Synthesis of Linear Azolo and Pyrido Quinolines from Quinoline Derivatives

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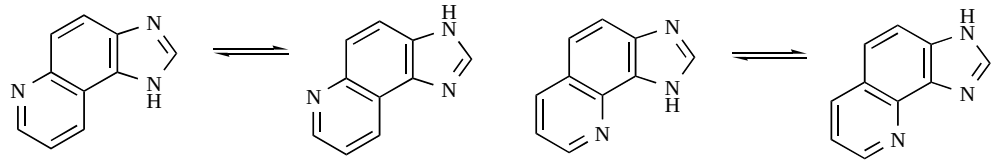
Abstract: Angular *N*-tricyclic systems as triazolo[4,5-*f*]quinolines, triazolo[4,5-*h*]quinolines, imidazo[4,5-*f*]quinolines, imidazo[4,5-*h*]quinolines were in the past obtained by connection of either *f* or *h* sides of the quinoline ring and both the adjacent carbon atoms of five-membered rings containing nitrogen atoms. Several attempts at obtaining the corresponding linear *N*-tricycles were made in the last century, but only the angular derivatives were obtained. Since 2000 a new simple pathway, involving suitable quinoline derivatives, which afforded the linear azolo and pyrido quinolines (imidazo[4,5-*g*]quinolines, triazolo[4,5-*g*]quinolines and pyrido[2,3-*g*]quinoxalines) has been developed. Several linear *N*-tricyclic derivatives have shown some interesting pharmaceutical activity.

Keywords: Imidazo[4,5-*g*]quinolines, triazolo[4,5-*g*]quinolines, pyrido[2,3-*g*]quinoxalines, aminoquinolines, antitubercular activity, antifungal activity, anticancer activity, antiviral activity.

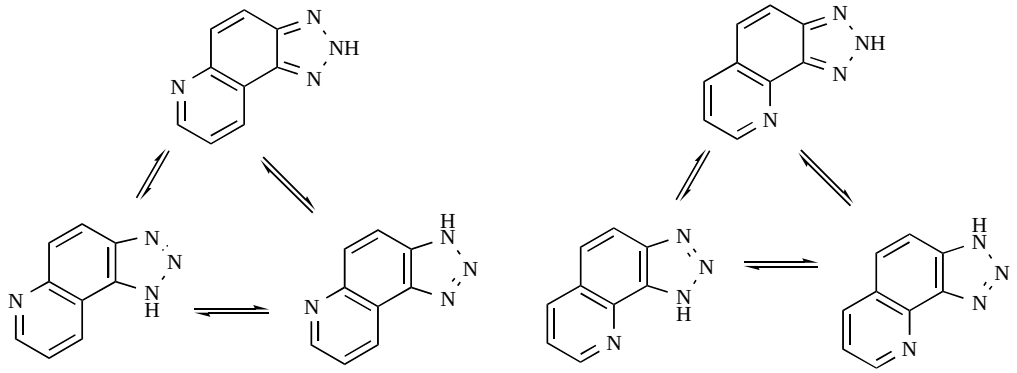
INTRODUCTION

In the last century several authors reported the syntheses and the biological and pharmaceutical properties of a number of angular imidazoquinolines. Between them some researchers focused their studies on imidazo[4,5-*f*]quinoline (**1**) and imidazo[4,5-*h*]quinoline (**2**) nuclei and their derivatives (Fig. **1**). Imidazo[4,5-*f*]quinoline (**1**) was obtained for the first time in 1948 by the reaction of 5,6-diaminoquinoline with formic acid [1], while other authors synthesized this compound using alternative routes [1-4]. Imidazo[4,5-*h*]quinoline (**2**) was prepared for the first time by E. Lenbenstedt in 1974, and some of its derivatives were studied as histamine analogs [2].



Imidazo[4,5-*f*]quinoline (**1**) Imidazo[4,5-*h*]quinoline (**2**)

Fig. (1). Angular imidazoquinolines.



Triazolo[4,5-*f*]quinoline (**3**) Triazolo[4,5-*h*]quinoline (**4**)

Fig. (2). Angular triazoloquinolines.

By connection of *f* side of the quinoline ring and both the adjacent carbon atoms of [1,2,3]triazole (here named triazole) the angular *N*-tricyclic triazolo[4,5-*f*]quinoline (**3**) was obtained and first reported by German authors in 1934 [5], while connection of the *h* side afforded triazolo[4,5-*h*]quinoline (**4**), as a side product during the preparation of 7,8-triazoloquinolin-5-arsonic acid [6] and recently obtained through an alternative route [7] (Fig. **2**).

Several triazoloquinoline derivatives have been reported in the literature during the last century. Among them, carboxylic acid derivatives of 4-oxo-triazolo[4,5-*f*]quinoline (**5**) and 4-oxo-triazolo[4,5-*h*]quinoline (**6**) showed antimicrobial [8,9] and in particular antitubercular [10,11] activities, whereas some 9-aminoalkylaminotriazolo[4,5-*f*]quinolines (**7**) exhibited anticancer activity [12] (Fig. **3**).

Syntheses *via* Gould-Jacobs reaction and spectral properties of the angular azoloquinolines (**1-4**) and some of their derivatives were reported by Milata in 1988 [13].

Also pyrido[3,2-*f*]quinoxaline (**8**) and pyrido[2,3-*f*]quinoxaline (**9**) were in the past obtained by connection of either *f* or *h* sides of the quinoline ring with both carbon atoms in positions 2 and 3 of the pyrazine ring by Ohta in 1979 [14] and Case in 1959 [15] respectively (Fig. **4**).

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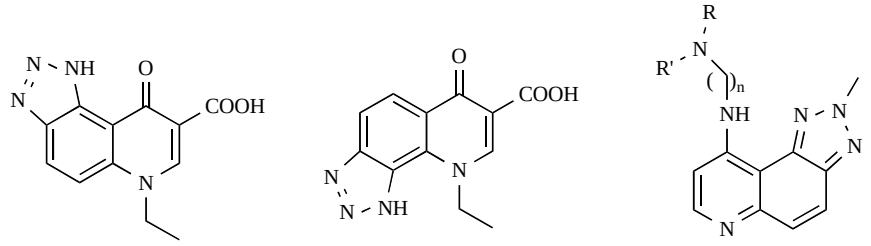
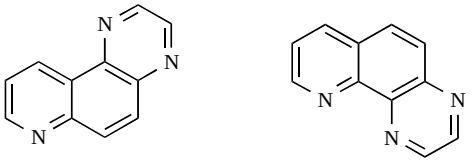


(**5**) (**6**) (**7**)

Fig. (3). Angular triazoloquinolines endowed with biological properties.



Pyrido[3,2-f]quinoxaline (**8**) Pyrido[2,3-f]quinoxaline (**9**)

Fig. (4). Angular pyridoquinoxalines.

In the light of the interest for both the chemical and biological properties of the angular *N*-tricyclic systems (**1-4**) several attempts at obtaining the corresponding linear *N*-tricycles imidazo[4,5-*g*]quinolines (**12**) and triazolo[4,5-*g*]quinolines (**13**) were made in the last century (Fig. **5**).

Unfortunately, when 5-aminobenzotriazole derivatives were submitted to condensation reaction with suitable β-ketoesters [16], β-diketones [17], activated acetylenic esters [12,18,19], dialkyl ethoxymethylenemalonate [8,9,20] or *via* the Skraup synthesis [21] only the angular derivatives were obtained. On the contrary, imidazo[4,5-*g*]quinoline (**13**) and its 5-Cl-derivative were obtained by Lenbenstedt in 1975 [22] by condensation of a crude reaction mixture containing 6,7-diaminoquinoline, 6,7-diamino-8-chloroquinoline and formic acid, but no further studies were developed for years.

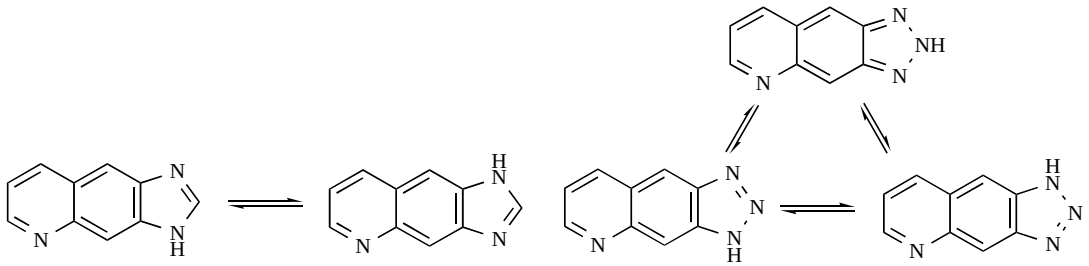
quinolines (**12-14**) and their numerous derivatives has been developed.

Syntheses of Substituted Quinoline Intermediates

7,8-Dichloro-6-nitroquinoline (**15a**) and 7,8-dichloro-6-nitroquinolin-4(1H)-one (**15b**) of Fig. (**7**) represent the key intermediates necessary to prepare all the quinolines which, in turn, are used as synthons for the syntheses of the *N*-tricycles described above.

The synthetic route to **15a** (Scheme **1**) was reported for the first time in 2000 [23], to **15b** (Scheme **2**) in 2003 [24], and successively modified in 2007 in order to improve the yields [25].

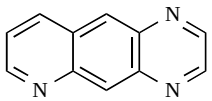
A suspension of commercially available 2,3-dichloroaniline (**17**) in acetic anhydride was stirred overnight at room temperature, affording 2,3-dichloroacetanilide (**18**) in 98% yield. Nitration of **18** with potassium nitrate in sulfuric acid, keeping the temperature at 2-5ºC for 4 h, afforded the solid mixture of nitroaniline which was dissolved in concentrated sulfuric acid and heated at 100-110ºC under stirring for 2 h. On cooling at room temperature, a crude precipitate was obtained, which was then purified by flash chromatography to give 2,3-dichloro-6-nitroaniline (**19**) in 24% yield and *2*,3-dichloro-4-nitroaniline (**20**) in 55% yield. Finally 7,8-dichloro-6-nitroquinoline (**15a**) was obtained in 58% yield *via* Skraup synthesis starting from **20** [25].



Imidazo[4,5-*g*]quinoline (**12**) Triazolo[4,5-*g*]quinoline (**13**)

Fig. (5). Linear imidazoquinoline and triazoloquinoline.

Finally, no attempts to synthesize the pyrido[2,3-*g*]quinoxaline ring (**14**) shown in Fig. (**6**) have been reported until recent years.



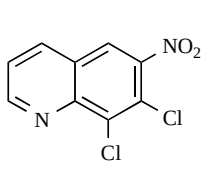
Pyrido[2,3-*g*]quinoxaline (**14**)

Fig. (6). Linear pyrido[2,3-*g*]quinoxaline.

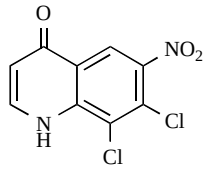
On this ground, since 2000 a new simple pathway, involving suitable quinoline derivatives, able to afford the linear azolo and pyrido

The nitroquinoline (**20**) was first reacted with diethyl ethoxymethylenemalonate (EMME) in Dowtherm at 150ºC for 17 h to give the anilinoacrylate (**21**), which was in turn cyclized at 250ºC for 2.5 h in the same solvent [24]. Alternatively, EMME was added to **20** in Dowtherm and heated at 250ºC for 4 h [26]. The ethyl 7,8-dichloro-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**22**) thus obtained was hydrolyzed, in sulfuric acid at 100ºC for 2 h yielding **23**, which was finally decarboxylated in Dowtherm at 250ºC for 15 h to give the dichloronitroquinoline **15b** [24].

15a and **15b** are the key intermediates to an effective approach for the synthesis of a number of quinoline derivatives [27]. Intermediates used as synthons for the syntheses of the linear *N*-tricycles below reported are shown in Scheme **3**. Compounds **24a,b** were obtained in 87-98% yield from **15a,b** by nucleophilic displacement of

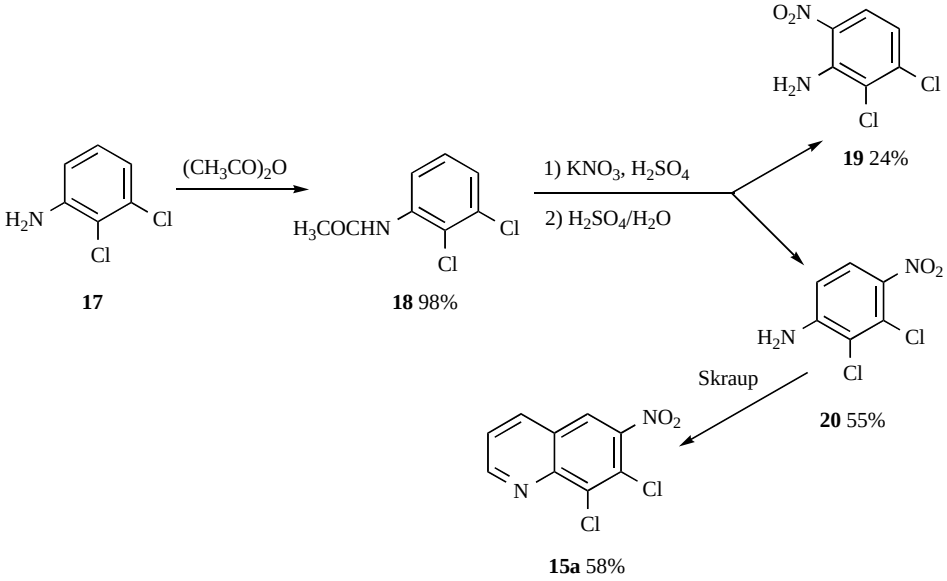


7,8-Dichloro-6-nitroquinoline (**15a**)



7,8-Dichloro-6-nitroquinolin-4(1*H*)-one (**15b**)

Fig. (7). Quinoline intermediates.



17 **18** 98% **19** 24% **20** 55% **15a** 58%

Scheme 1. Synthesis of the key intermediate 7,8-dichloro-6-nitroquinoline (**15**).

the chlorine atom with ethanol saturated with dry gaseous ammonia in a sealed vessel at 160ºC under stirring for 24 h, On the contrary, nucleophilic displacement of the chlorine atom with an suitable alkylamine in DMF at 100ºC under stirring for 8 h afforded the corresponding 7-alkylaminoderivatives (**29c-e**) in 35-50% yield [26]. Reduction of the nitro-group of **24a,b** and **29c-e** with methylhydrazine in ethanol at 100°C for 80 h in a sealed vessel afforded the amines (**25a,b**) in 80-95% yield [27] and (**30c-e**) in 80-90% yield [26] respectively. On the other hand, when the 7-amino-8-chloro-6-nitroquinoline (**15a**) was treated with hydrazine hydrate in ethanol in the presence of 10% Pd/C under reflux for 3h, the corresponding diaminoquinoline (**27**) was obtained in 70% yield with complete removal of the chlorine atom. 4-Chloroderivative **28** was prepared in 50% yield by reaction of **25b** with refluxing phosphorus oxychloride for 24 h. Finally, ethylation of **15b** with diethyl sulfate occurred at oxygen to give **26** in 60% yield.

Syntheses of imidazo[4,5-*g*]quinolines

Recently imidazo[4,5-*g*]quinoline (**12**) was obtained by the reaction of 6,7-diaminoquinoline (**27**) with formic acid at 100ºC for 2 h (37% yield) [23]. Further imidazo[4,5-*g*]quinolines, unsubstituted on the imidazo moiety, were prepared in the same manner starting by substituted aminoquinolines (**25a**,**b**) in 66-90% yield [23,24] (Scheme **4**).

A large number of imidazo[4,5-*g*]quinoline derivatives carrying substituents on the imidazo moiety (**32**) were obtained in good yield (50-90%) when the appropriate diaminoquinolines (**25a**,**b**, **27**,**28** and **30c-e**) were condensed with the Bertagnini's salt (**Bs**) of the desired aldheyde under the same conditions [26,28] (Scheme **5**).

When the 6,7-diamino-8-chloroquinoline (**25a**) was refluxed for 1 hour with a large excess of acetone, in the presence of hydrazine, 4-chloro-2,2-dimethyl-2,3-dihydro-imidazo[4,5-*g*]quinoline (**33**) was obtained in 60% yield [24] (Scheme **6**).

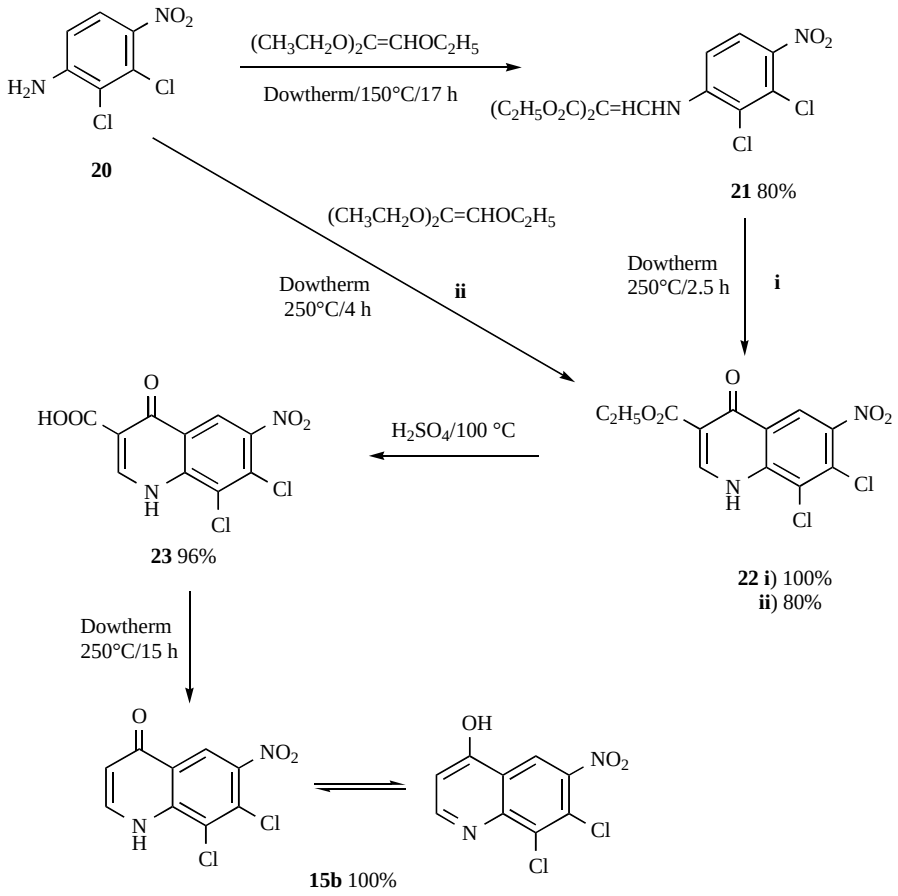
A similar behavior was observed in the case of the reaction of unsubstituted 6,7-diaminoquinoline **27** with α-ketoesters and α-ketoacids, in refluxing ethanol (Scheme **4**), since both imidazoline (**34**) and imidazo (**35**) derivatives were obtained in 50-90% yield [28] (Scheme **7**).

These results are seemingly due to the absence of 8-Cl atom which causes equivalence in the starting diamine groups. In this case condensation with the ketocarbonyl groups of both α-ketoesters and α-ketoacids takes place leading to an identical imidazoline intermediate (**34**). In the case of R = CH_2CH_3, **34** is stable whereas for R = H the intermediate undergoes decarboxylation followed by dehydrogenation as reported in the literature for the formation of benzimidazoles [29].

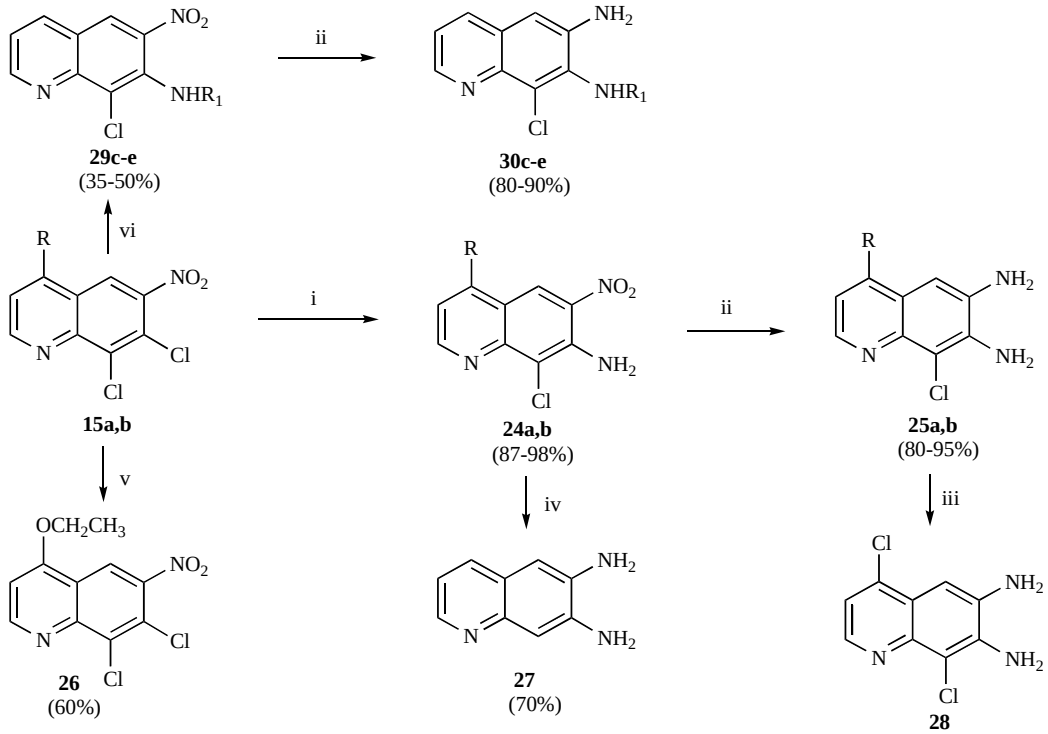
Imidazo[4,5-*g*]quinolines were also obtained (in mixture with pyrido[2,3-*g*]quinoxalines) by reaction of N_7-alkylated chlorodiamines (**30c-e**) with α-ketoacids (see below).

Syntheses of pyrido[2,3-*g*]quinoxalines

Pyrido[2,3-*g*]quinoxaline (**14**) was first obtained (90% yield) in 2000 by condensation of 6,7-diaminoquinoline (**27**) with glyoxal in refluxing ethanol for 2 h [23]. Further pyrido[4,5-*g*]quinoxalines, unsubstituted on the pyrazino moiety, were prepared in the same manner starting by substituted 6,7-diaminoquinolines (**25a**,**b**) in 65-86% yield [23,24] (Scheme **8**).

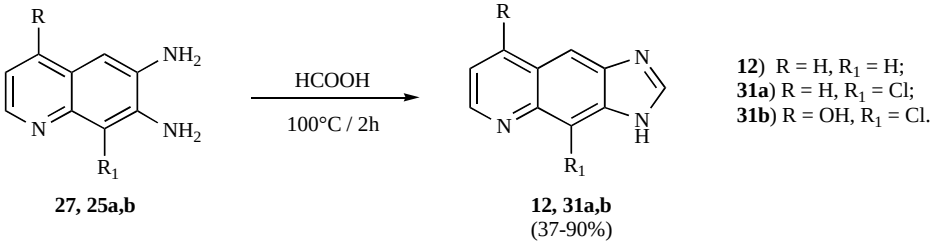


Scheme 2. Synthesis of the key intermediate 7,8-dichloro-6-nitroquinolin-4(1H)-one (**15b**).



a) R = H; b) R = OH; c) $R_1 = C_3H_7$; d) R_1 = cyclohesyl; e) $R_1 = CH_2$-cyclohexyl.
i) NH_3, EtOH, 160 °C, 24 h, sealed steel vessel; ii) CH_3HNNH_2, EtOH, 100 °C, 80 h, sealed steel vessel;
iii) $POCl_3$, reflux, 24 h; iv) H_2NNH_2, EtOH, reflux, 10% Cd/C, 3 h; v) Et_2SO_4; vi) R_1NH_2, DMF, 100 °C, 8 h.

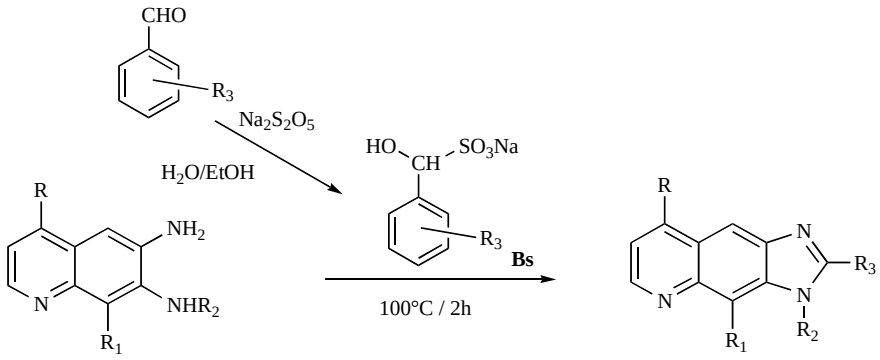
Scheme 3. Synthesis of quinoline intermediates (**24**-**30**).



27, 25a,b **12, 31a,b** (37-90%)

12) R = H, R_1 = H;
31a) R = H, R_1 = Cl;
31b) R = OH, R_1 = Cl.

Scheme 4. Synthesis of imidazo[4,5-*g*]quinolines unsubstituted on the imidazo moiety (**12, 31a,b**).

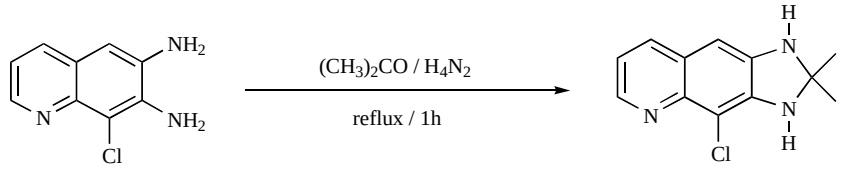


25a,b, 27, 28, 30c-e

R= H, Cl, OH
R_1= H, Cl
R_2= H, C_3H_7, cyclohexyl, CH_2-cyclohexyl
R_3 = H, alkyl, cyclohexyl, aryl, heteroaryl, etc.

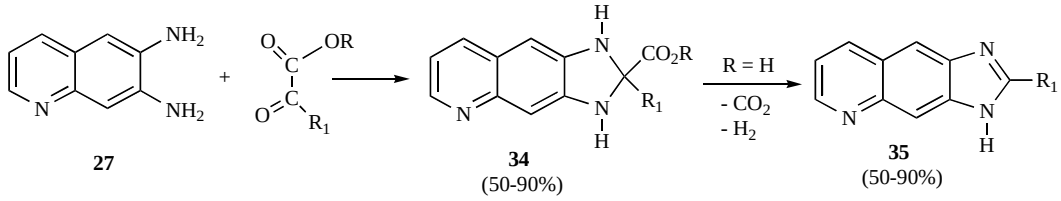
32 (50-90%)

Scheme 5. Synthesis of substituted imidazo[4,5-*g*]quinolines (**32**).



25a **33** (60%)

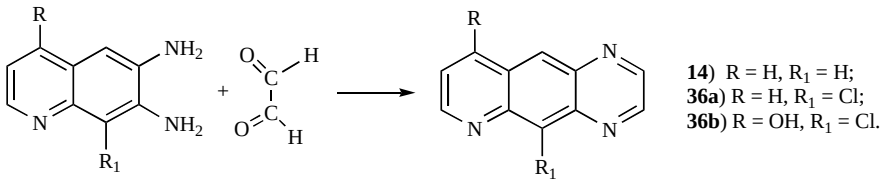
Scheme 6. Synthesis of the imidazoline (**33**).



27 **34** (50-90%) **35** (50-90%)

R = H, CH_2CH_3; R_1 = alkyl, benzyl, phenyl, aryl

Scheme 7. Syntheses of imidazolines **34** and imidazo derivatives **35**.

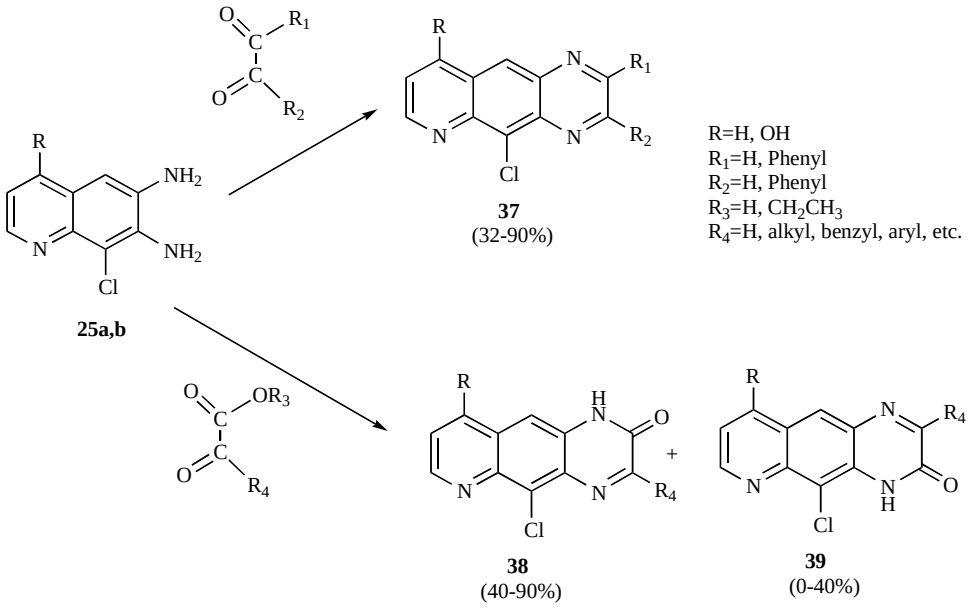


27, 25a,b **14, 36a,b** (65-90%)

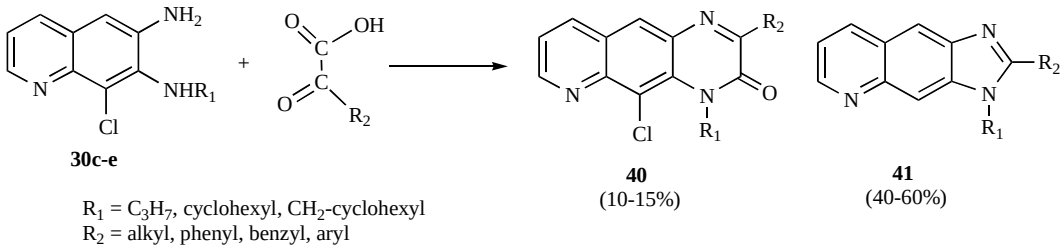
14) R = H, R_1 = H;
36a) R = H, R_1 = Cl;
36b) R = OH, R_1 = Cl.

Scheme 8. Syntheses of pyrido[4,5-*g*]quinolines unsubstituted on the pyrazino moiety (**12, 36a,b**).

Reaction of **25a**,**b** with α-diketones or α-ketoaldheydes in refluxing ethanol for 1-2 h, gave the derivatives **37** in good yield (32-90%). On the other hand, condensation of 6,7-diaminoquinoline bearing a Cl atom in position 8 (**25a,b** and **28**) with α-ketoesters or α-ketoacids in refluxing ethanol for 3-15 h, or in 10% aqueous solution of sulfuric acid at 45-50ºC for 2 h, afforded mixtures of pyrido[2,3-*g*]quinoxalin-



Scheme 9. Syntheses of pyrido[2,3-*g*]quinoxalines (**37-39**).



Scheme 10. Reaction of N_7-alkylated chlorodiamines **30c-e** with a-ketoacids.

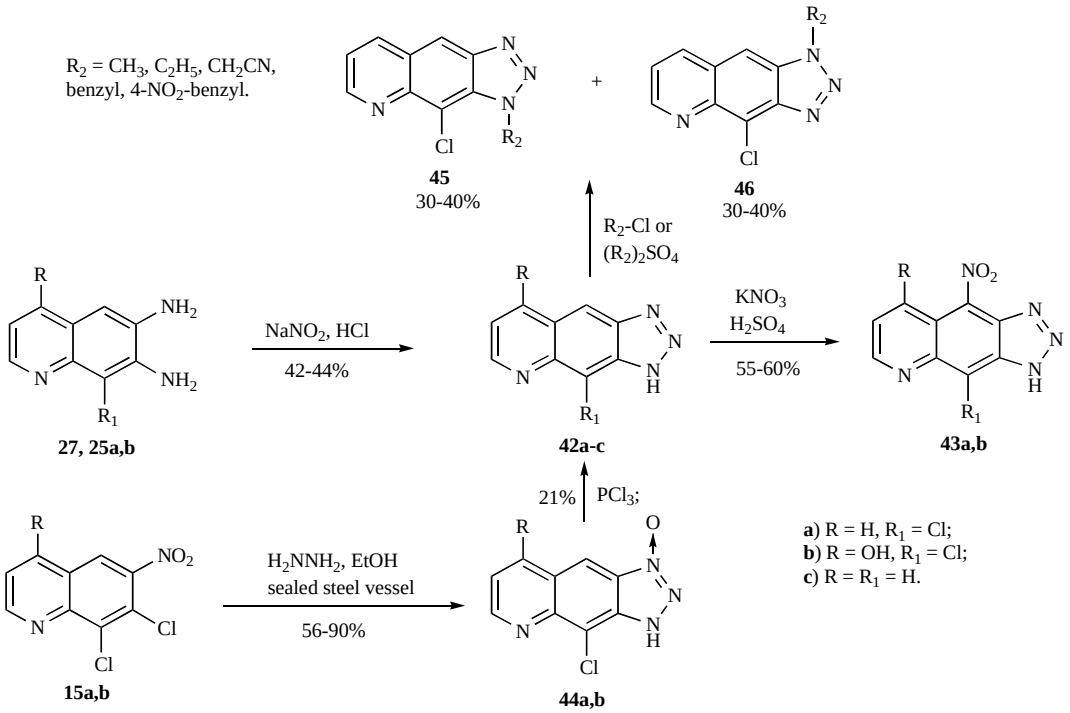
2-ones (**38** in 40-90% yield) and pyrido[2,3-*g*]quinoxalin-3-ones (**39**) in 0-40% yield) instead of the expected imidazoline (**34**) and imidazo (**35**) derivatives. The mixture containing **38** and **39** was separated and purified by chromatography. The amount of **38** was in general slightly higher than **39** in neutral conditions (between 5:4 and 2:1), being the transformation almost selective under acidic conditions (between 9:1 and 1:0) [28,30] (Scheme **9**).

As summarized in Scheme **10**, reaction of N_7-alkylated chlorodiamines **30c-e** with α-ketoacids in refluxing ethanol for 3-12 h afforded a mixture of pyrido[2,3-*g*]quinoxalines (**40**) and imidazo[4,5-*g*]quinolines (**41**). In this case, not only formation of **41** was prevailing over the expected **40** (ratio 4:1) but imidazoquinolines (**41**) underwent unusual chlorine elimination. The different behavior found with the N_7–unsubstituted diamines suggested that the elimination is partly due to the reinforced basicity of N_7 in the presence of an alkyl substituent [27].

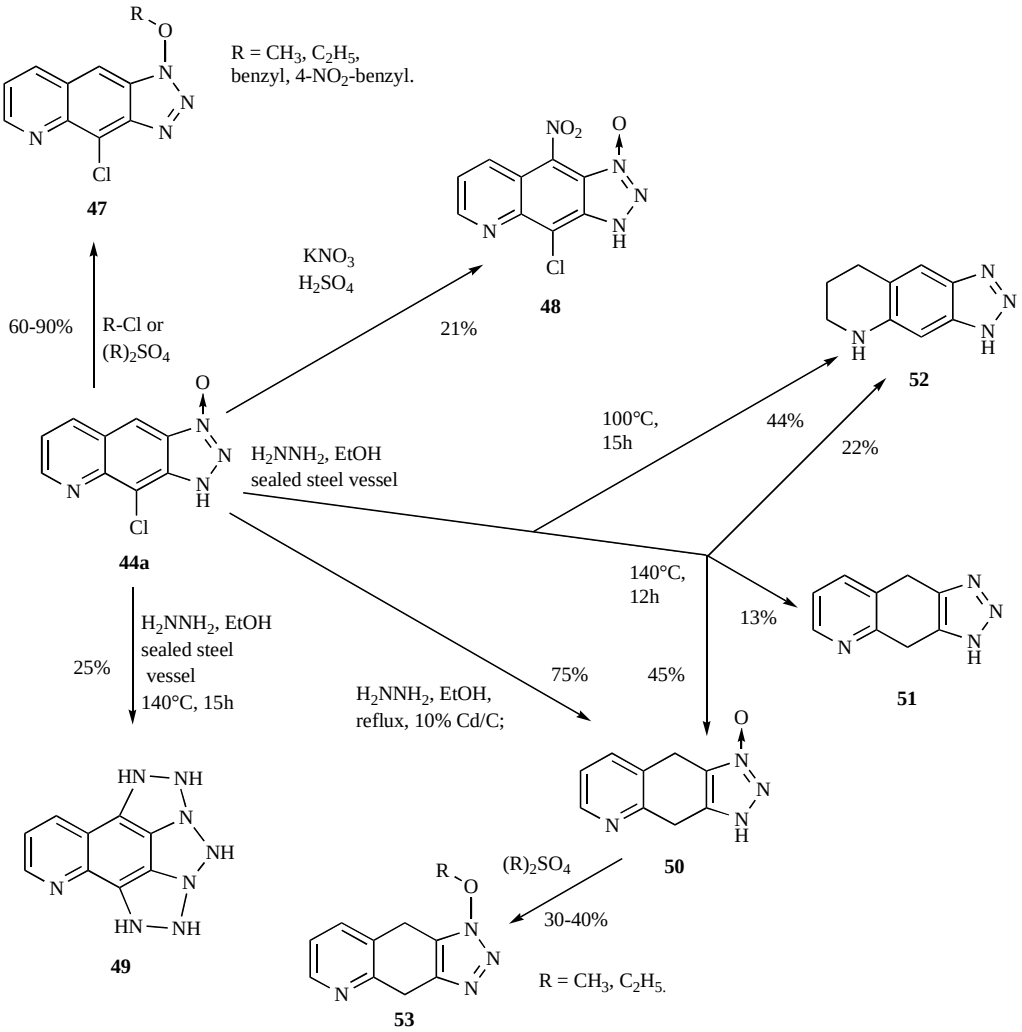
Syntheses of triazolo[4,5-*g*]quinolines

Quinolines **15a**,**b**, **25a**,**b** and **27** represent the necessary synthons for the preparation of a wide number of triazolo[4,5-*g*]quinoline derivatives (Scheme **11**). The unsubstituted ring **42c** was obtained (42% yield) by submitting the diamine **27** to ring closure by diazotization with HNO_2 followed by cyclization of the corresponding diazonium salt at room temperature [23]. Triazoloderivatives unsubstituted on the triazolo moiety **42a,b** were prepared in the same manner starting by diaminoquinolines (**25a**,**b**) in comparable yield (43-44%) [23,24]. Nitration of both **42a,b** by treatment with potassium nitrate in concentrated sulfuric acid at 50ºC for 3 h, gave the corresponding 9-nitro-derivatives (**43a,b**) in 55% [31] and 60% [26] yields respectively. On the other hand, 7-chloro-8-nitroquinolines (**15a,b**) submitted to reaction with a large excess of hydrazine hydrate in ethanol in a sealed steel vessel at 70ºC for 80-90 h afforded in good yields (56-90%) the corresponding triazolo[4,5-*g*]quinoline-1-oxides (**44a,b**) [23,24]. Subsequent deoxygenation of **44a**, by treatment with PCl_3 at 78ºC for 120 h, gave triazolo[4,5-*g*]quinoline (**42a**) in moderate yield (21%) [31].

Reaction of **42a** with chloroacetonitrile or dialkyl sulfates in dimethylformamide (DMF) catalyzed by KOH afforded a mixture of 1- and 3-alkyl-triazolo[4,5-*g*]quinolines (**45** and **46**) in about 1:1 ratio (total yield 60-80%) [31,32] (Scheme **12**). Unexpectedly no 2-alkyl-derivative was isolated; this fact seems to differentiate this behavior in comparison with previous observations on alkylation of simple benzotriazoles [33-36]. On the other hand, alkylation of 1-oxide-derivative **44a** resulted highly regioselective using various alkylating agents as benzyl chloride, 4-nitrobenzyl chloride and dialkyl sulfates in DMF and in the presence of Cs_2CO_3 as catalyst [32]. In fact, from this reaction only the derivatives **47** (in 60-90% yield) were obtained. Nitration of **44a** in the same condition above reported gave the corresponding 9-nitro-derivatives (**48**) in low yield 21% [31]. Unexpectedly heating **44a** in a sealed steel vessel with hydrazine in ethanol at 140ºC for 15 h, the pentacyclic derivative **49** was obtained in 25% yield. The formation of **49** was explained as a nucleophilic attack on the electrophilic 1 and 4 positions of **44a** followed by symmetrical ring closure [31]. Furthermore, when **44a** was reacted under similar conditions except for the presence of 10% palladised charcoal, it afforded derivatives **50**-**52**, the proportion of which seems to be de-



Scheme 11. Syntheses of triazolo[4,5-*g*]quinolines **42-46**.



Scheme 12. Syntheses of triazolo[4,5-*g*]quinolines **47-53**.

pendent on both temperature and reaction time. In fact compound **52** was obtained in 44% yield by heating at 100ºC for 15 h, while compound **50** was obtained in 45% yield (together with both **51** and **52** in 13% and 22% yield respectively) at 140ºC for 12 h. When compound **44a** was reacted with hydrazine and 10% palladised charcoal in refluxing ethanol, only compound **50** was obtained in 75% yield [26].

This behavior may be due to a similarity of the linear tricyclic feature between **44a** and anthracene which undergoes catalytic hydrogenation to dihydro and tetrahydro stages under mild conditions [37]. Finally, alkylation of the 4,9-dihydrotriazolo[4,5-*g*]quinoline-1-oxide (**50**) with dialkyl sulfates under the above reported conditions takes place on the oxygen on *N*-1, affording compounds **53** in 30-40% yield [26].

Pharmaceutical Activity

In vitro antimicrobial screening of the above described pyrido[2,3-*g*]quinoxaline derivatives showed that this scaffold is endowed with antibacterial (*P. aeruginosa*, *S. aureus* and *E. coli*), anticandida (hospital isolated strains of *Candida spp*.) [30] and antimycobacterial (*M. tuberculosis* and *M. smegmatis*) activities [24]. In anticancer screening performed at the National Cancer Institute some of them stood out for their selective, although not very potent, antitumoral activity against various panel cell lines, such as leukemia, non-small cell lung cancer, colon cancer, CNS cancer and melanoma [30]. Both imidazo[4,5-*g*]quinolines and pyrido[2,3-*g*]quinoxalines have shown to be endowed with potent antiflaviviridae activity [38]. Viruses belonging to the *Flaviviridae* family cause clinically significant diseases in humans and animals. This virus family includes Hepatitis C virus (HCV) which is a major cause of human hepatitis.

Finally, by *in vitro* screening against HIV, 4,9-dihydro-1*H*-triazolo[4,5-*g*]quinoline-1-oxide (**44a**) stood out for its selective activity. This derivative resulted to be not toxic, and is not only able to prevent wild-type HIV-1 replication in acutely infected cells, but is also well active against the most frequently observed mutant forms, i.e. K103N, Y181C, and the double mutant K103N/Y181C [39].

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