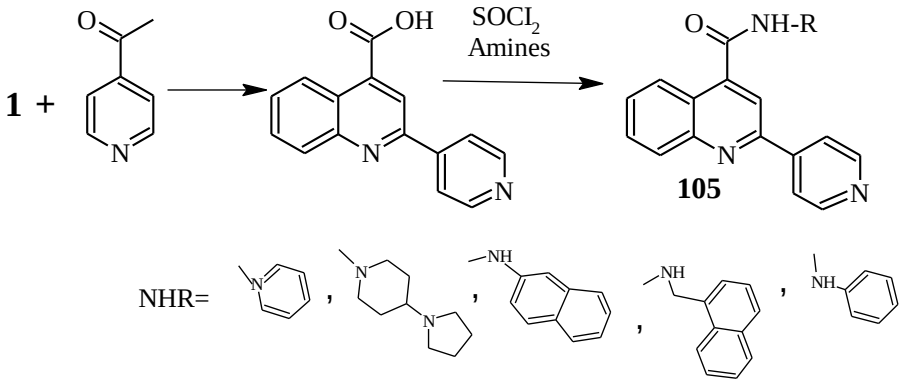
As described in the work, the Pfitzenger reaction of 5-fluorisatin with the corresponding methyl ketone **102** afforded acids **103** and treatment of the latter with the corresponding amines at room temperature yielded the target amides **104a-d.** Optimal conditions for the synthesis of methyl ketone have been developed (Scheme 25) [36].

Scheme 25



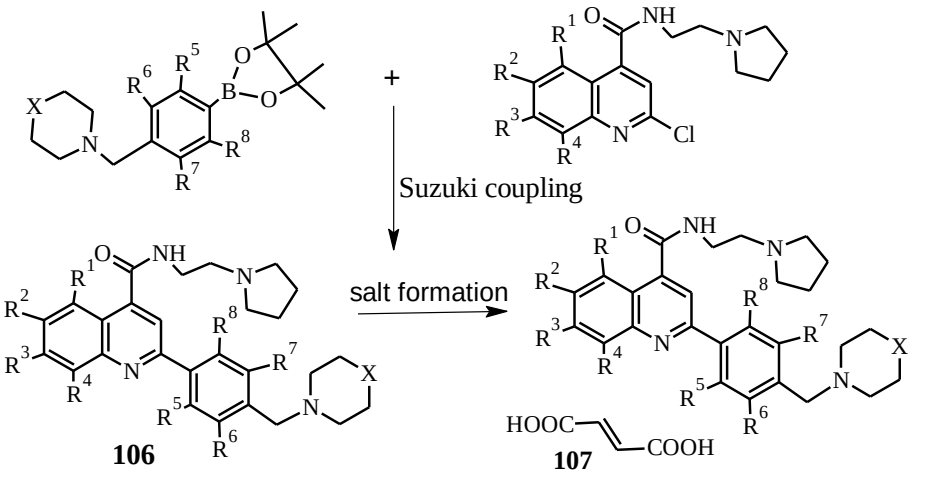
In the work, analogues of quinoline-4-carboxamides **105** were used to study SAR. All compounds were synthesized, as indicated in the diagram, with slight changes for each analog. The general procedure for the preparation of quinoline-4-carboxamide analogues is given in Scheme 26 [37].

Scheme 26



The patent relates to a new class of inhibitors of quinolone-4-carboxamide Pf3D7 of the general formula **106 (107),** their use in medicine and, in particular, malaria, the methods for their preparation and the intermediate compounds used in such processes (Scheme 27) [38].

Scheme 27



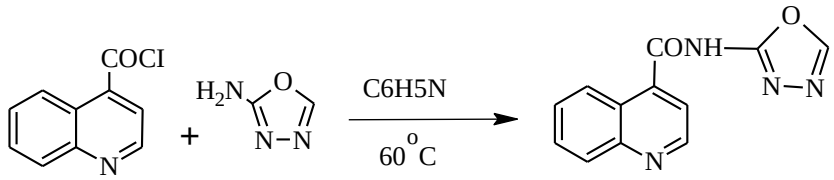
106 107

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R8 irrespective of each other = H, CI or F,X = -O-.

Heterylamides of substituted-4-quinolinecarboxylic acids

The synthesis of 4-quinolinecarboxylic acid heterylamide **110** was achieved by condensation of equimolecular amounts of quinoline-4-carboxylic acid chloride **108** and 2-amino-1,3,4-oxadiazole **109** with gentle boiling in pyridine for 4 hours (Scheme 28) [39].

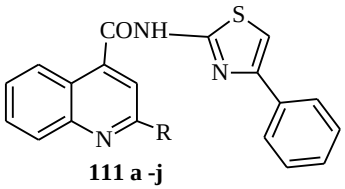
Scheme 28



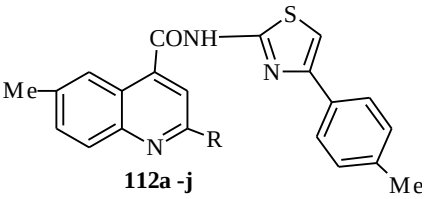
108 **109** **110**

In this work, we report the synthesis of a large number of 2-substituted heterylamides - **111a-j** and 6-R-2-substituted cinchoninic acids **112a-j** by the interaction of the corresponding acid chlorides with heterylamines in benzene or dichloroethane in the presence of several drops of DMF when boiling (Scheme 29) [40].

Scheme 29



111 a -j

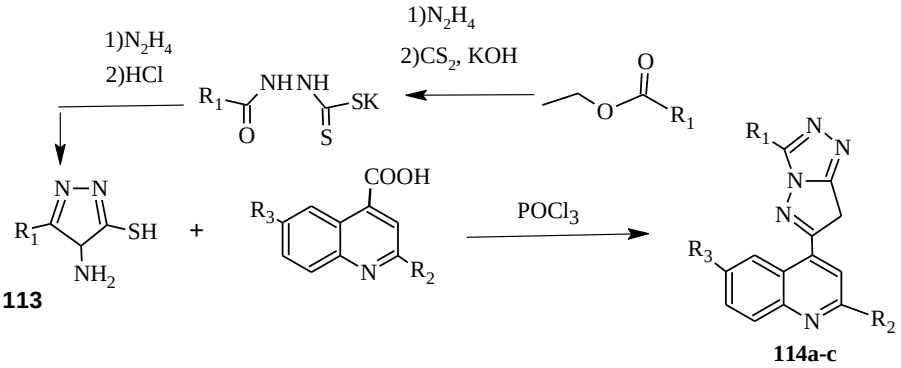


112a -j

111a-j, 112a-j: R = 4-nitrophenyl (a), 3-nitrophenyl (b), diphenyl-4-yl (c), 5-nitro-2-furyl (d), 2-yenyl (e), 5-nitro-2-thienyl (f), 5-nitro-2-thienyl vinyl (e), 2-thienyl vinyl (f), 2,2-bitienyl-5-yl (g), 5-nitro-2,2 β-bitienyl-5-yl (h), 2,2-bitienyl-5-vinyl (i), 5-nitro-2,2-bitienyl-5-yl vinyl (j) as viral inhibitors.

The authors found that substituted 4-amino-4H-1,2,4-triazole-3-thiols **113a-f** of quinoline-4-carboxylic acids when heated with phosphoryl chloride, cyclized to form substituted 4-([1,2,4] triazolo [3,4-b]-[1,3,4]thiadiazol-6-yl)quinolines **114a-c** with various substituents R1-R3. This reaction can be used for the combinatorial synthesis aimed at studying them for biological activity (Scheme 30) [41].

Scheme 30



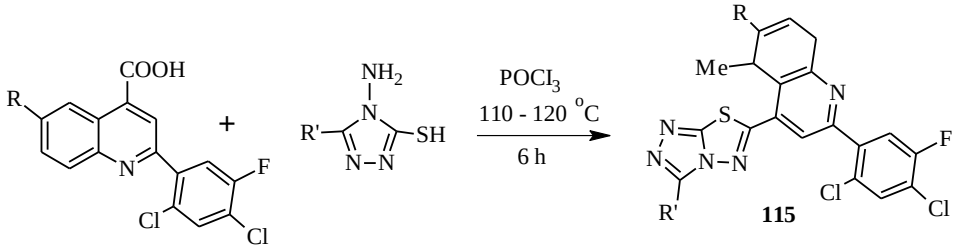
113 **114a-c**

114a-c: R_1 = Et (a), Pr (b), 2-furyl (c), Ph (d), $PhCH_2$ (e), 4-$MeOC_6H4CH_2$ (f); II, R_2 = Me, R_3 = H (a), Cl (b), Br (c); R_2 = Ph, R_3 = H (d), Me (e), Br (f); R_2 = 4-MeC_6H_4, R_3=H (g); III, R1 = Et: R_2 = Me, R_3 = Cl (a), Br (b); R_2 = Ph, R_3 = H (c), Me (d), Br (e); R1 = Pr, R_2 = Ph, R_3 = Me (f), Br (g); R_1 = 2-furyl: R_2 = Me, R_3 = H (h); R_2 = Ph, R_3 = H (i), Br (j); R_1 = Ph: R_2 = Me, R_3 = H (k); R_2 = Ph,R_3 = Me (l), Br (m); R_2 = 4-MeC_6H_4, R_3 = H (n); R_1 = $PhCH_2$, R_2 = Ph, R_3 = Me (o), Br (p); R_1 = 4-$MeOC_6H_4CH_2$, R_2 = Ph, R_3 = Br (r); V, R_3 = H (a), Me (b), Cl (c), Br (d); VI, R_2 = Me (a), Ph (b), 4-MeC_6H_4 (c).

Upon condensation of substituted quinoline-4-carboxylic acids with various 3-substituted-4-amino-5-mercapto-1,2,4-triazoles, a number of still unregistered 3-substituted -1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6-yl-2-(2,4-dichloro-5-

fluorophenyl)quinolines **115** were obtained. The new synthesized compounds were evaluated by their antibacterial activity (Scheme 31) [42].

Scheme 31

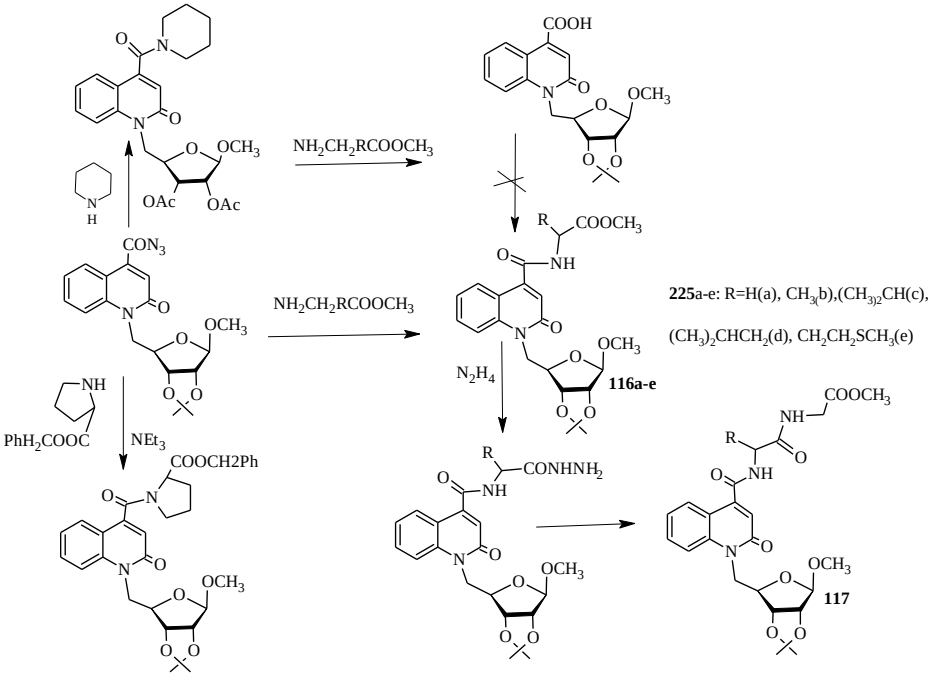


R = H, Br; R_1 = H, CH_3, $CH_3CH_2CH_2$, $C_6H_5CH_2$, $C_6H_5NHCH_2$, 2-$ClC_6H_4OCH_2$, 4-$ClC_6H_4OCH_2$, 2,4-$Cl_2C_6H_3OCH_2$, 3,4-$(CH_3)_2C_6H_3OCH_2$, 4-Cl-3-$CH_3C_6H_3OCH_2$

Quinoline nucleosides

The studies relate to the syntheses of a series of quinoline nucleosides substituted at position 4 with a number of amino acids and dipeptides of carboxamides as potential chemotherapeutic agents. Quinoline nucleosides containing a moiety of amino acid ester **117** were obtained by azide synthesis from **116a-e** esters (Scheme 32) [43].

Scheme 32



ՔԻՆՈԼԻՆ ԿԱՐԲՈՆԱԹԹՎԻ ՆՈՐ ԱԾԱՆՑՅԱԼՆԵՐԸ ԿԵՆՍԱԲԱՆՈՐԵՆ ԱԿՏԻՎ ՄԻԱՑՈՒԹՅՈՒՆՆԵՐԻ ՍԻՆԹԵԶՆԵՐՈՒՄ

Ա. Ն. ԻՍԱԽԱՆՅԱՆ և Ա. Ա. ՀԱՐՈՒԹՅՈՒՆՅԱՆ

Գրական ակնարկը ընդգրկում է վերջին 10 տարիներին բազմատեղակալված քինոլինային ցիկլեր և կարբօքսիլ խմբի տարբեր տեղակալված ածանցյալներ պարունակող քինոլին-4-կարբոնաթթուների ստացման մեթոդների և կենսաբանական ակտիվության վերաբերյալ տվյալներ: Ներկայացնելով քինոլինի ածանցյալների կարևորությունը կենսաբժշկական նպատակներով՝ նոր խոստումնալից միացությունների որոնման գործընթացում, ակնարկը տեղեկատվություն է տալիս տեղակալված քինոլին-4-կարբոնաթթուների նոր ածանցյալների կենսաբանական գործունեության մեթոդների վերաբերյալ:

НОВЫЕ ПРОИЗВОДНЫЕ ХИНОЛИНКАРБОНОВЫХ КИСЛОТ В СИНТЕЗЕ БИОЛОГИЧЕСКИ АКТИВНЫХ ВЕЩЕСТВ

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Обобщены данные за последние 10 лет по синтезу и биологическим свойствам производных хинолин-4-карбоновых кислот. В обзоре рассмотрены производные, замещенные по различным положениям гетероциклического кольца, и производные карбоксильной группы хинолин-4-карбоновой кислоты. С учетом важности производных хинолина в изыскании новых перспективных соединений биомедицинского применения в обзоре приведены сведения о способах получения и биологической активности описанных новых производных замещенных хинолин-4-карбоновых кислот.

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