Synthesis and Biological Activities of Quinolone Analogues: Pyridazino[3,4-*b*]quinoxalin-4-ones

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Quinolone analogues **I** - **VI** with pyridazino[3,4-*b*]quinoxaline ring system were synthesized from the (1-alkylhydrazino)quinoxaline *N*-oxides **1** *via* oxidation of pyridazino[3,4-*b*]quinoxalines **2**,**3**,**5**,**7**, quinoxalino[2,3-*c*]cinnolines **4**, and 1,2-diazepino[3,4-*b*]quinoxalines **6**. The biological activities of quinolone analogues **IVa** (N_1-methyl-C_3-methyl), **Va** (N_1-methyl-C_3-ethyl), and **VI** (N_1-methyl-C_3-H) were superior to those of quinolone analogues **I** (N_1-ethyl-C_3-carboxyl), **26b** (N_1-ethyl-C_3-carboxylate), and **IIIc**,**d** [N_1-alkyl-C_3-$(CH_2)_3COOC_2H_5$].

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Introduction.

Since the discovery of nalidixic acid [1,2] (Figure 1) in 1962 and its introduction in the treatment of urinary tract infection in 1963, a number of research groups have developed quinolone antibacterials such as cinoxacin [3,4], oxolinic acid [5-7], rosoxacin [8,9], pipemidic acid [10-14], piromidic acid [15-18], miroxacin [19], and pyrido[2,3-*b*]quinoxaline-3-carboxylic acids [20] in the 1970s. Thereafter, plenty of researchers have devised the introduction of a fluorine atom into the quinolone nucleus, and flumequine [21,22] (Figure 2) has been produced initially as a fluoroquinolone derivative. Successively, many research groups in some pharmaceutical companies have developed various kinds of new quinolones with 6-fluoro and 7-piperazinyl (or other basic) group, which involve norfloxacin [23], pefloxacin [23], ofloxacin [24,25], ciprofloxacin [26,27], levofloxacin [25], enoxacin [28], amifloxacin [29] in the early 1980s; A-56620 [30], tosufloxacin [31,32], difloxacin [33], DR-3354 [34,35], sparfloxacin [36], BMY-40062 [37], pazufloxacin [38], sitafloxacin [39], WIN-57273 [40], HSR-903 [41] (Figure 3), and some others in 1985 to the 1990s.

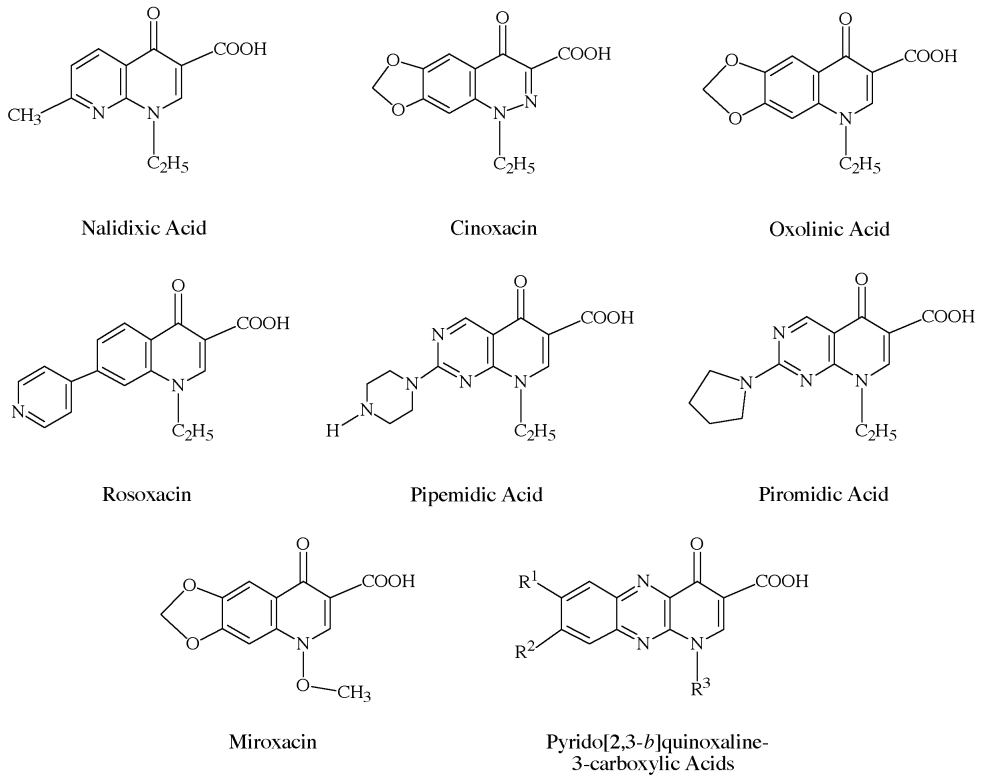


Figure 1

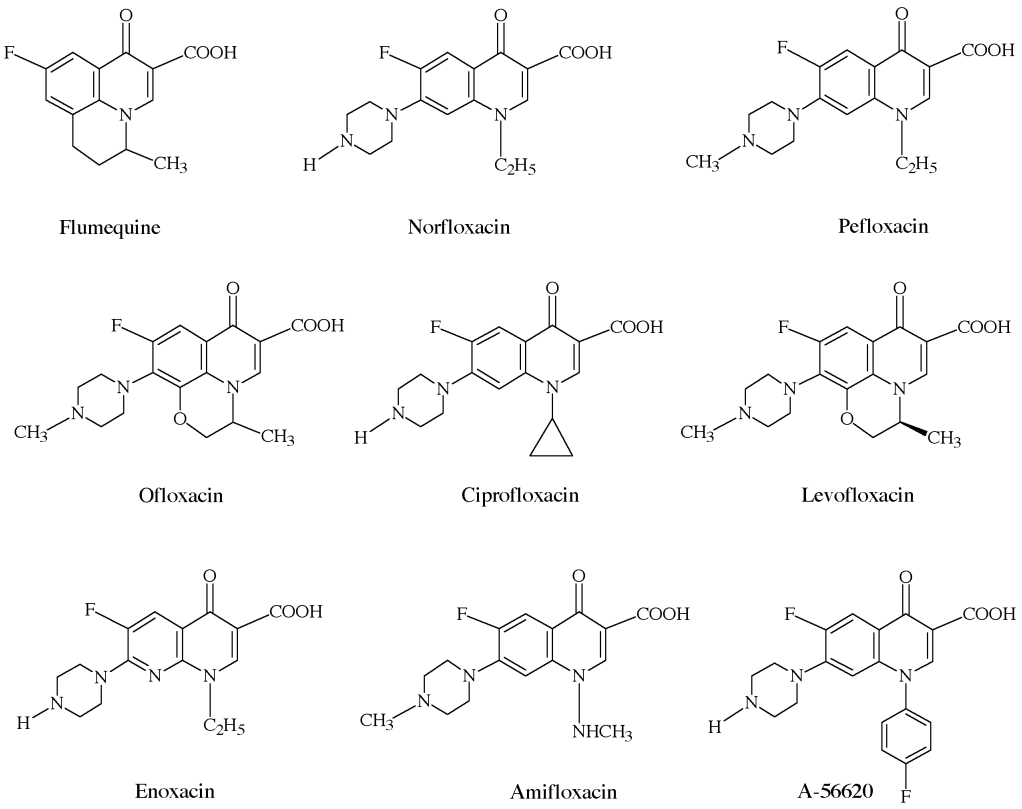
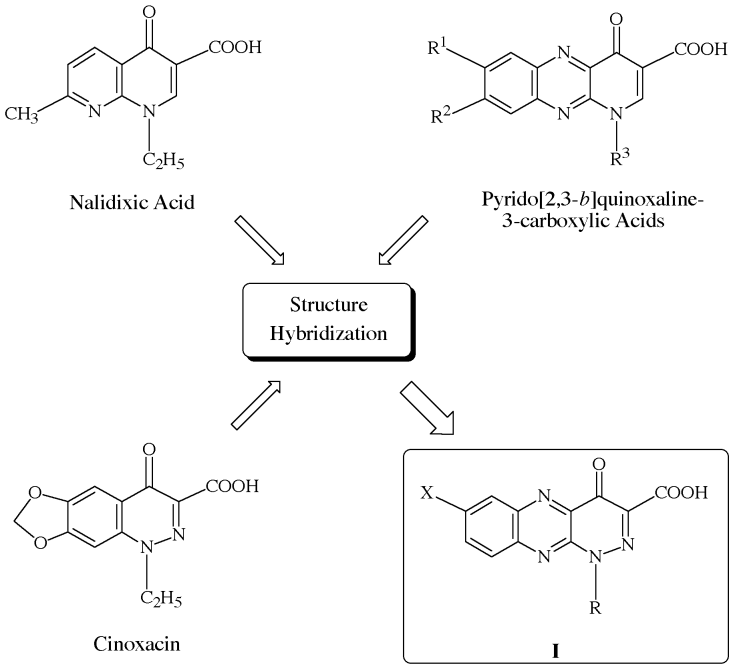


Figure 2

Scheme 1



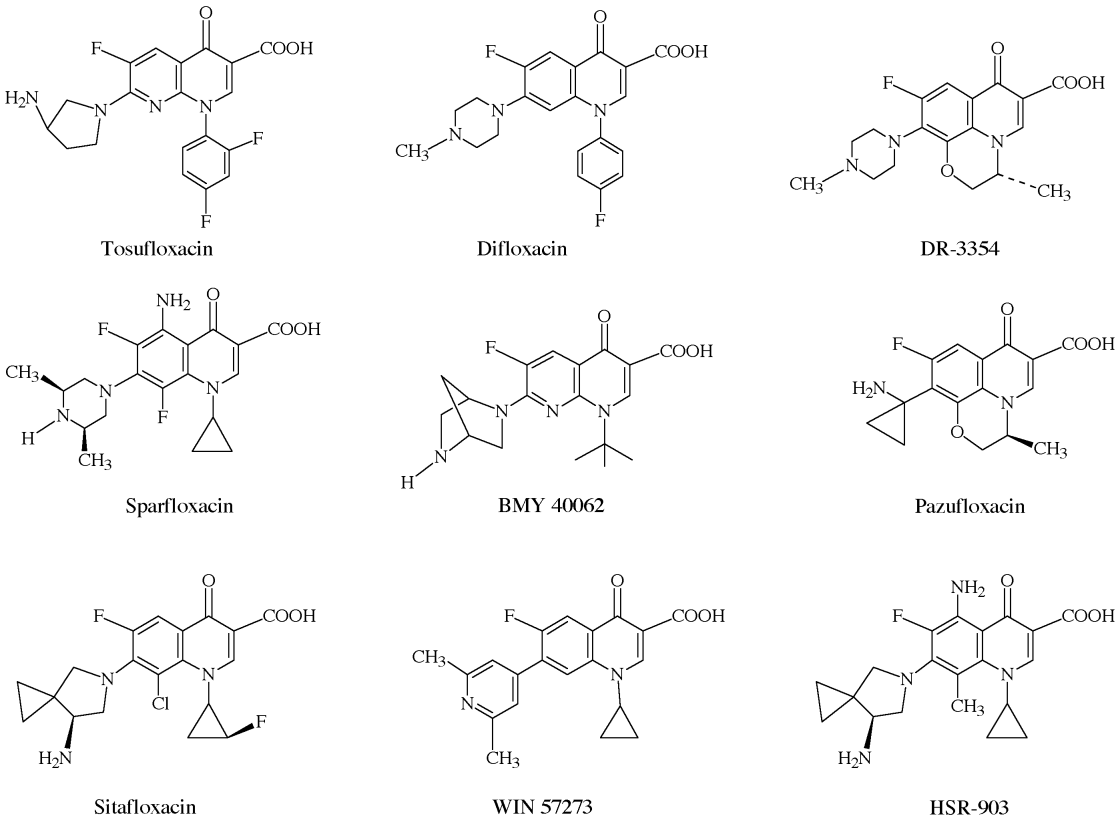
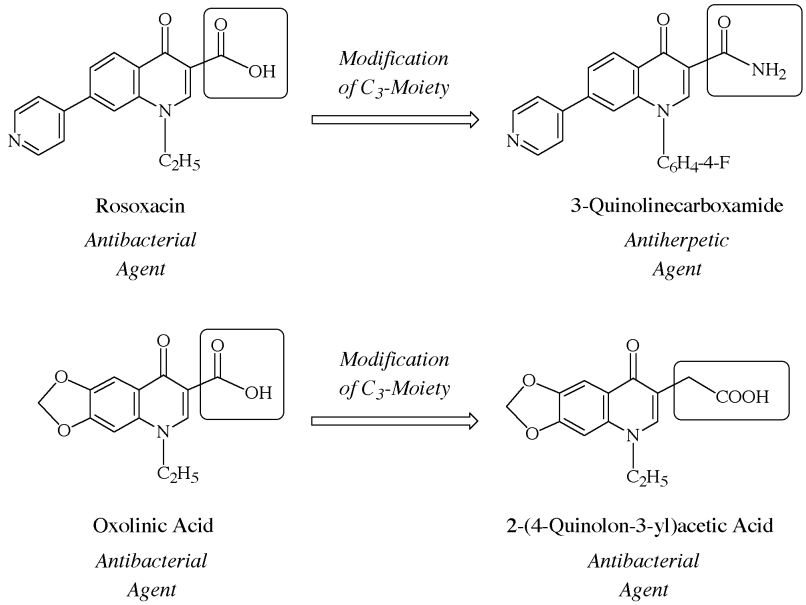


Figure 3

Scheme 2



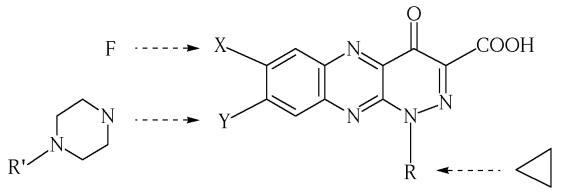


Figure 4
An example for substituent modification
(but this plan was suspended)

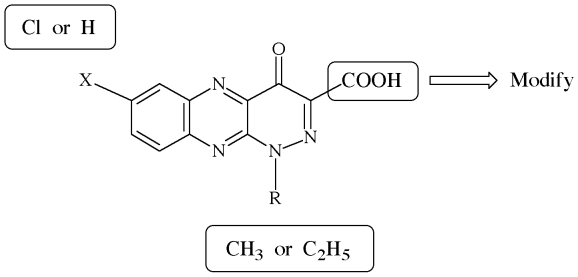
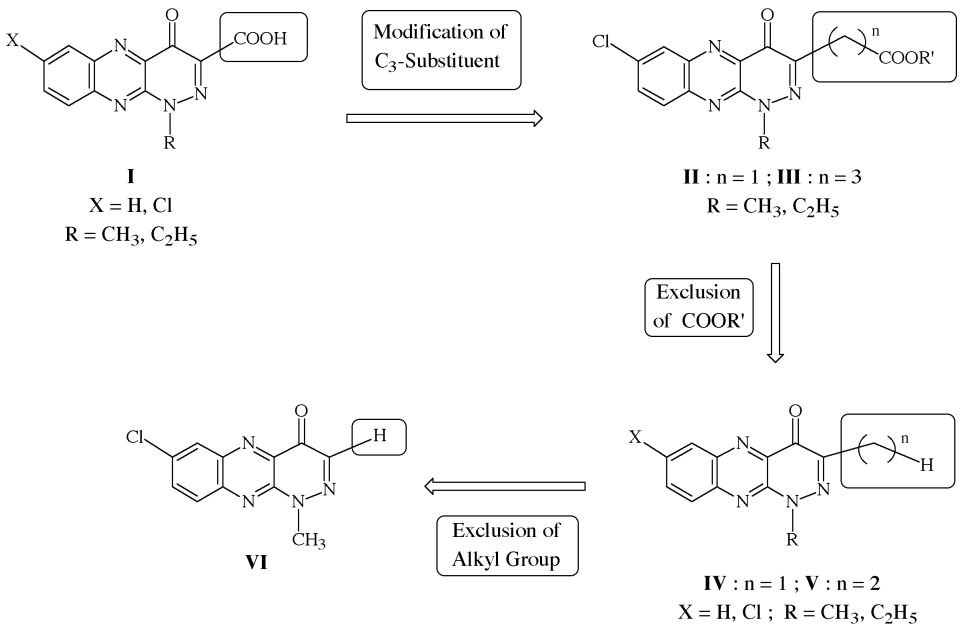


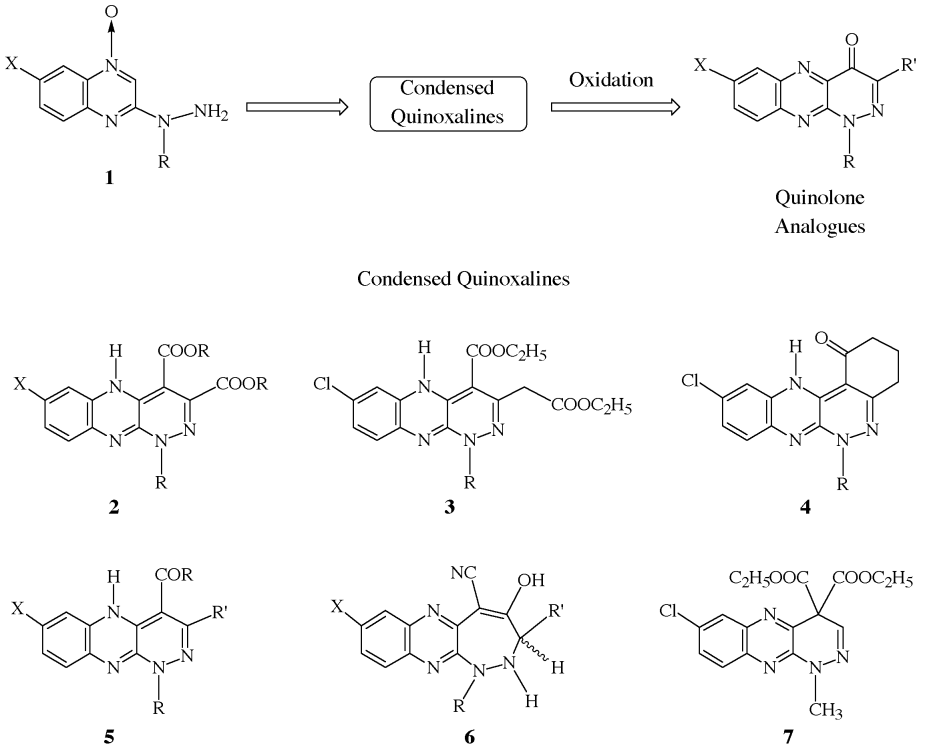
Figure 5

Recently, we have also synthesized 1-alkyl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **I** [42] as candidates of antibacterial quinolone analogues, which are provided by the structure hybridization among nalidixic acid, cinoxacin, and pyrido[2,3-*b*]quinoxaline-3-carboxylic acids (Scheme 1). From the screening data, one of our compounds (**Ib**: X = Cl, R = C_2H_5) was found to exhibit weak antibacterial activities in comparison with new quinolones. For example, a minimum inhibitory concentration of compound **Ib** was 12.5 μg/ml against *Staphylococcus aureus*, while some of the new quinolones such as ofloxacin [43], pefloxacin [43] and norfloxacin [43] showed excellent antibacterial activities against *Staphylococcus aureus* and other bacteria. In order to search for more potent compounds in our ring system, it appeared better to introduce fluorine atom, piperazinyl moiety, and cyclopropyl group into 7-, 8-, and 1-positions as shown in Figure 4. However, a number of excellent new quinolones for clinical use have already been developed by the pharmaceutical companies in the world, which further study to reduce side effects [44,45] and for activities against *Streptococci*, *Mycoplasma*, *Chlamydia*, anaerobic bacteria, and quinolone-resistant bacteria. Namely, several problems still remain for new quinolones, most of which are however excellent in clinical use. Accordingly, we have undertaken the modification of the C_3-substituent in order to improve biological activities of our quinolone analogues, suspending the introduction of fluorine atom, piperazinyl moiety, and cyclopropyl group into our pyridazino[3,4-*b*]quinoxaline ring system (Figure 5). In the literature, there are some examples for the modification of C_3-carboxyl group in quinolones as follows. Rosoxacin was modified at the 1-, 2-, 3-, and 7-positions of quinolone ring, which led to the production of the 3-quinoline-

Scheme 3

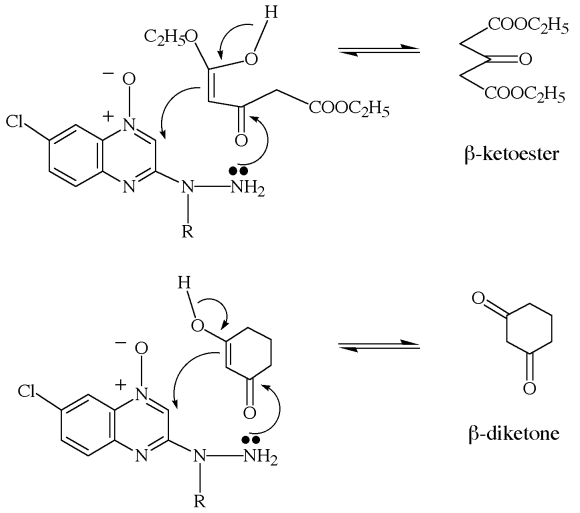


Scheme 4



carboxamide [1-(4-fluorophenyl)-7-(4-pyridyl)-4-quinolone-3-carboxamide] with antiherpetic activity [46] (Scheme 2). Meanwhile, various C_3-homologues of oxolinic acid were synthesized, and one of them was the methylene-inserted carboxylic acid [2-(4-quinolon-3-yl)-acetic acid] (Scheme 2), which maintained an antibacterial activity against *Proteus vulgaris* [47]. Thus, we carried out the modification of the C_3-substituent as shown in Scheme 3, wherein the carboxyl group of compounds **I** was initially converted into the methylene-inserted carboxyl derivatives **II** and **III** [48]. Subsequently, the exclusion of the carboxyl or its ester moiety in compounds **II** and **III** led us to synthesize C_3-alkyl quinolone analogues **IV** and **V** [49]. Then, the elimination of the C_3-alkyl group in compounds **IV** and **V** provided the C_3-H quinolone analogue **VI** [50]. From the screening data of our quinolone analogues, some of compounds **II** and **III** showed an antibacterial activity against *Bacillus subtilis*, which was similar to that of compounds **I**. However, some of compounds **IV** and **V** were superior to compounds **I**, **II**, and **III** in the antibacterial activity against *Bacillus subtilis*. Moreover, compounds **IV** and **V** had a good antifungal activity against *Trichophyton mentagrophytes*. In the oxolinic acid homologues, the C_3-H compound was reported to possess no antibacterial activity, whereas our compound **VI** possessed good antibacterial activity [51].

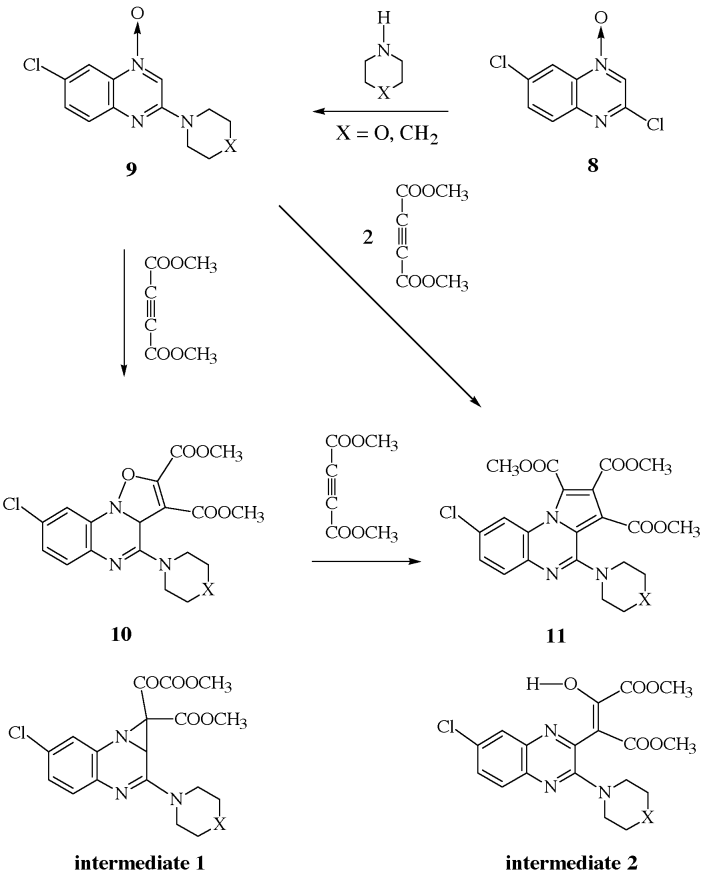
Figure 6



Methods for the Synthesis of Our Quinolone Analogues.

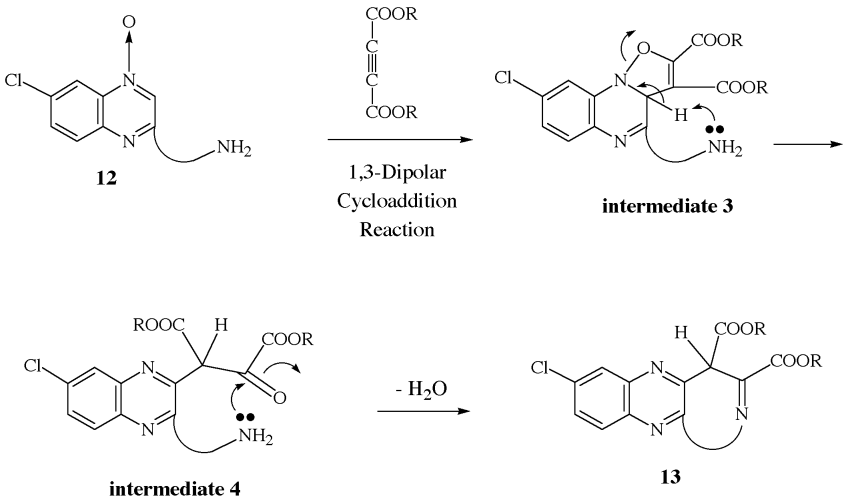
An outline of our method for the synthesis of quinolone analogues is shown in Scheme 4. The (1-alkylhydrazino)-quinoxaline *N*-oxides **1** [52,53] are converted into the pyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **2** [52,53], 2-(pyridazino[3,4-*b*]quinoxalin-3-yl)acetates **3** [48],

Scheme 5

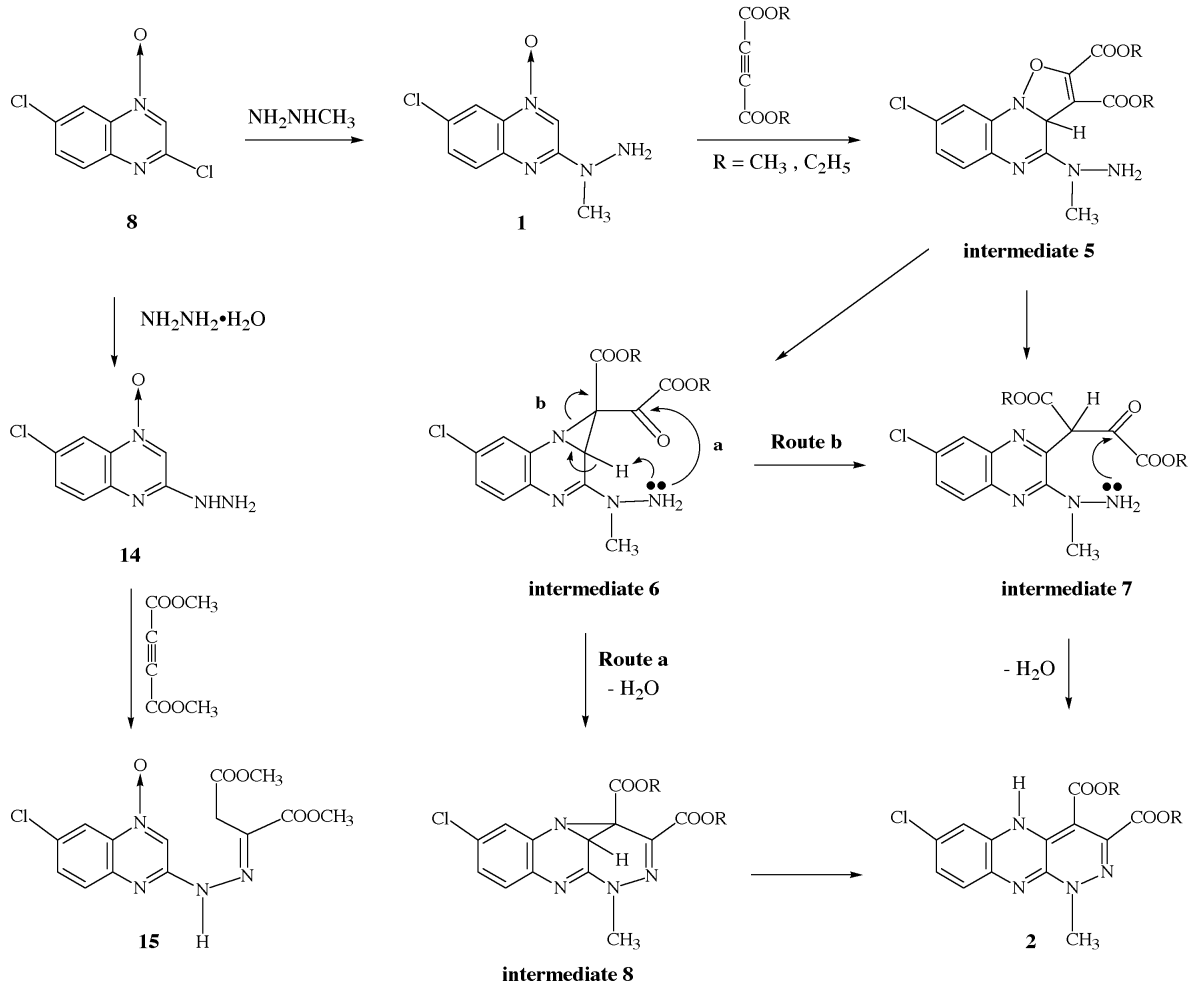


quinoxalino[2,3-*c*]cinnolines **4** [48], 4-acylpyridazino-[3,4-*b*]quinoxalines **5** [54], 1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitriles **6** [55,56], and pyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylate **7** [50], which are precursors to our quinolone analogues. These compounds **2**-**7** were further transformed into quinolone analogues *via* oxidation step.

Scheme 6



Scheme 7



Synthesis of Precursors **2** - **7**.

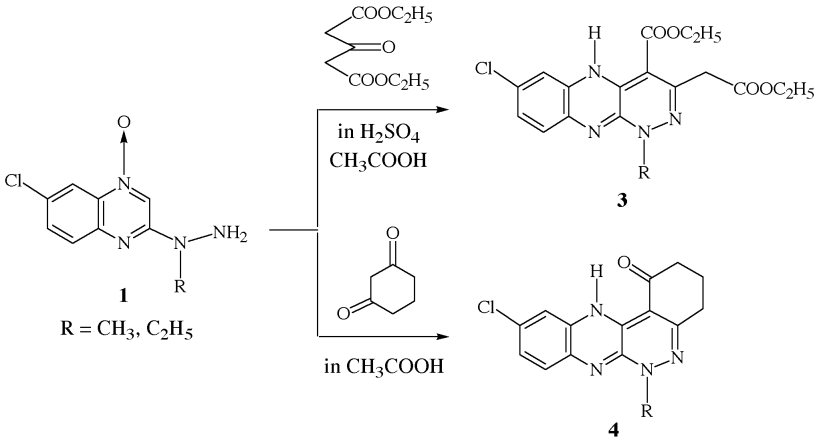
Pyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **2**.

The dichloroquinoxaline *N*-oxide **8** was transformed into the quinoxaline *N*-oxides **9**, and the 1,3-dipolar cycloaddition reaction of the quinoxaline *N*-oxides **9** with dimethyl acetylenedicarboxylate gave the isoxazolo[2,3-*a*]quinoxalines **10**, whose reaction with another dimethyl acetylenedicarboxylate resulted in ring transformation to afford the pyrrolo[1,2-*a*]quinoxalines **11** presumably *via* an intermediate **1** or **2** [57,58] (Scheme 5). Scheme 6 shows a postulated reaction mechanism to trap an intermediate **1** or **2**. Namely, the quinoxaline *N*-oxide **12** having an NH_2 function in the side chain would be converted into the linearly condensed quinoxaline **13** *via* 1,3-dipolar cycloaddition reaction leading to an intermediate **3** and then ring opening giving an open chain intermediate **4**. Thus, the 2-hydrazinoquinoxaline *N*-oxide **14** and 2-(1-methylhydrazino)quinoxaline *N*-oxide **1** were synthesized from the dichloroquinoxaline *N*-oxide **8** (Scheme 7). The reaction of compound **14** with dimethyl acetylenedicarboxylate resulted in addition of the hydrazino moiety to the acetylene carbon to give the hydrazone derivative **15**. On the contrary, the reaction of compound **1** with acetylenedicarboxylates effected 1,3-dipolar cycloaddition reaction to afford the pyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **2** presumably *via* intermediates **5** - **8**. An intermediate **6** or **7** is corresponding to an intermediate **1** or **2** in Scheme 5, respectively.

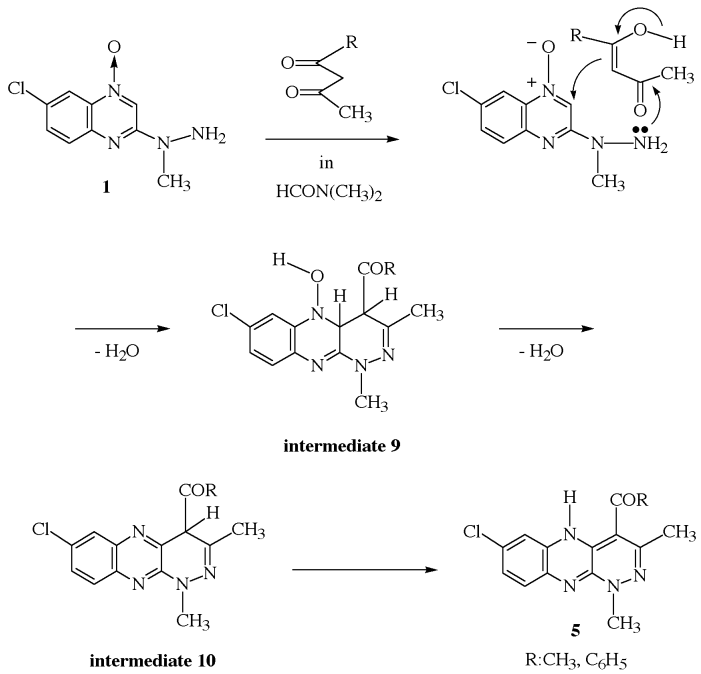
2-(Pyridazino[3,4-*b*]quinoxalin-3-yl)acetates **3** and Quinoxalino[2,3-*c*]cinnolines **4**.

The reaction of the quinoxaline *N*-oxides **1** with 1,3-acetonedicarboxylate or 1,3-cyclohexanedione provided the 2-(pyridazino[3,4-*b*]quinoxalin-3-yl)acetates **3** or quinoxalino[2,3-*c*]cinnolines **4**, respectively (Scheme 8), in a mechanism shown in Figure 6. A detailed reaction mechanism is exhibited in the next section.

Scheme 8



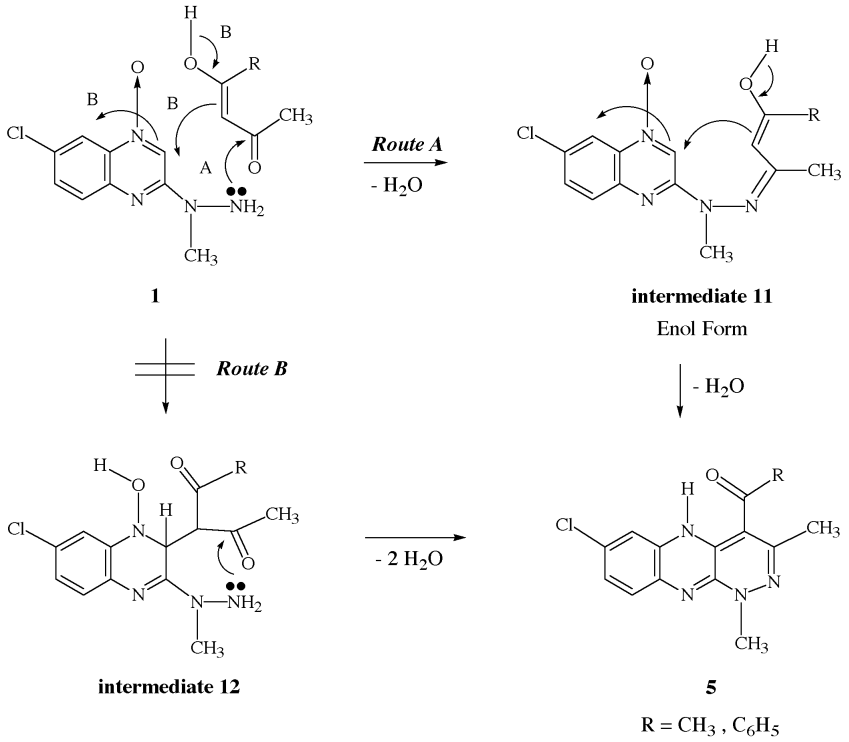
Scheme 9



4-Acylpyridazino[3,4-*b*]quinoxalines **5**.

The reaction of compound **1** with β-diketones produced the 4-acylpyridazino[3,4-*b*]quinoxalines **5** presumably *via* intermediates **9** and **10** (Scheme 9) [54]. There are two possible cyclization routes A and B in the formation of compounds **5** from compound **1**, as shown in Scheme 10 [59]. However, route A *via* intermediate **11** was preferred to the route B *via* intermediate **12** based on the results shown below. The reaction of the hydrazone derivative **16** with acetylacetone did not give the diacetylmethylene derivative **17** (Scheme 11), while the reaction of the 2-hydrazino derivative **14** with acetylacetone afforded the 2-(1-pyrazolyl)quinoxaline *N*-oxide **18** presumably *via* an intermediate **13** (Scheme 12). The above results are summarized in Scheme 13. The reaction of compound **1** or **14** with β-diketones would provide a hydrazone intermediate **13**. When R of a hydrazone intermediate **13** is hydrogen, the cyclization into the pyrazole ring in the side chain gave the 2-(1-pyrazolyl)quinoxaline *N*-oxides **18**.

Scheme 10



On the other hand, when the R group of a hydrazone intermediate **11** is methyl, the cyclization into the pyridazine ring afforded the 4-acylpyridazino[3,4-*b*]-quinoxalines **5**. The *N*-oxide moiety of compounds **18** was confirmed by the 1,3-dipolar cycloaddition reaction with dimethyl acetylenedicarboxylate, providing the 4-(1-pyrazolyl)pyrrolo[1,2-*a*]quinoxalines **19**.

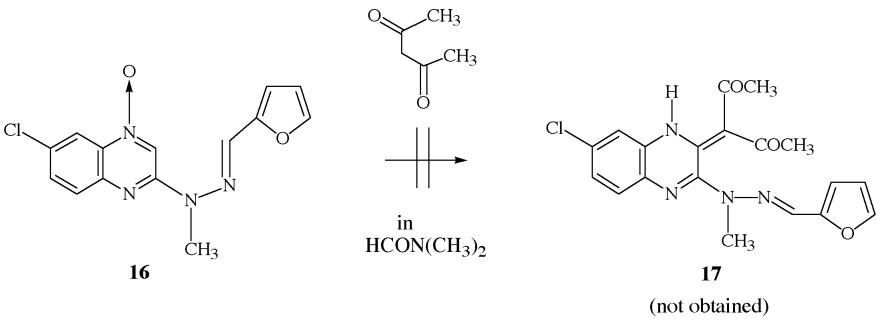
1,2-Diazepino[3,4-*b*]quinoxaline-5-carbonitriles **6**.

The reaction of compound **1** with 2-chloroacrylonitrile was found to result in 1,3-dipolar cycloaddition reaction to give the pyrazolo[3,4-*b*]quinoxaline **20** [53] (Scheme 14). In the meantime, the NH_2 moiety of compound **1** was blocked with aldehydes to produce the hydrazones **21**, whose reaction with 2-chloroacrylonitrile afforded the 1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitriles **22** presumably *via* intermediates **14** - **17** (Scheme 15). The 1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitriles **6** (Scheme 4) were synthesized by this method (Scheme 22).

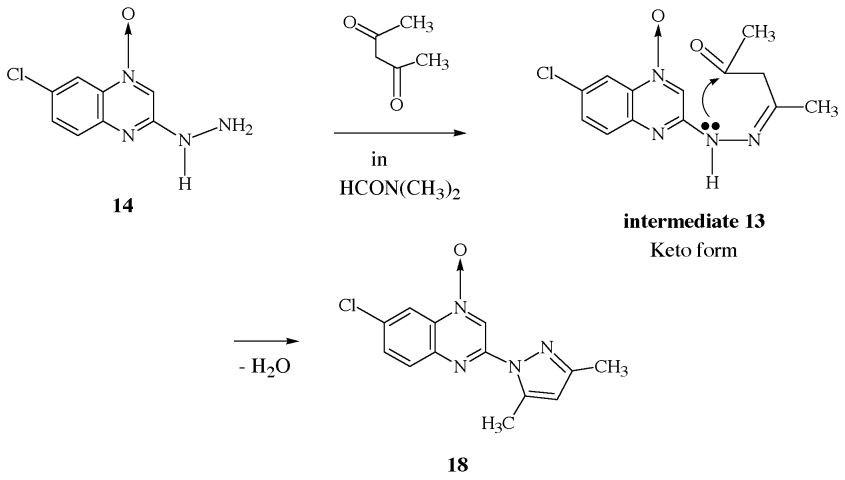
Pyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylates **7**.

The reaction of compound **1** with ethyl ethoxymethyl-enecyanoacetate or ethoxymethylenemalononitrile in ethanol gave the 2-(2-cyanovinyl-1-methylhydrazino)-quinoxaline *N*-oxide **23a** or **23b** [60], whose reflux in acetic acid effected intramolecular dehydration to afford the 4-cyanopyridazino[3,4-*b*]quinoxaline-4-carboxylate **24a** or pyridazino[3,4-*b*]quinoxaline-4,4-dicarbonitrile

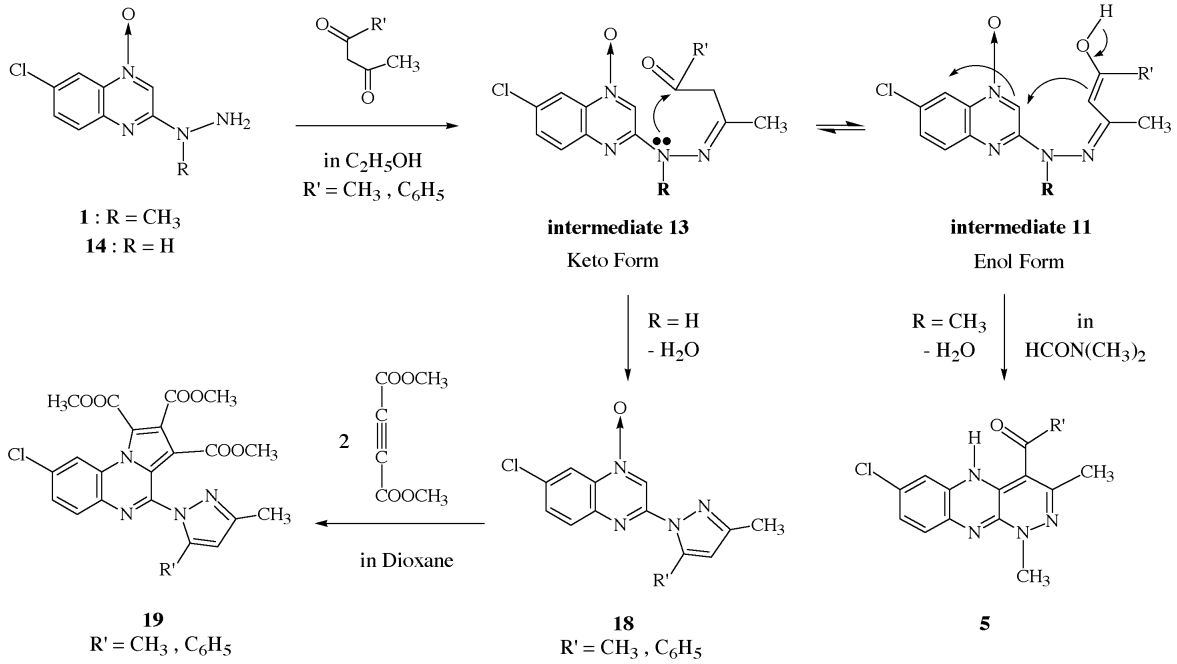
Scheme 11



Scheme 12



Scheme 13



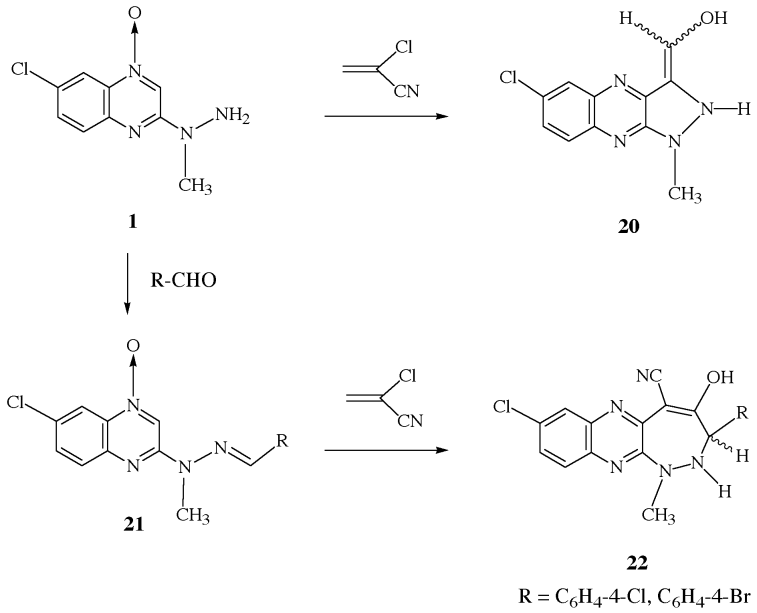
24b, respectively (Scheme 16) [50]. In the meanwhile, the reaction of compound **1** with diethyl ethoxymethylenemalonate in acetic acid directly provided the pyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylate **7** [50].

Synthesis of Quinolone Analogues **I** - **VI**.

Quinolone Analogues **I**: 1-Alkyl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic Acids **Ia-d**.

The 1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **2a-d** were obtained from the quinoxaline *N*-oxides **8a,b** *via* the (1-alkylhydrazino)quinoxaline *N*-oxides **1a-d**, respectively (Scheme 17) [42]. The reaction of compounds **2a-d** with nitrous acid resulted in oxidation to give the 1,4-dihydro-4-hydroxypyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **25a-d**, whose reaction with 1,8-diazabicyclo[5.4.0]-7-undecene in ethanol effected ester exchange and elimination of formate to afford the 1,4-dihydro-4-oxopyridazino[3,4-*b*]-quinoxaline-3-carboxylates **26a-d**, respectively. The reaction of compounds **25a-d** or **26a-d** with potassium hydroxide provided the 1-alkyl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **Ia-d**.

Scheme 14

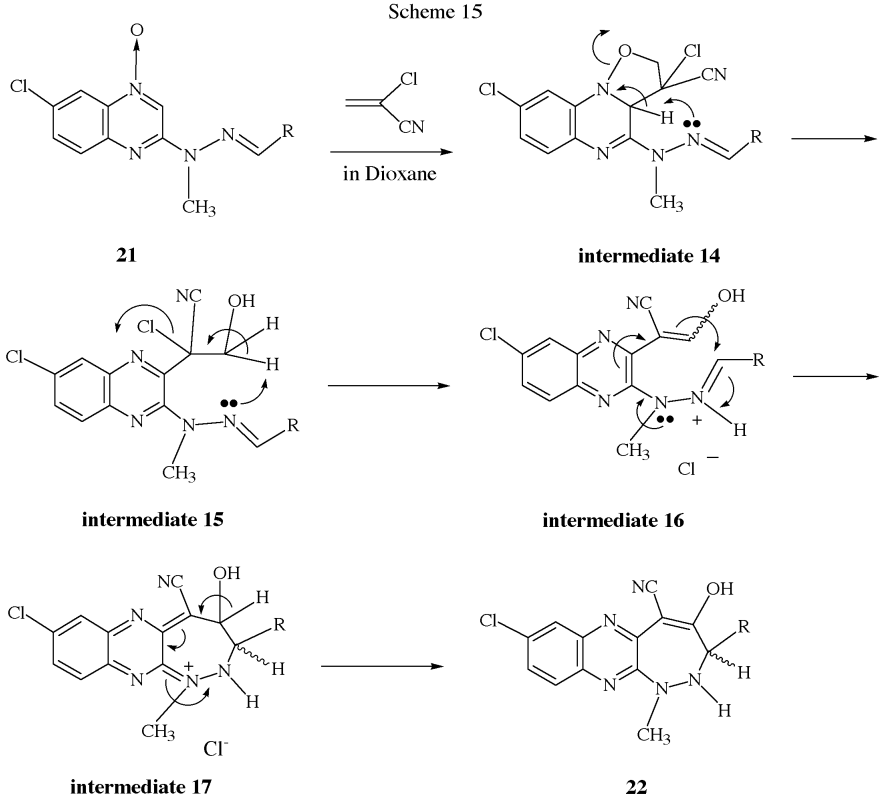


1 **20** **21** **22**

When nitrous acid acts as an oxidizing agent, it generates nascent oxygen (Figure 7). Accordingly, the oxidation of 1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **2a-d** with nitrous acid would proceed in a mechanism A, B, or C.

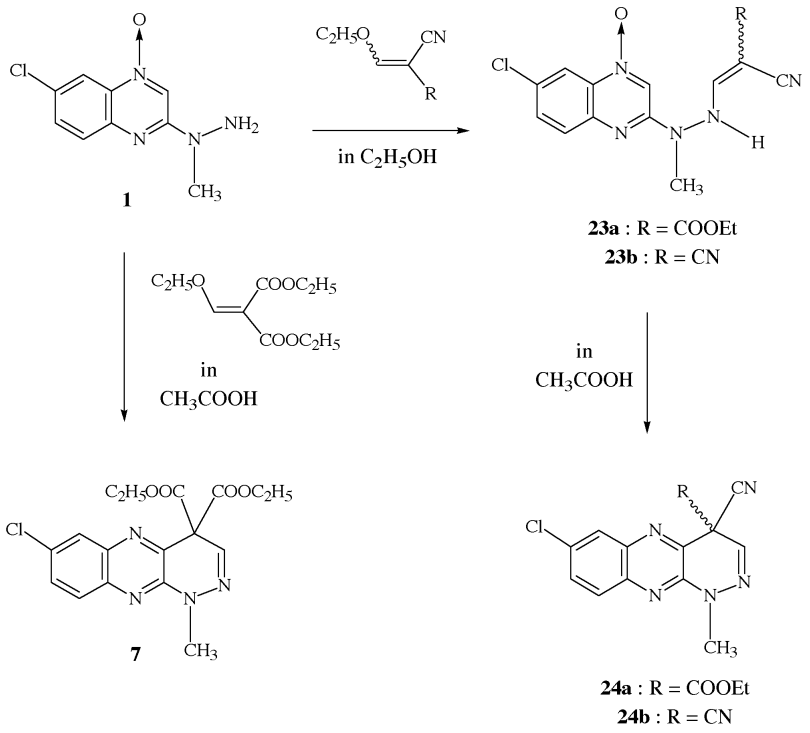
On the other hand, the 4-hydroxy derivative **25a** was converted into the 4-keto derivative **26a** both under nitrogen (79% yield) and under aerobic condition (83% yield) (Scheme 18). Therefore, a mechanism *via* elimination of formate was preferred to a mechanism *via*

Scheme 15



21 **intermediate 14** **intermediate 15** **intermediate 16** **intermediate 17** **22**

Scheme 16



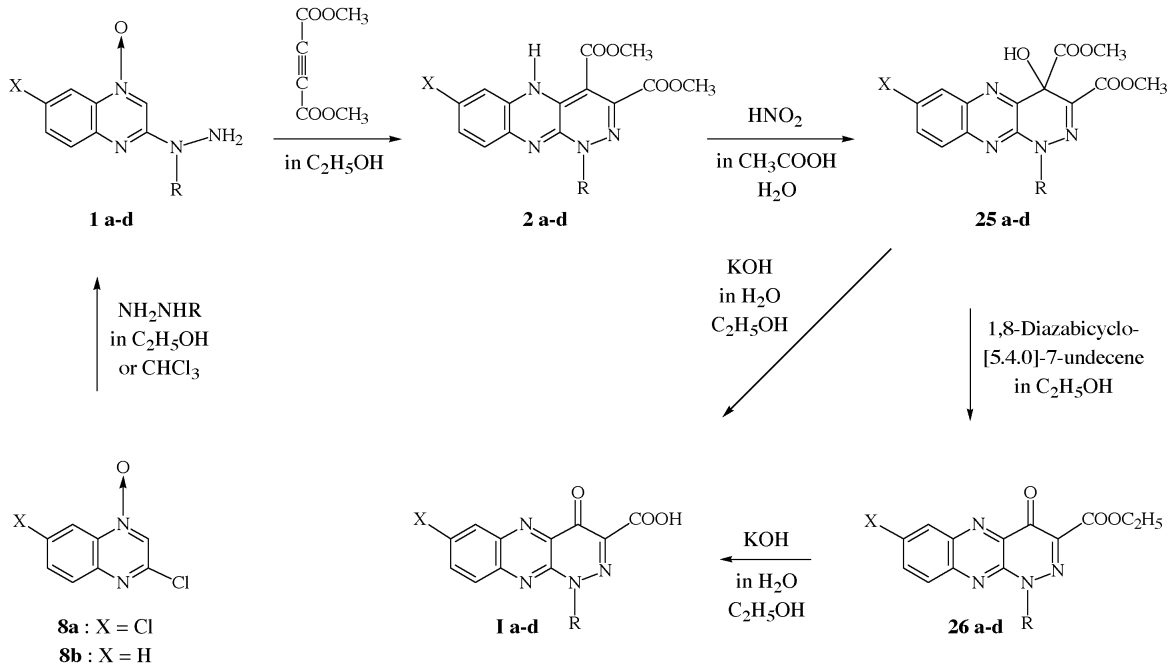
1

23a : R = COOEt
23b : R = CN

7

24a : R = COOEt
24b : R = CN

Scheme 17



1 a-d

2 a-d

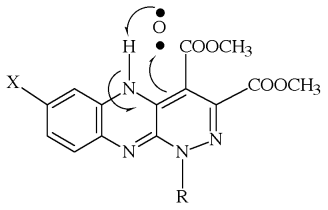
25 a-d

8a : X = Cl
8b : X = H

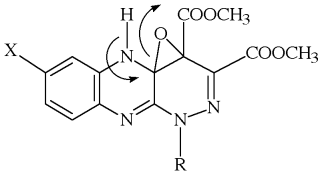
I a-d

26 a-d

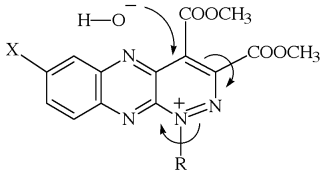
a: X = Cl, R = CH_3 ; **b**: X = Cl, R = C_2H_5 ; **c**: X = H, R = CH_3 ; **d**: X = H, R = C_2H_5



Postulated Oxidation Mechanism A



Postulated Oxidation Mechanism B



Postulated Oxidation Mechanism C

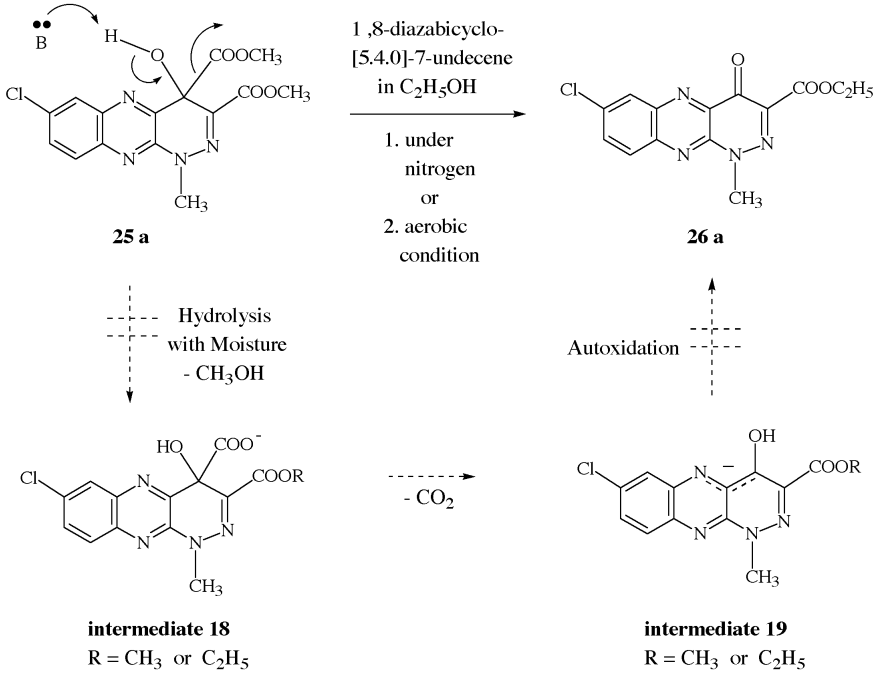
Decomposition of HNO_2

$2\ HNO_2 \longrightarrow H_2O + \bullet O\bullet + 2\ \bullet N{=}O$

$2\ \bullet N{=}O + O_2 \longrightarrow 2\ O{=}N{-}O\bullet$

Figure 7

Scheme 18

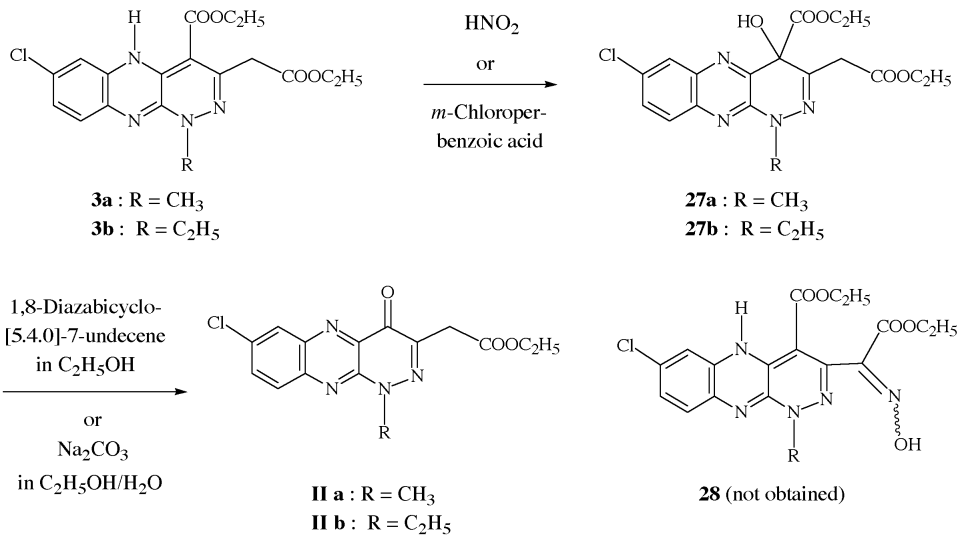


intermediates **18** and **19**, which would be formed by the hydrolysis and then decarboxylation of the C_4-ester group in compound **25a**.

Quinolone Analogues **II** and **III**: 2-(1-Alkyl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxalin-3-yl)acetates **IIa**,**b** and 4-(1-Alkyl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxalin-3-yl)butyric Acids **IIIa**,**b** and Ester Derivatives **IIIc**,**d**.

The reaction of compound **3a** or **3b** with nitrous acid or *m*-chloroperbenzoic acid resulted in oxidation to give the 2-(1,4-dihydro-4-hydroxypyridazino[3,4-*b*]quinoxalin-3-yl)acetate **27a** or **27b**, respectively, wherein compound **27b** was not isolated (Scheme 19) [48]. Treatment of compound **27a** or **27b** with 1,8-diazabicyclo[5.4.0]-7-undecene or sodium carbonate afforded the 2-(1-alkyl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxalin-3-yl)acetate

Scheme 19



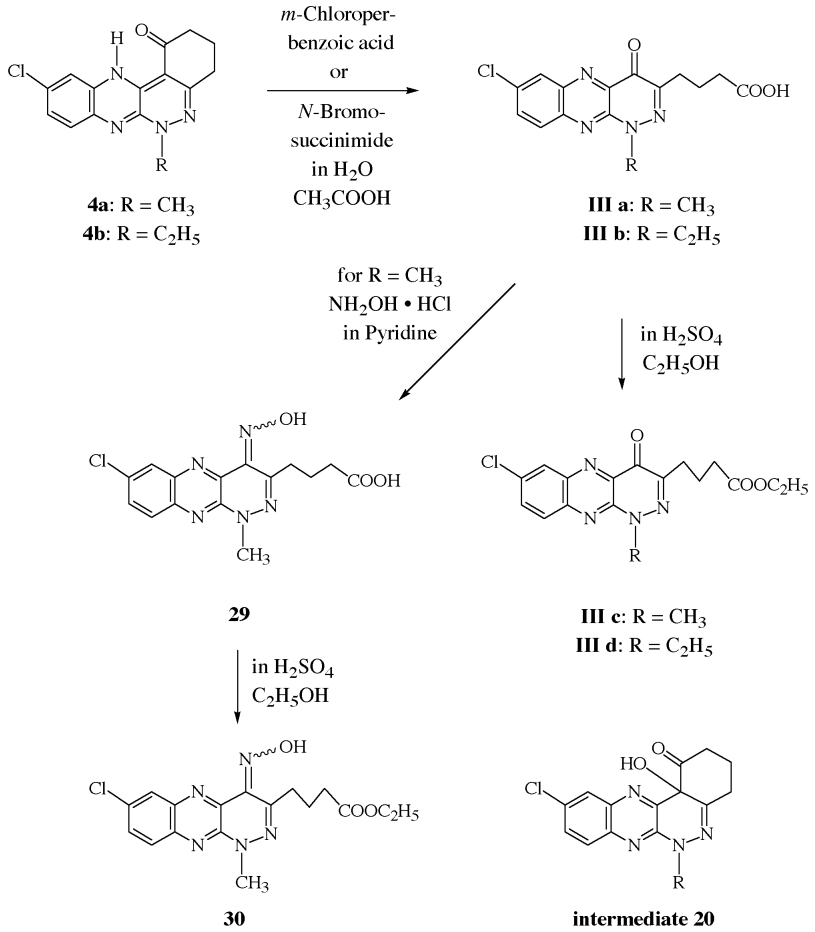
3a : R = CH_3
3b : R = C_2H_5

27a : R = CH_3
27b : R = C_2H_5

II a : R = CH_3
II b : R = C_2H_5

28 (not obtained)

Scheme 20



4a: R = CH_3
4b: R = C_2H_5

III a: R = CH_3
III b: R = C_2H_5

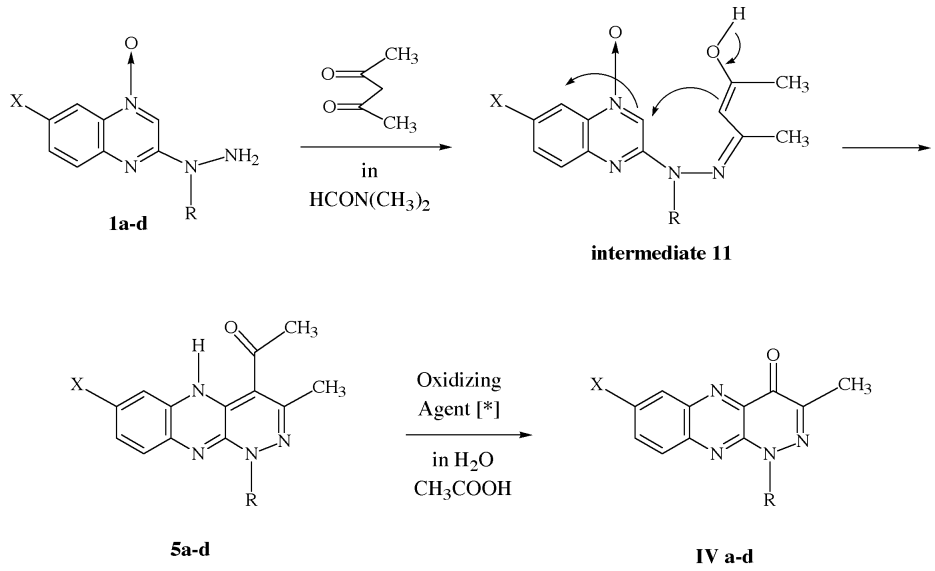
29

III c: R = CH_3
III d: R = C_2H_5

30

intermediate 20

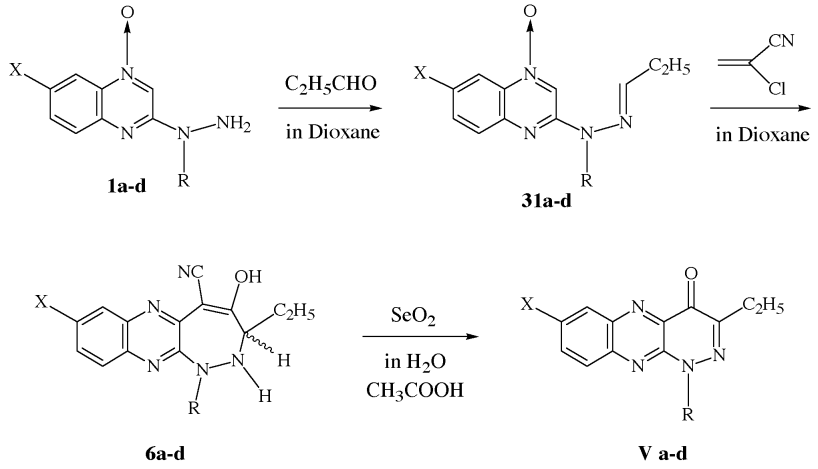
Scheme 21



[*] for **a** and **c** - *N*-Bromosuccinimide / H_2O ; for **b** and **d** - Sodium bromate

a : X = Cl, R = CH_3 ; **b** : X = Cl, R = C_2H_5 ; **c :** X = H, R = CH_3 ; **d :** X = H, R = C_2H_5

Scheme 22

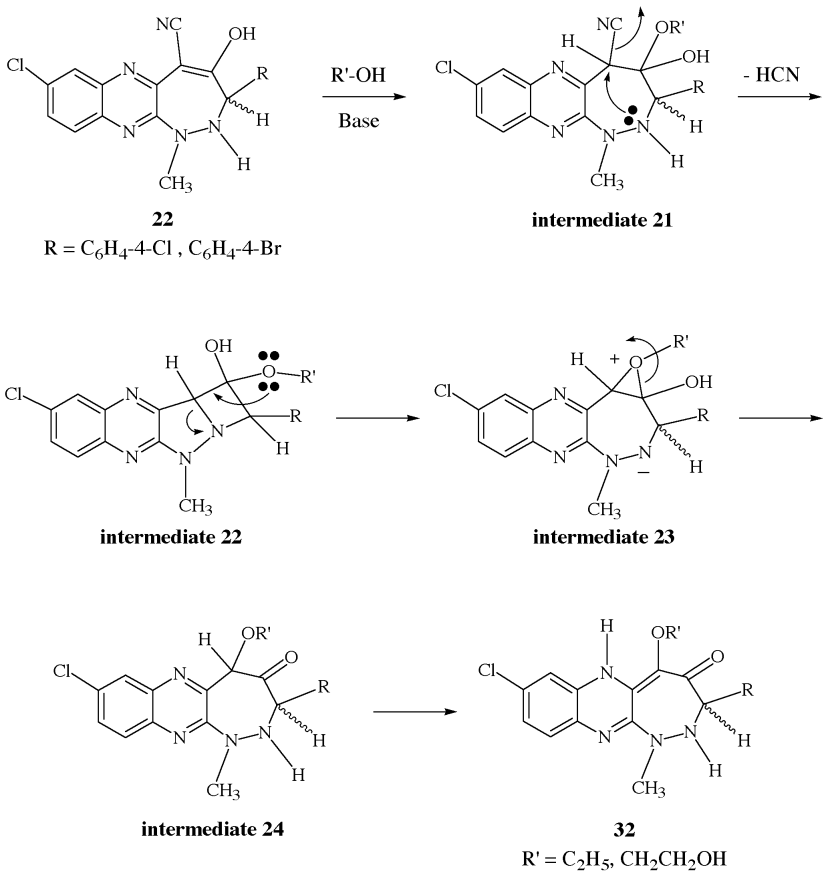


a : X = Cl, R = CH_3 ; **b** : X = Cl, R = C_2H_5 ; **c :** X = H, R = CH_3 ; **d :** X = H, R = C_2H_5

IIa or **IIb**, respectively. The expected oxime derivative **28** was not obtained by the reaction of compounds **3a,b** with nitrous acid.

In the meantime, the reaction of the quinoxalino-[2,3-*c*]cinnoline **4a** or **4b** with *m*-chloroperbenzoic acid or *N*-bromosuccinimide/water resulted in oxidation to provide the 4-(1-alkyl-1,4-dihydro-4-oxopyridazino-[3,4-*b*]quinoxalin-3-yl)butyric acid **IIIa** or **IIIb**, respectively, presumably *via* an intermediate **20** (Scheme 20). The reaction of compound **IIIa** with hydroxylamine gave the oxime derivative **29**. The esterification of compounds **IIIa**,**b** and **29** in sulfuric acid/ethanol afforded the ester derivatives **IIIc**,**d** and **30**, respectively.

Scheme 23



Quinolone Analogues **IV** and **V**: 1-Alkyl-1,4-dihydro-3-methylpyridazino[3,4-*b*]quinoxalin-4-ones **IVa-d** and 1-Alkyl-3-ethyl-1,4-dihydropyridazino[3,4-*b*]quinoxalin-4-ones **Va-d**.

The reaction of the quinoxaline *N*-oxides **1a-d** with acetylacetone gave the 4-acetyl-3-methylpyridazino[3,4-*b*]-quinoxalines **5a-d**, respectively (Scheme 21) [49]. Oxidation of compounds **5a,c** or compounds **5b,d** with *N*-bromosuccinimide/water or sodium bromate afforded the 1-alkyl-1,4-dihydro-3-methylpyridazino[3,4-*b*]qunoxaln-4-ones **IVa-d**.

The reaction of the quinoxaline *N*-oxides **1a-d** with propionaldehyde gave the hydrazones **31a-d**, whose reaction with 2-chloroacrylonitrile afforded the 3-ethyl-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitriles **6a-d**, respectively (Scheme 22) [49]. The reaction of compounds **6a-d** with selenium dioxide resulted in oxidative ring transformation to provide the 1-alkyl-3-ethyl-1,4-dihydropyridazino[3,4-*b*]quinoxalin-4-ones **Va-d**, respectively.

The alcoholysis of the 1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitriles **22** was found to give the 5-alkoxy-1,2-diazepino[3,4-*b*]quinoxalin-4-ones **32**, respectively, presumably *via* intermediates **21** - **24** (Scheme 23) [55,56]. According to this alcoholysis mechanism, the hydrolysis of compounds **6a-d** would afford a 5-hydroxy-4-one intermediate **25**, which is converted into the quinolone analogues **Va-d** presumably *via* intermediates **26** - **29** (Scheme 24) [61].

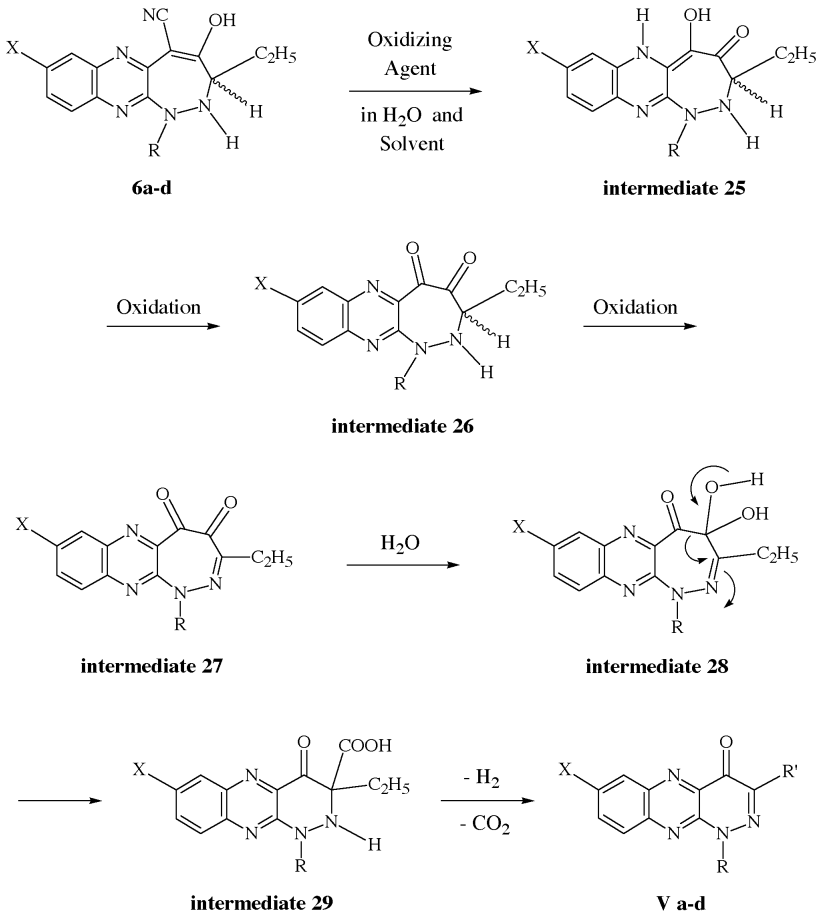
Quinolone Analogue **VI**: 1-Methyl-1,4-diydropyridazino[3,4-*b*]quinoxalin-4-one **VI**.

The reaction of the pyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylate **7** with hydrazine hydrate resulted in hydrolysis and decarboxylation to give the pyridazino-[3,4-*b*]quinoxaline-4-carboxylate **33**, whose reaction with nitrous acid effected oxidation to afford the 4-hydroxypyridazino[3,4-*b*]quinoxaline-4-carboxylate **34** (Scheme 25) [50]. The reaction of compound **34** with potassium hydroxide provided the 1-methyl-1,4-dihydropyridazino[3,4-*b*]-quinoxalin-4-one **VI**.

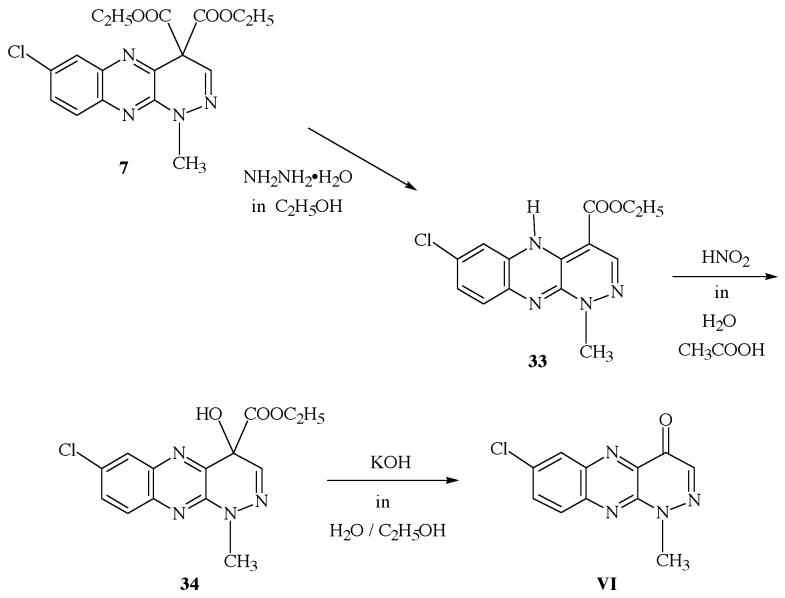
Oxidizing Agents.

Suitable oxidizing agents are shown in Schemes 26 and 27. Nitrous acid and *m*-chloroperbenzoic acid are available for the oxidation of the 1,5-dihydropyridazino[3,4-*b*]-quinoxaline-4-carboxylates, giving the 1,4-dihydro-4-

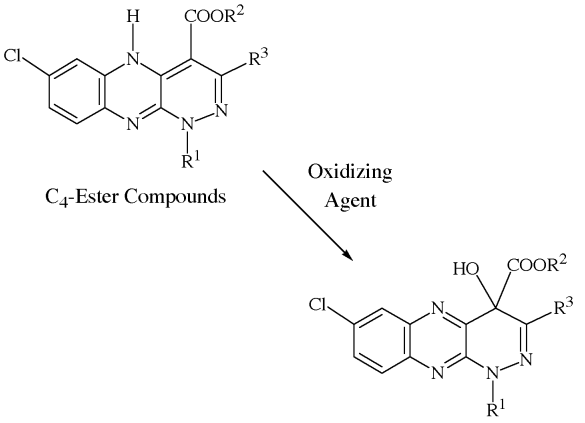
Scheme 24



Scheme 25



Scheme 26



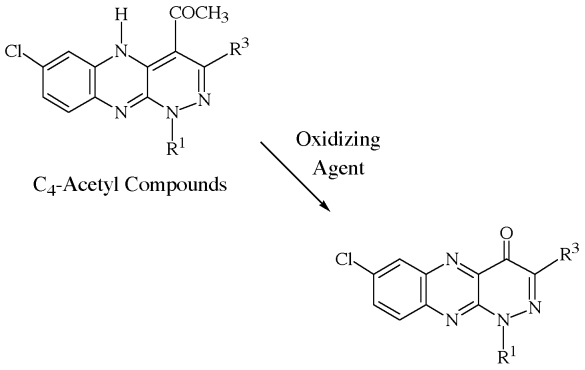
Suitable Oxidizing Agent: HNO_2 , *m*-Chloroperbenzoic Acid

hydroxypyridazino[3,4-*b*]quinoxaline-4-carboxylate (Scheme 26). Meanwhile, *N*-bromosuccinimide/water, sodium bromate, selenium dioxide, and *m*-chloroperbenzoic acid are suitable for the oxidation of the 4-acetyl-1,5-dihydropyridazino[3,4-*b*]quinoxalines, affording the 1,4-dihydropyridazino[3,4-*b*]quinoxalin-4-ones presumably *via* a 4-hydroxy intermediate (Scheme 27).

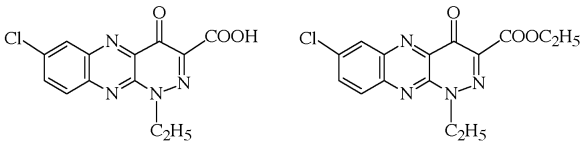
Biological Activities [62].

The *in vitro* screening was carried out for our quinolone analogues **I - VI**. The antibacterial and antifungal activities of quinolone analogue **Ib** and its ester derivative **26b** are shown in Figure 8, wherein the minimum inhibitory concentration (MIC) are above 12.5 μg/ml (ppm). In the antibacterial activity against *Bacillus subtilis*, quinolone analogues **Ia,b** were inferior to their ester derivatives **26a,b**, which were similar to quinolone analogues **IIIc,d**

Scheme 27

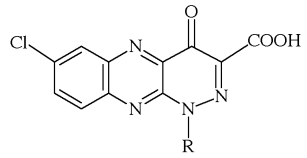


Suitable Oxidizing Agent: *N*-Bromosuccinimide/ H_2O , $NaBrO_3$, SeO_2 , *m*-Chloroperbenzoic Acid

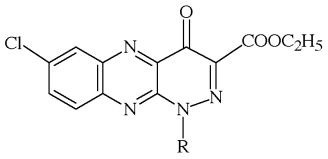


Bacteria	**I b**	**26b**
Mycobacterium ranae	above 100	12.5
Staphylococcus aureus	12.5	12.5
Staphylococcus epidermis	12.5	12.5
Klebsiella pneumoniae	50.0	25.0
Fungi		
Candida albicans	50.0	12.5

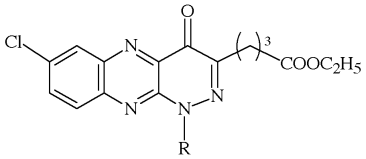
Figure 8
In vitro Antimicrobial Screening Data (figures indicate MIC in ppm)



Ia : R = CH_3 15.6
Ib : R = C_2H_5 15.6



26a : R = CH_3 2.0
26b : R = C_2H_5 7.8

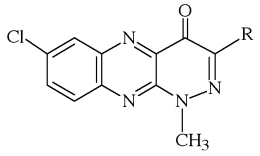


IIIc : R = CH_3 7.8
IIId : R = C_2H_5 7.8

Figure 9
In vitro Screening Data against *Bacillus subtilis* (figures indicate MIC in ppm)

(Figure 9). However, quinolone analogues **IVa** and **Va** were superior to quinolone analogues **IIIc,d** and **26b** in the antibacterial activity against *Bacillus subtilis* (Figure 10). Moreover, quinolone analogues **IVa** and **Va** showed good antifungal activity against *Trichophyton mentagrophytes*. Quinolone analogue **VI** also exhibited good antibacterial activity [62].

Thus, we have found that the biological activities of quinolone analogues without C_3-carboxyl (or carboxylate) moiety tend to be superior to those of quinolone analogues with C_3-carboxyl (or carboxylate) moiety in the pyridazino[3,4-*b*]quinoxaline ring system.



	Bac. sub.	*Tri. men.*
IVa : R = CH_3	2.0	2.0
Va : R = C_2H_5	2.0	1.0

Figure 10
In vitro Screening Data against *Bacillus subtilis* and *Trichophyton mentagrophytes* (figures indicate MIC in ppm)

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