RECENT ADVANCES IN THE SYNTHESIS OF ANTIBACTERIAL QUINOLONES

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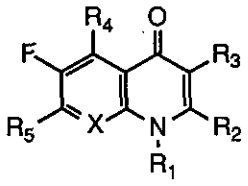
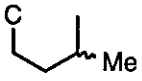
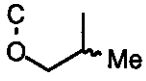
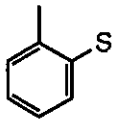
Abstract - This review surveys the main synthetic approaches used for the construction of antibacterial quinolones, including aza analogs (naphthyridones, cinnolones) and condensed polycyclic analogs, with an emphasis on the more versatile methods which are potentially useful in other fields of heterocyclic chemistry. Simpler non-condensed monocyclic analogs, i.e., pyridone and pyridazinone carboxylic acids are also briefly mentioned.

1. Introduction

Biopharmacological features of antibacterial quinolones have attracted the considerable attention of many major pharmaceutical companies, as an incredible number of new congeners have appeared. Several new analogs have been introduced recently and even more are in various phases of their clinical investigation.

Figure 1



	X	R^1	R^2	R^3	R^4	R^5
Norfloxacin	CH	Et	H	COOH	H	piperazinyl
Enoxacin	N	Et	H	COOH	H	piperazinyl
Ciprofloxacin	CH	*c*-Pr	H	COOH	H	piperazinyl
Amifloxacin	CH	NHMe	H	COOH	H	4-methylpiperazinyl
Sparfloxacin	CF	*c*-Pr	H	COOH	NH_2	(3S,5R)-dimethylpiperazinyl
Flumequine	C		H	COOH	H	H
Ofloxacin	C		H	COOH	H	4-methylpiperazinyl
A-57,207	CH			COOH	H	piperazinyl
A-62,824	CH	*c*-Pr	S-NH-CO		H	piperazinyl

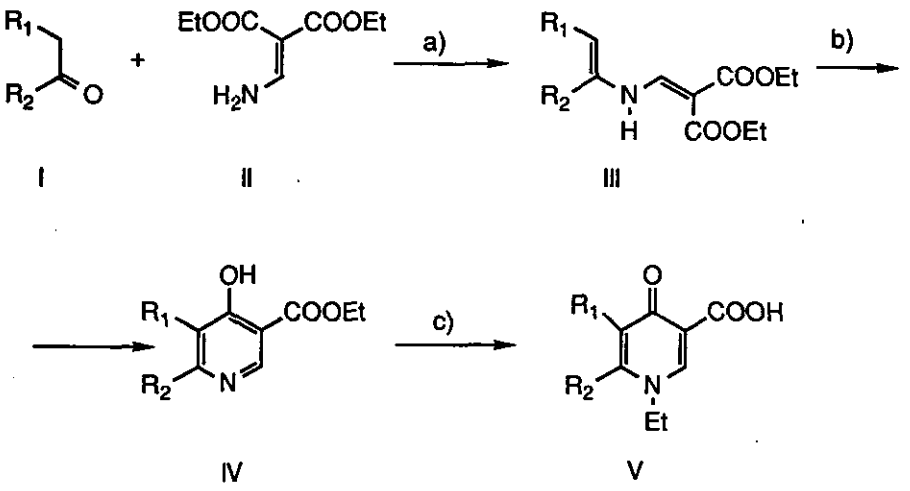
The aim of this review is not to discuss the structure-activity relationships, which have been discussed recently in several reviews,[1-6] but to pay attention to the synthetic point of view. During the course of the extensive research into antibacterial quinolones, several new methods have been discovered which could be generally useful for the synthesis of other heterocyclic structures. So, the aim of this review is to introduce these potentially useful methods into the arsenal of more heterocyclic chemists.
In spite of the fact that this therapeutic group is usually called antibacterial quinolones, it includes also various aza analogs (naphthyridones, cinnolones) and analogs condensed with other rings. From several typical examples depicted in Figure 1 is evident that only the presence of an oxo group at the position 4 and a fluorine atom at the position 6 is considered to be necessary for the high and broad spectrum antibacterial activity of this type of compounds. Most drugs used and in clinical studies have hydrogen atoms at the positions 2 and 5, a carboxylic group at the position 3 and various cyclic amino groups (mainly piperazine and pyrrolidine derived) at the position 7. Due to the aim of this review, some examples which failed to provide perspective antibacterial agents will also be mentioned, in cases the authors consider them synthetically useful.

2. Synthesis of heterocyclic skeletons

2.1. Monocyclic derivatives

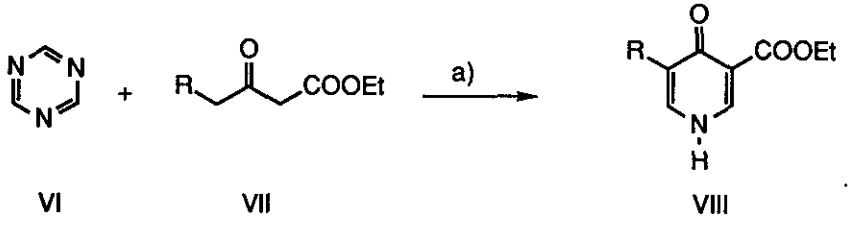
Attempts to prepare the simplest congeners retaining the particular activity of the lead compound are common in medicinal chemistry. Accordingly, research into antibacterial quinolones led also to corresponding 1,4-dihydro-4-oxo-3-pyridinecarbo-xylic acids. In the early years, when *N*-ethyl group was considered to be the most advantageous, suitably substituted 4-hydroxynicotinates were assembled and (Figures 2, 3) following *N*-alkylation and hydrolysis provided the acids.[7-9]

Figure 2



a) P_2O_5/THF or PTSA/xylene; b) Dowtherm A/255°C; c) 1. EtI/NaH/DMF, 2. OH^-, 3. H^+

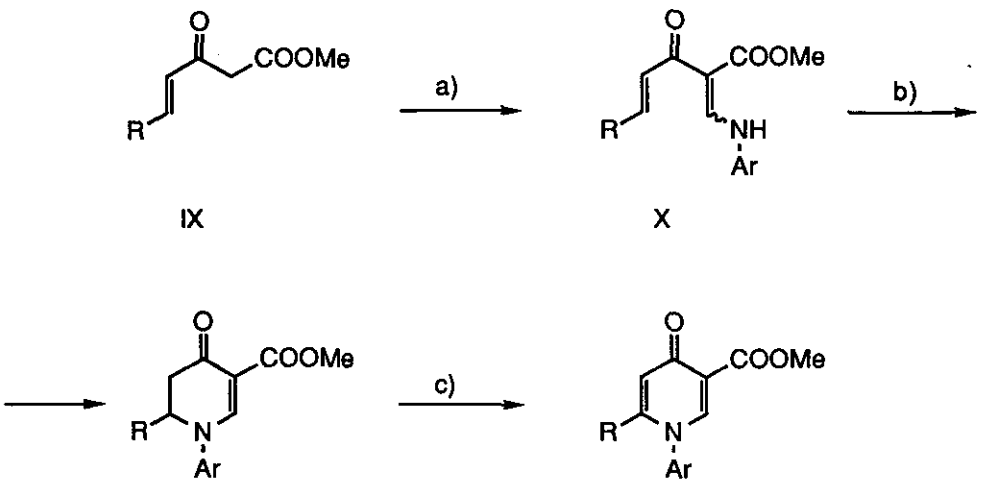
Figure 3



a) EtONa/EtOH

After the discovery of some highly active *N*-arylquinolones, corresponding monocyclic analogs were also prepared. One method used Wittig reaction products (IX), which were successively treated with *N*,*N*-dimethylformamide dimethyl acetal and then with the corresponding arylamines to provide intermediates (X). Their cyclization followed by oxidation yielded esters (XII) (Refs. 10-12). Compounds with various substituents at the positions 1 and 6 could be prepared by this route (Figure 4).

Figure 4

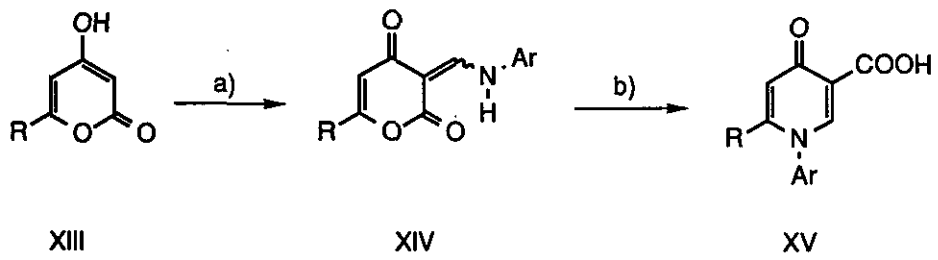


IX X XI XII

a) 1. DMF-DMA, 2. $ArNH_2$; b) 150°C, DMF; c) DDQ or chloranil

4-Hydroxy-2-pyrones (XIII) have also proved to be useful starting compounds. Upon reaction with *N,N*-dimethylformamide dimethyl acetal (or with trialkyl orthoformate) and arylamines the corresponding 3-arylaminomethylene derivatives (XIV) were obtained which rearranged under either acidic or alkaline conditions to acids (XV) (Figure 5). However, this rearrangement did not take place if R is an aryl group.[13]

Figure 5

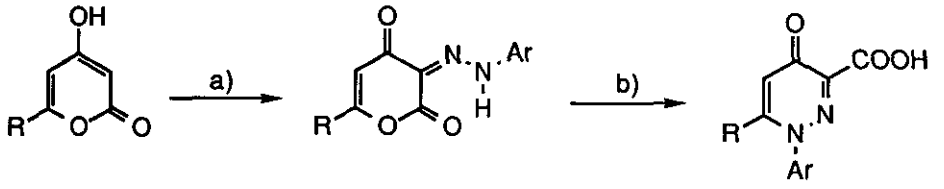


XIII XIV XV

a) 1. DMF-DMA or $(EtO)_3CH$, 2. $ArNH_2$; b) H^+ or OH^-

By a similar reaction sequence (Figure 6) pyridazine derivatives (XVII) were also prepared. In this case the rearrangement was successful also for 6-aryl derivatives.[14]

Figure 6



XIII XVI XVII

a) $ArN_2^+ Cl^-$; b) H^+ or OH^-

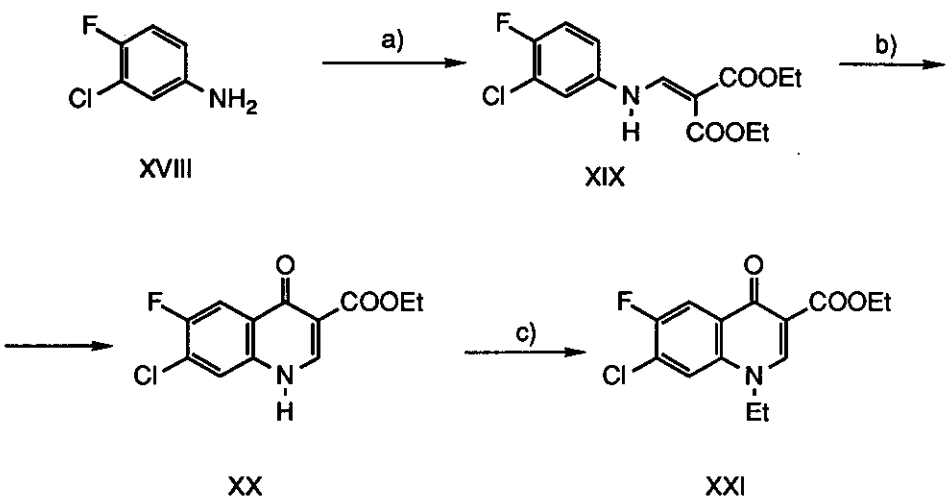
2.2. Bicyclic derivatives

2.2.1. Quinolones

Early synthesis of these compounds was accomplished exclusively by a classical method starting from aniline derivatives, which were condensed with diethyl ethoxymethylenemalonate and the intermediates thermally condensed to the corresponding 4-hydroxyquinoline-3-carboxylates (Gould-Jacobs reaction), which after *N*-alkylation and hydrolysis provided quinolone carboxylic acids.[1] The preparation of XXI, an intermediate for the synthesis of norfloxacin,[15] is depicted in Figure 7 as an example of this method. Compounds bearing various C-5 and C-8 substituents have also been prepared by this route.

N-Arylations of 4-hydroxy-3-quinolinecarboxylates with 4-nitrofluorobenzene and 2,4-dinitrochlorobenzene have been recently reported.[16,17] However, in general this method is not suitable for the synthesis of quinolones substituted at the position 1 with aryl groups and secondary or tertiary alkyl groups. In addition, when utilizing an unsymmetrically substituted aniline, a mixture of both possible isomers might be obtained, especially if an acidic condensation reagent is used.

Figure 7



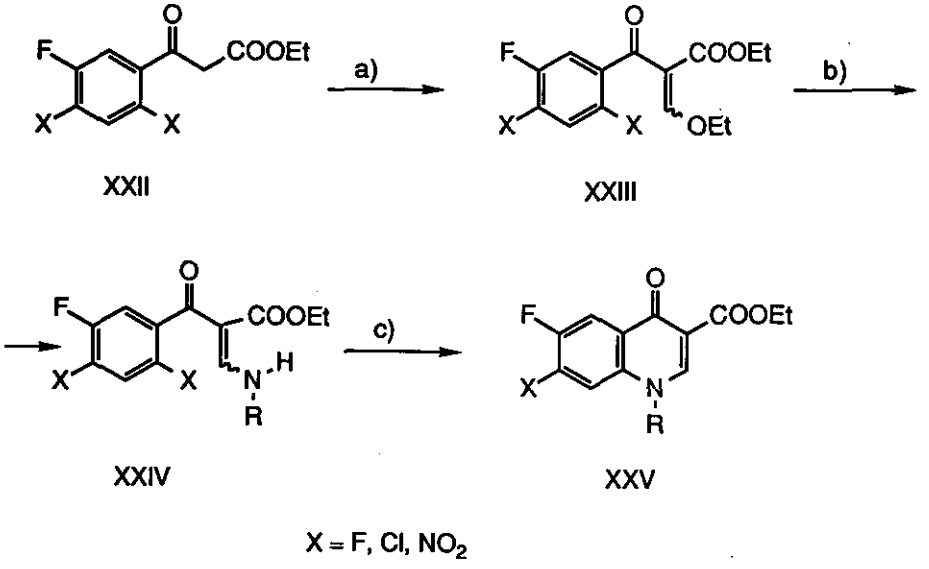
XVIII XIX XX XXI

a) EMME; b) 250°C; c) 1. EtI/K_2CO_3/DMF, 2. OH^-, 3. H^+

Both of these problems were elegantly solved by Bayer chemists (Figure 8, X = Cl) in the course of the synthesis of ciprofloxacin.[18] Benzoylacetate (XXII) with orthoformate provided the corresponding ethoxymethylene derivative (XXIII) which when treated with the respective amine yielded intermediate (XXIV). This intermediate can be cyclized to XXV using various bases. This method is very versatile[19,20] and can be used for the preparation of various *N*-aryl-,[21-25] *N*-secondary alkyl-[17-20,26,27] and tertiary alkylquinolones[28,29] which can bear various substituents at the positions 5 and 8.

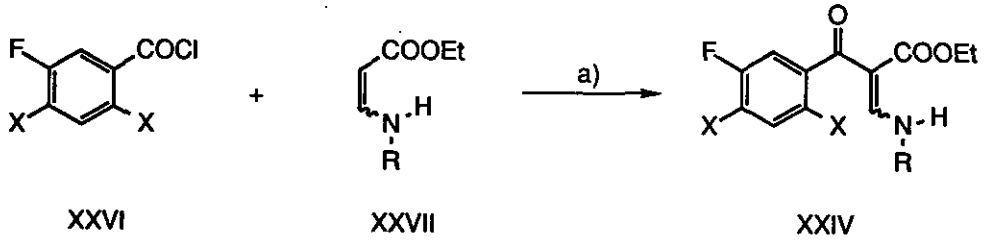
The chloro derivative (XXII) (X = Cl) could be replaced by more reactive fluoro analog (X = F). A similar denitrocyclization reaction of compound (XXIV) (X = NO_2), where the nitro group is used as a leaving group, has also been described.[20,30] Intermediates (XXIV) were also prepared by a direct reaction of corresponding benzoyl chlorides (XXVI) with enamino esters (XXVII), which were easily prepared from ethyl acetylene-carboxylate and corresponding amines [20] (Figure 9).

Figure 8



a) $(EtO)_3CH$, Ac_2O; b) RNH_2; c) NaH/Dioxane, KF/DMF, Bu_4NF/THF or other bases

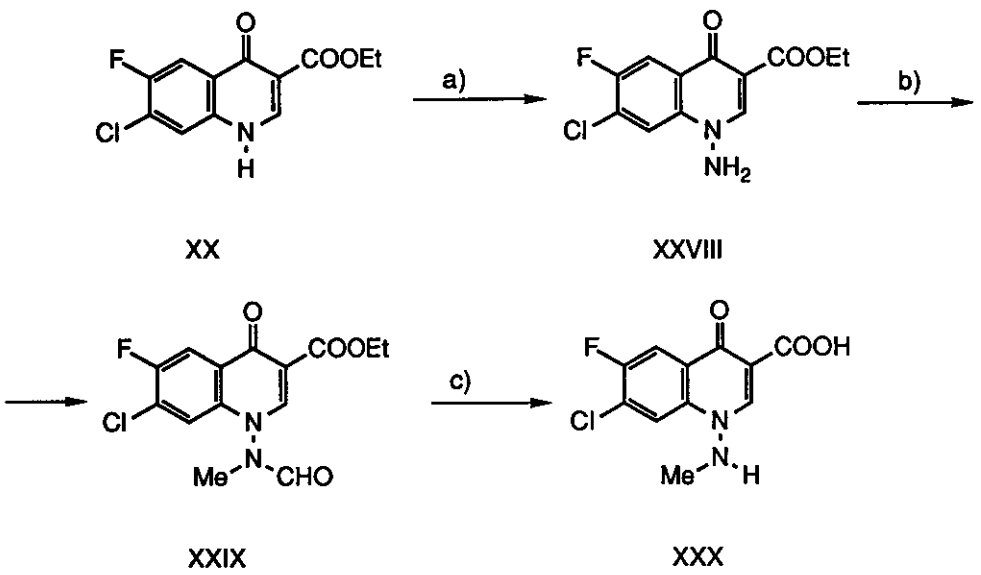
Figure 9



a) Et_3N or Py/Dioxane

Quinolones bearing an alkylamino group at the position 1 are exemplified by amifloxacin (See Figure 1). The original synthesis[31] was based on *N*-amination of XX which provided intermediate (XXVIII), which after *N*-alkylation and deformylation yielded the key intermediate (XXX) (Figure 10).

Figure 10

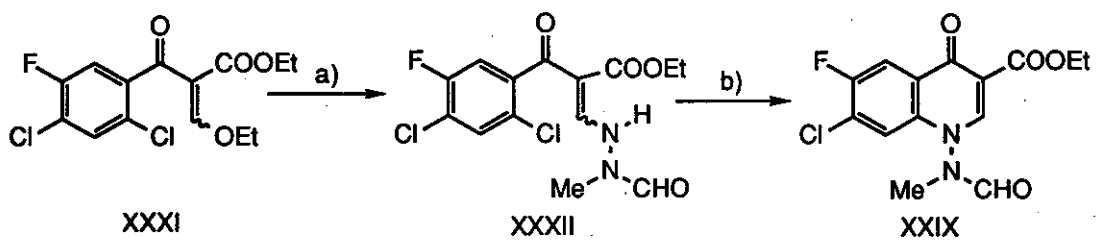


XX XXVIII XXIX XXX

a) O-(2,4-Dinitrophenyl)hydroxylamine/K_2CO_3/DMF; b) 1. MeCOOCHO, 2. MeI/K_2CO_3/DMF; c) 1. OH^-, 2. H^+

The intermediate (XXIX) can be easily prepared[32] from benzoylacrylate (XXXI) (Figure 11).

Figure 11

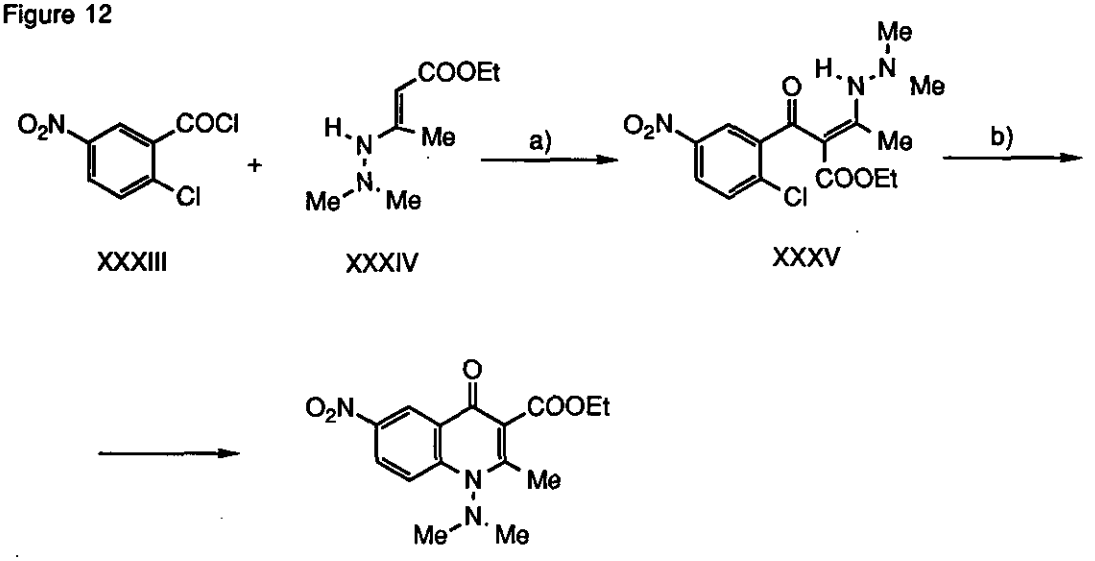


XXXI XXXII XXIX

a) *N*-Formyl-*N*-methylhydrazine; b) 1. NaH/DMF, 2. OH^-, 3. H^+

Compounds having *N,N*-dialkylamino group at the position 1 could also be prepared[33] from the corresponding 2-halobenzoyl chloride and *N,N*-dialkylhydrazino ester (XXXIV) (Figure 12).

Figure 12

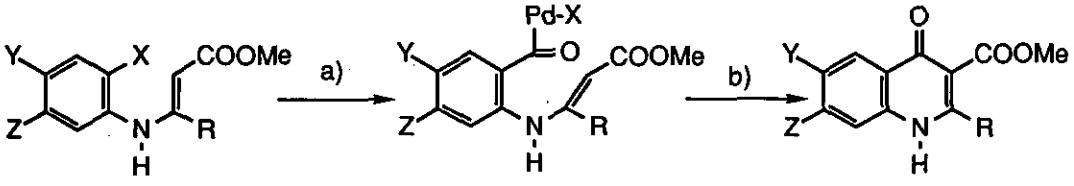


XXXIII XXXIV XXXV XXXVI

a) Et_3N; b) DBU

A new method, based on a catalytic carbonylation reaction, has been recently reported.[34-36] The method is especially suitable for the preparation of 2-substituted quinolones (Figure 13).

Figure 13



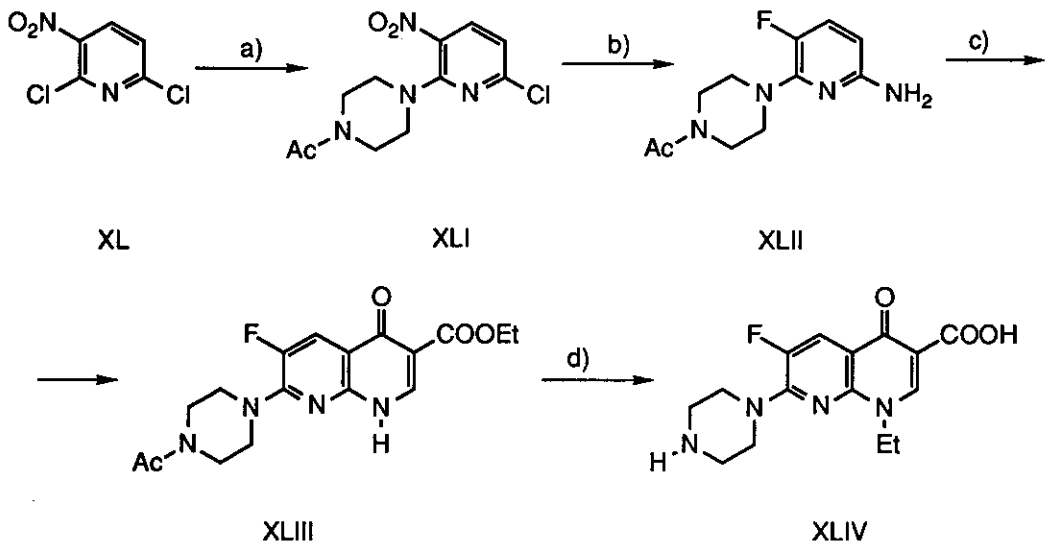
XXXVII XXXVIII XXXIX

a) CO, Pd(0); b)

2.2.2. 1,8-Naphthyridones

The most active antibacterial drugs of this type are represented by quinolone and 1,8-naphthyridone derivatives. Synthetic methods for the preparation of 1,8-naphthyridine derivatives are similar to those used for the synthesis of quinoline derivatives. The requisite cyclic amine can be introduced into the molecule in early steps of the synthesis due to the higher reactivity of the halogen atoms adjacent to the pyridine nitrogen. This strategy was used in the synthesis of enoxacin[37] (XLIV) (Figure 14) and proved to be useful also for the synthesis of other analogs.[37-40] Only in exceptional cases could the fluorine atom be introduced into the 1,8-naphthyridine moiety in acceptable yields via corresponding tetrafluoroborates[41] or hexafluorophosphates.[38]

Figure 14

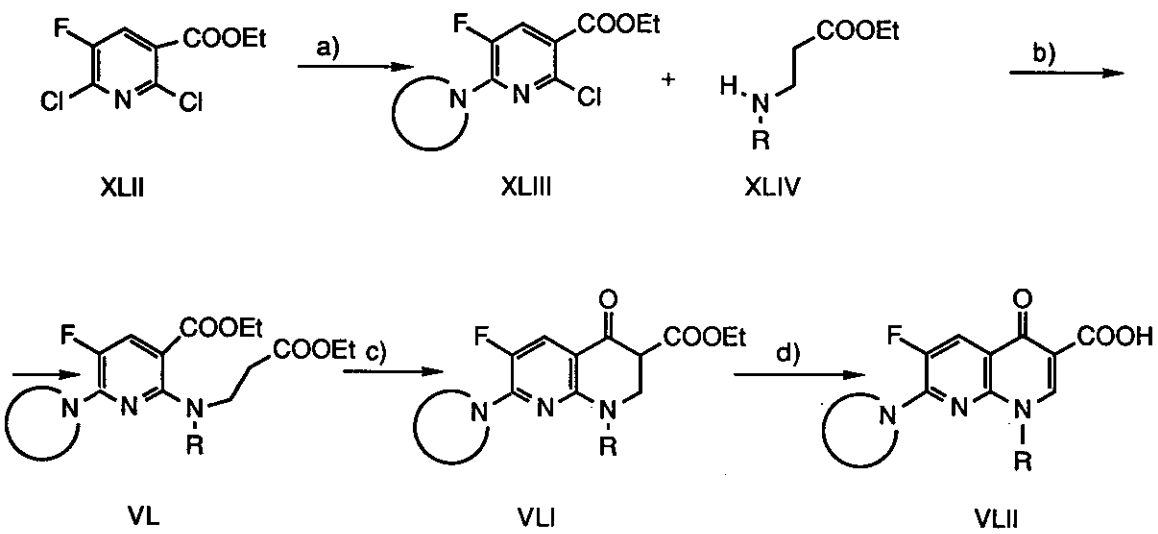


a) *N*-Acetylpiperazine; b) 1. NH_3/EtOH, 2. Ac_2O, 3. Zn/AcOH, 4. $NaNO_2$, 5. HBF_4, 6. Cyclohexane-reflux; c) 1. EMME, 2. 250°C; d) 1. EtI/K_2CO_3/DMF, 2. OH^-, 3. H^+

The higher reactivity of halogens at the positions 2 and 6 of the pyridine nucleus made possible the method depicted in the Figure 15, which is suitable also for the preparation of *N*-cyclopropyl derivatives.[42,43]

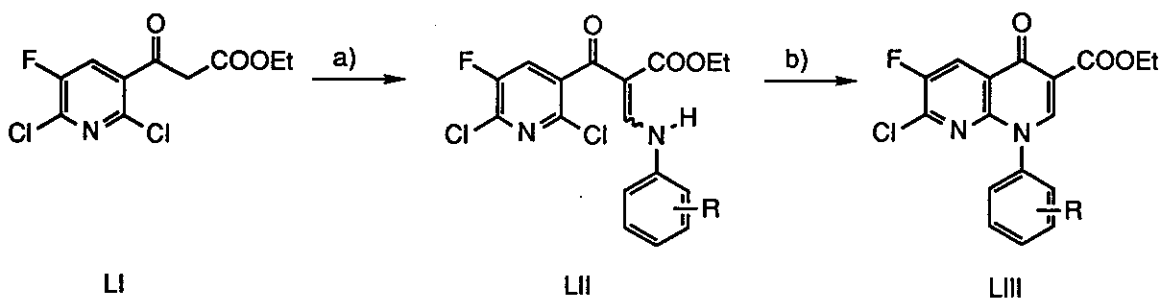
Similarly as for the quinoline derivatives, a method using aroylacetates (here 2,4-dichloro-5-fluoronicotinates) as starting compounds proved to be the most versatile and today is generally the method of choice,[29,44] especially for the synthesis of *N-tert*-alkyl and *N*-aryl-1,8-naphthyridones (Figure 16).

Figure 15



a) Cycl. amine; b) Na_2CO_3/DMF; c) NaH/Toluene; d) 1.Chloranil/Toluene, 2. H^+ or OH^-

Figure 16

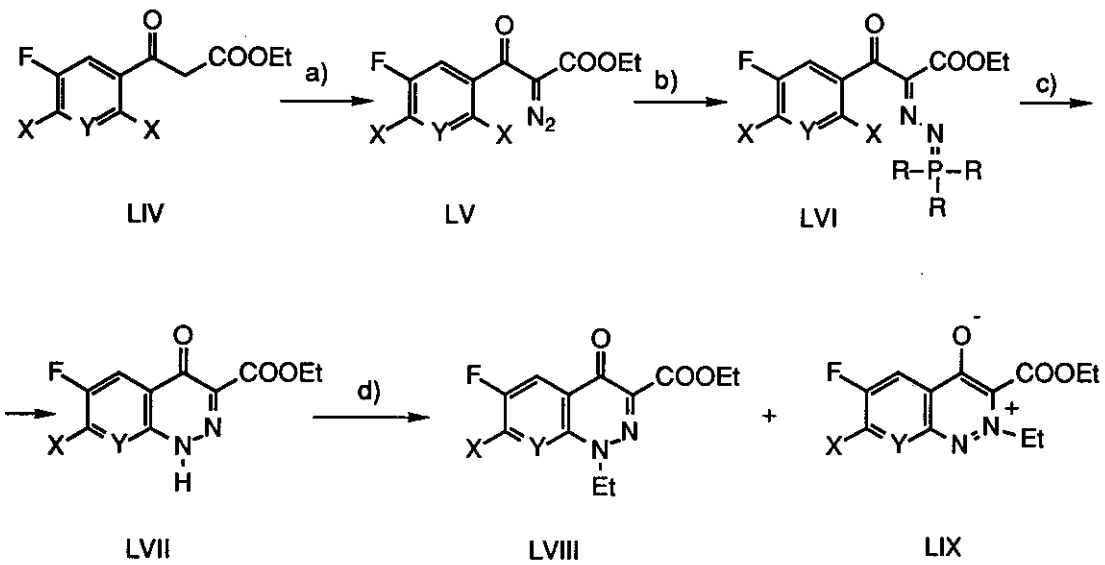


a) 1. $(EtO)_3CH/Ac_2O$, 2.Substituted Aniline; b) NaH/THF

2.2.3. Cinnolones

A new method for preparation of 1-alkylcinnolones, depicted in Figure 17, has been developed recently.[45,46] This method is based on the reaction of benzoylacetates (LIV) with tosyl azide which affords azo compounds (LV) which can be transformed into cinnolones (LVII). Subsequent alkylation of LVII provided a mixture of required *N*-1 alkyl derivatives (LVIII) and products of *N*-2 alkylation (LIX). Some 8-azaanalogs, i.e., pyrido[2,3-*c*]pyridazines, were also synthesized in this manner.[47-49]

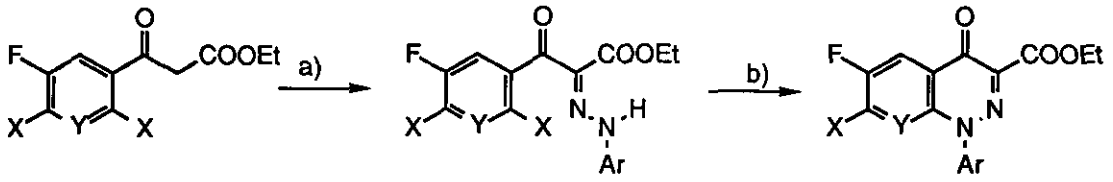
Figure 17



a) $TosN_3$; b) R_3P; c) Dioxane-reflux; d) EtI

A simpler method can be applied (See Figure 18) for the preparation of 1-arylcinnolones[50] or 1-arylpyrido[2,3-*c*]pyridazinones.[49] This method is based on the cyclization of compounds (LXI), which are easily prepared from corresponding benzoylacetates (Y = CH) or nicotinoylacetates (Y = N) of a general formula (LX) and an appropriate diazonium salt.

Figure 18



LX LXI LXII

X = F, Cl; Y = CH, N

a) $ArN_2^+Cl^-$; b) K_2CO_3/DMF/18-Crown-6

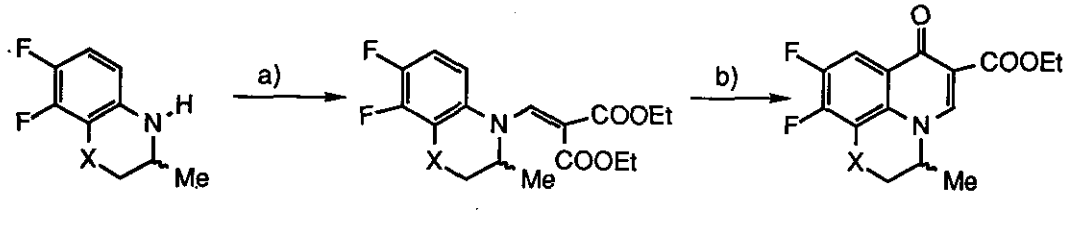
2.3. Compounds having annelated additional rings

The following part is divided according to the positions of the quinoline skeleton to which an additional ring is condensed.

2.3.1. N-1,C-8 Tricyclic derivatives

This structural feature is typical for several perspective compounds under development as well as for flumequine and ofloxacin (See Figure 1), which are in clinical use. The classical approach utilizes precursors which already contain the additional ring.

Figure 19



LXIII LXIV LXV

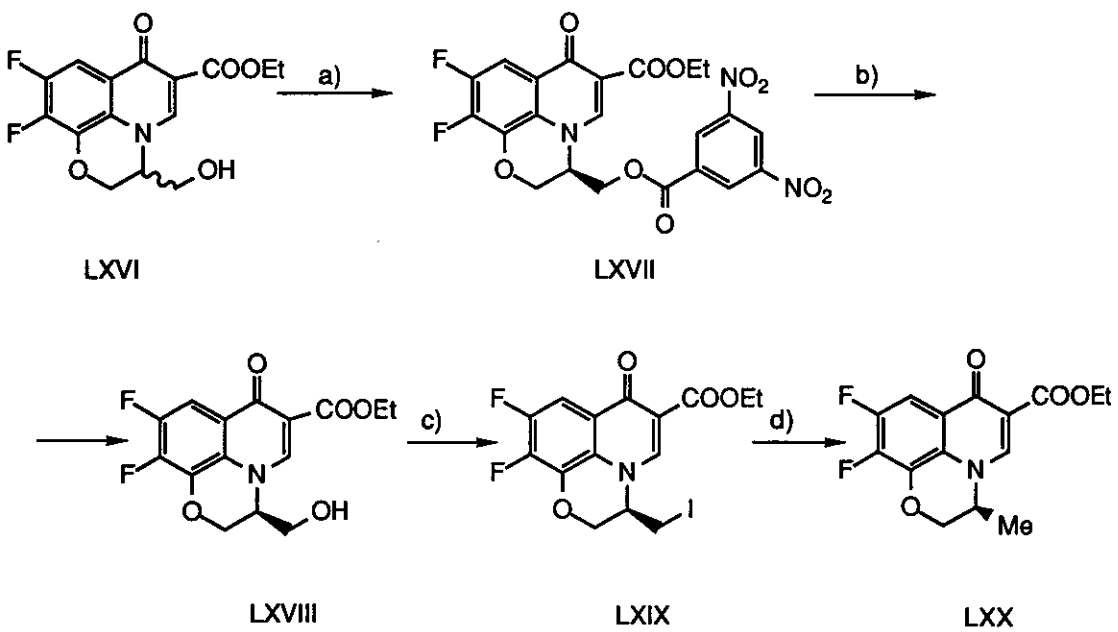
X = CH_2, O, S, bond

a) EMME; b) PPA or PPE

These precursors, when treated with EMME and then cyclized, provide the required tricycle. This approach was used in original synthesis of ofloxacin[51] (Figure 19, X = O) or flumequine and its analogs.[1,52-54]

Because S-isomers were found substantially more active than R-isomers, attempts to develop new methods useful for their production have been made. The first methods were based on resolution of suitable racemic precursors, as depicted in Figure 20. The S-isomer was then converted to the methyl derivative (LXX).[55,56]

Figure 20

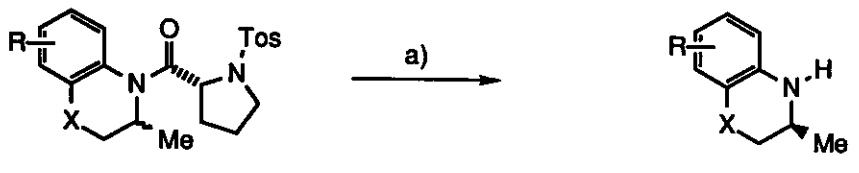


LXVI LXVII LXVIII LXIX LXX

a) 1. 2,4-Dinitrobenzoyl chloride, 2. Hplc resolution on a chiral support; b) $NaHCO_3$;
c) $Ph_3MeP^+I^-$/DMF; d) Bu_4SnH/EtOH

The method presented in Figure 19, using optically pure S-isomers of LXIII could also be used. The S-isomers can be prepared either by a chromatographic separation of isomers of LXXI[57-59] (Figure 21), or by an asymmetric reduction of the corresponding enamines,[60] e.g., LXXIII (Figure 22).

Figure 21

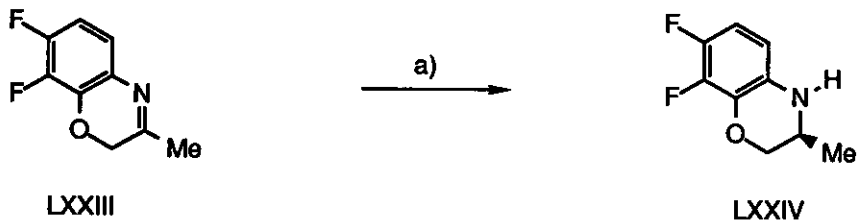


LXXI LXXII

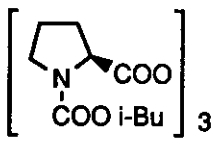
X = O, CH_2, bond

a) 1. Chromatography, 2. NaOEt

Figure 22

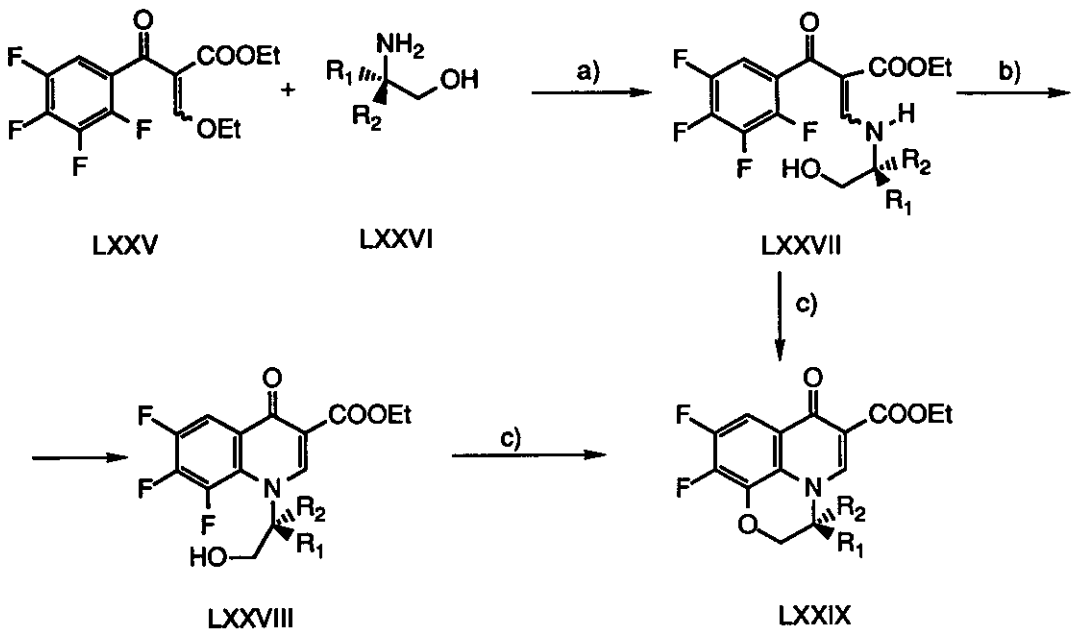


LXXIII LXXIV

a) NaBH 

A more useful procedure was arrived upon by several groups in quick succession. This method is based on the reaction of tetrafluorobenzoylacetate (LXXV) with the appropriate amino alcohol enantiomer (LXXVI) and subsequent cyclization[31,61-63] (Fig. 23). Depending on the method of cyclization, intermediate (LXXVIII) can be isolated or alternatively compound (LXXIX) can be directly produced.

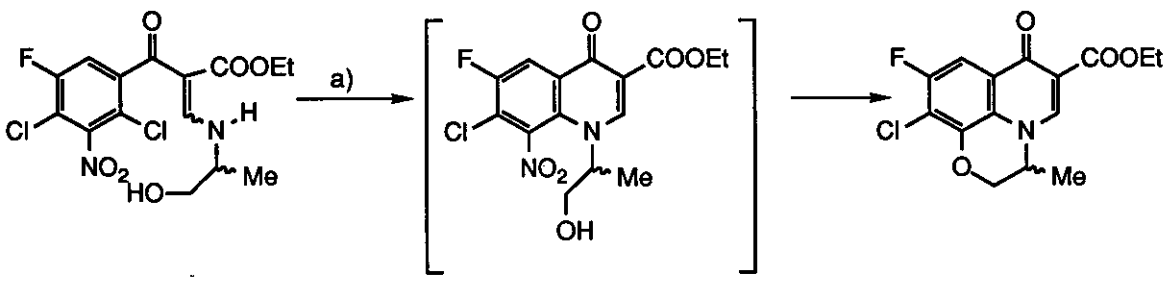
Figure 23



a) 20°C/EtOH; b) t-BuOK/THF or NaH/Dioxane; c) KF/DMF or Bu_4NF/THF

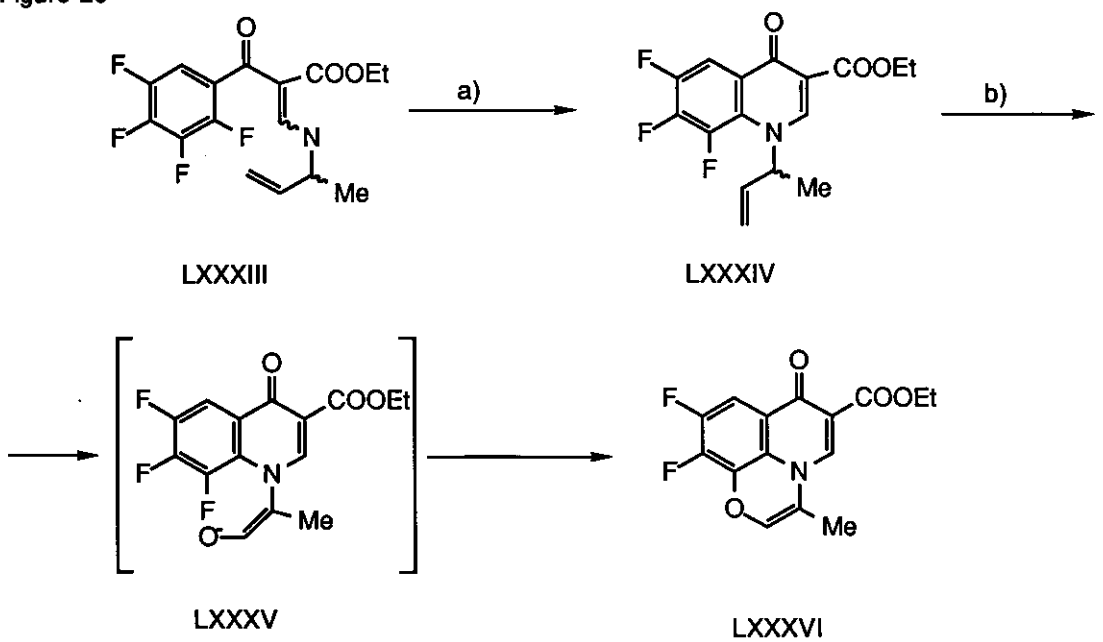
Similar denitrocyclization of LXXX was achieved under very mild conditions but compound (LXXXI), which was supposed as an useful intermediate for a new ofloxacin synthesis, could not be isolated.[64]

Figure 24



a) $NaHCO_3$/DMF or KF/DMF

Figure 25

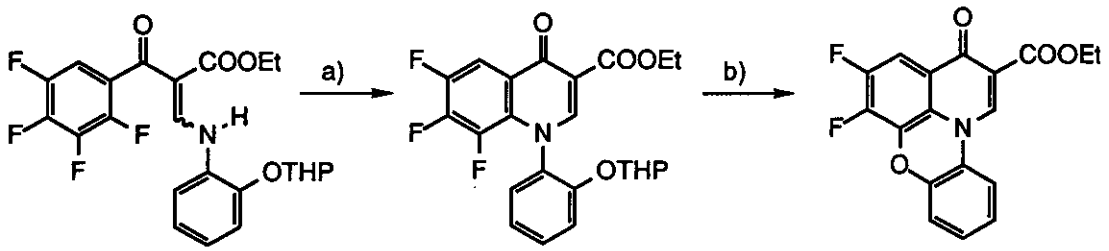


a) NaH/DMF; b) 1. O_3, 2. Me_2S, 3. NaH

2,3-Dehydro analog (LXXXVI) was prepared similarly[65] from enolate (LXXXV) which was generated in situ (Figure 25). A multistep synthesis of compound (LXXXVI) and its thia analog has been recently reported.[66]

Analogous tetracyclic pyrido[3,2,1-*kl*]phenoxazines were prepared using similar methodology[67] (Figure 26).

Figure 26

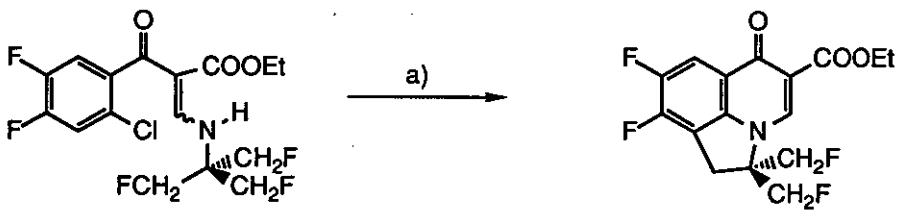


LXXXVII LXXXVIII LXXXIX

a) NaH/DMF; b) 1. H^+, 2. NaH/THF

An unusual intramolecular C-alkylation surprisingly led to XCI[68] (Figure 27).

Figure 27

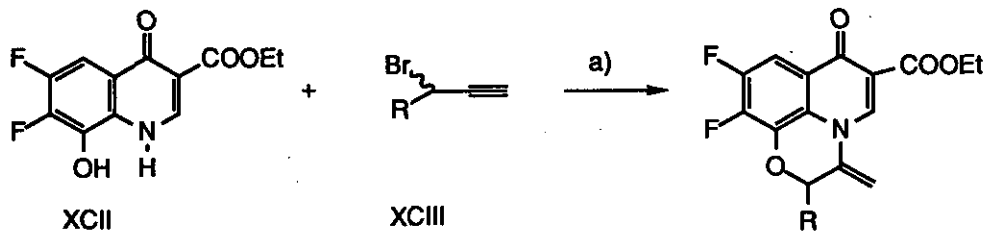


XC XCI

a) K_2CO_3/DMF-reflux

8-Hydroxy derivative (XCII) proved to be a useful intermediate to access this type of tricycles. The compound reacted with propargylic halogenides (XCIII) to afford 3-methylene derivatives (XCIV)[64,69] (Figure 28). This compound (R = H) was hydrogenated to ofloxacin intermediate (LXV) (X = O), and may also be exploited for an enantioselective reduction leading to LXX. A different synthesis of XCIV (R = H) starting from LXXV via corresponding 6,7,8-trifluoro-*N*-(3-oxethanyl)quinolone has been reported recently.[70]

Figure 28

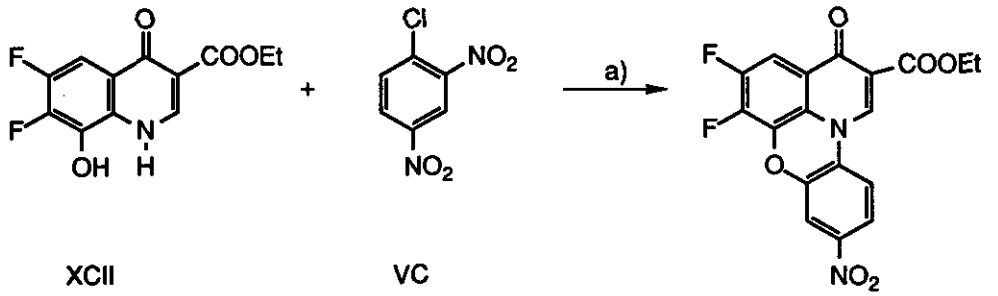


XCII XCIII XCIV

a) K_2CO_3/DMF

Compound (XCII) under very mild conditions also undergoes a Turpin-like reaction (Figure 29) yielding pyrido[3,2,1-*kl*]phenoxazine analogs.[71]

Figure 29

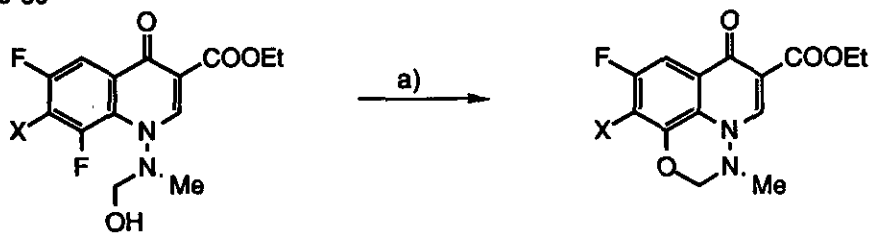


XCII VC VCI

a) 1. $NaHCO_3$/DMF, 2. OH^-, 3. H^+

C-8 Fluorine leaving group has been utilized[72] for the synthesis of VCIII from intermediates (VCII) (Figure 30), which could be prepared either by an amination route[73] (Fig. 10) or using methodology described earlier and depicted in Figure 11 (Ref. 74).

Figure 30



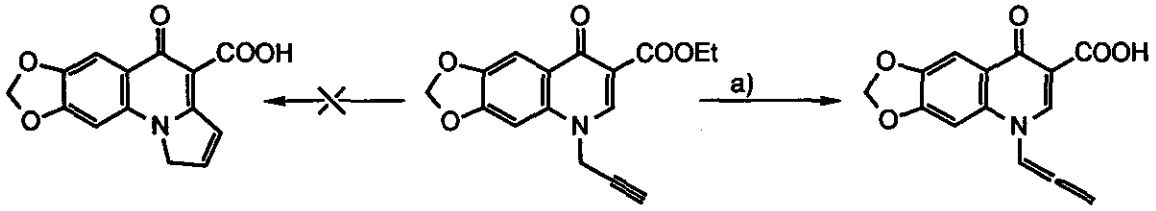
VCII VCIII

a) Bu_4NF/THF

2.3.2. N-1,C-2 Tricyclic derivatives

N-1,C-2 Cyclization of IC to C under alkaline conditions was reported.[75] The reaction has been revised recently[76,77] and the product of this reaction was disclosed as a relatively stable *N-allenylquinolone* CI (Figure 31).

Figure 31

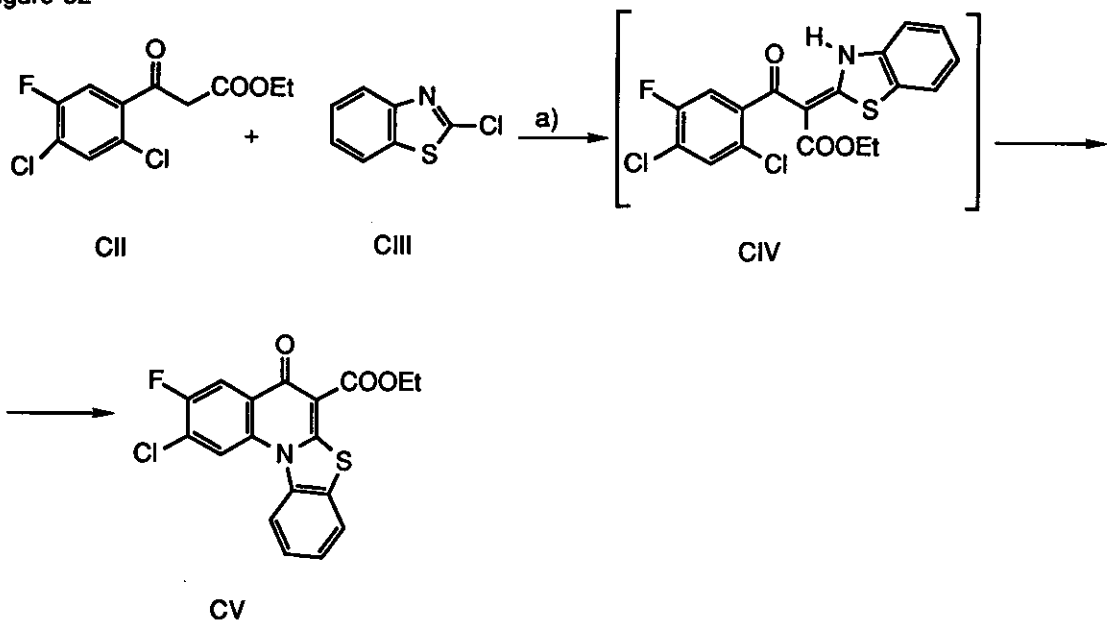


C IC CI

a) 1. OH^-, 2. H^+

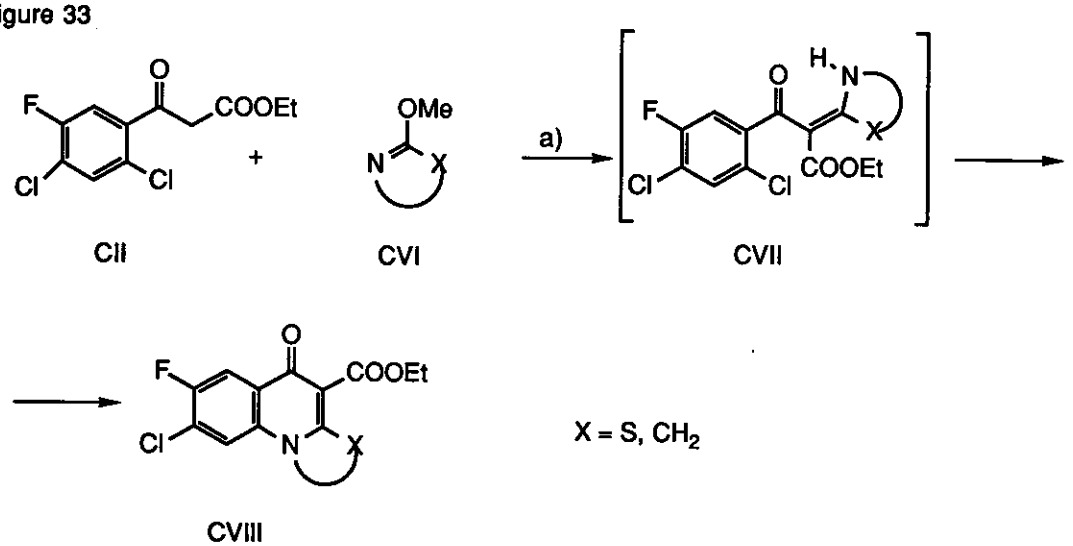
Recently several groups have developed methods providing this class of tricyclic compounds starting from benzoylacetate (CII), which upon a treatment with 2-chlorobenzothiazole (CIII),[78] or with iminoethers (CVI),[79,80] provides suitable precursors (CIV) and (CVII), respectively (Figures 32, 33).

Figure 32



a) NaH/Diglyme

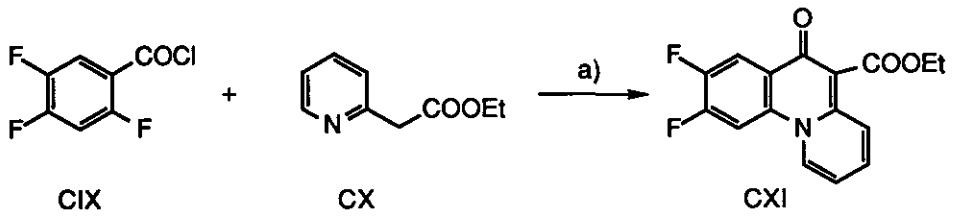
Figure 33



a) NaH/THF

Similar unsaturated derivative (CXI) was obtained by a direct reaction[81] of 2,4,5-trifluorobenzoyl chloride (CIX) with 2-pyridylacetate (CX) (Figure 34).

Figure 34

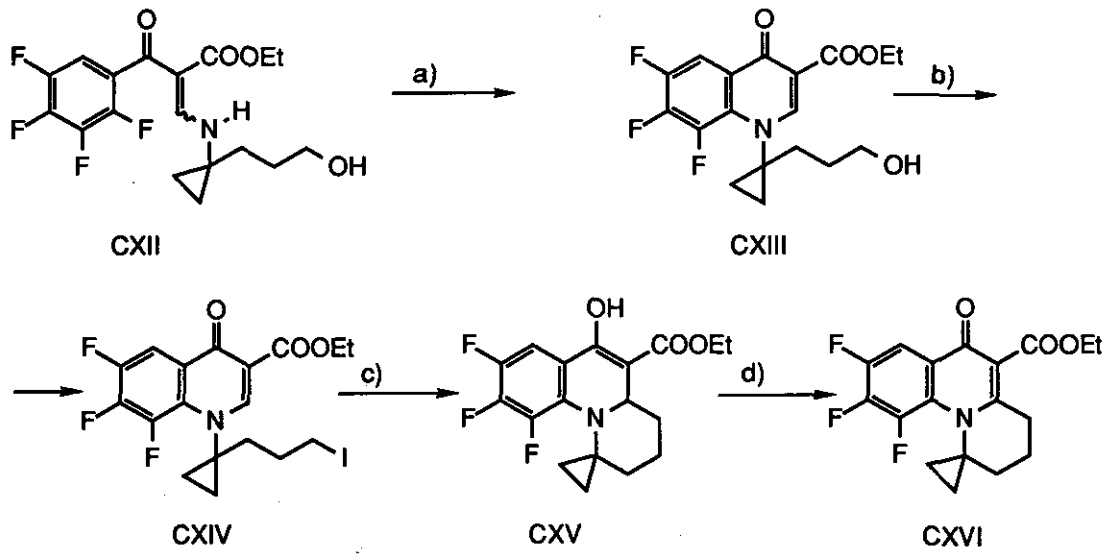


CIX CX CXI

a) $LiN(TMS)_2$/THF/-5°C

A different strategy[82] (Figure 35), based on a reaction of Grignard reagent formed from iodo derivative (CXIV), was used for the synthesis of spirocyclic quinolone (CXVI).

Figure 35



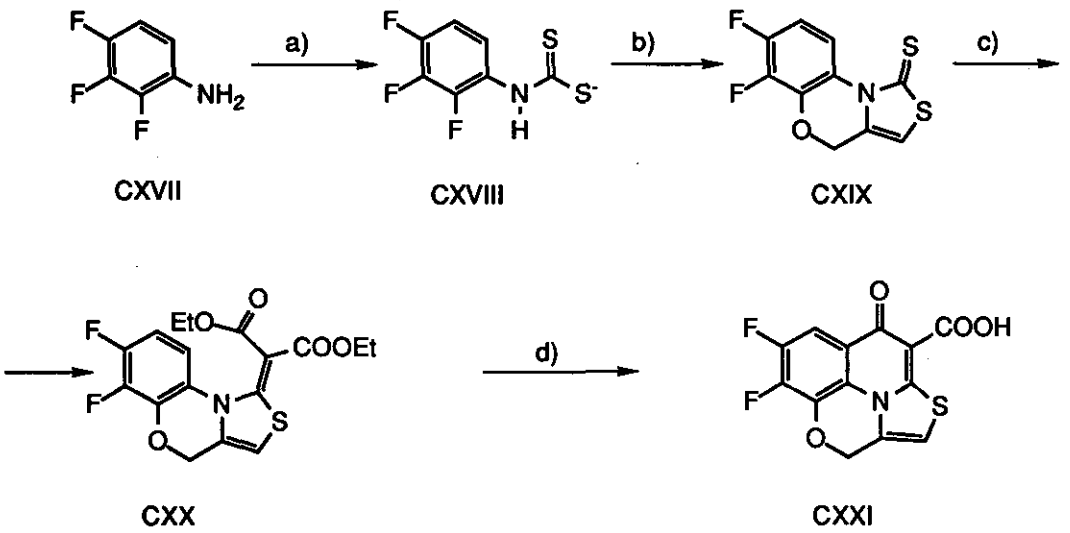
CXII CXIII CXIV CXV CXVI

a) t-BuOK; b) 1. MsCl/Et_3N/THF, 2. NaH/Acetone; c) Mg/CuI/THF; d) 1. NaH/THF, 2. PhSeCl, 3. H_2O_2

2.3.3. N-1,C-8,C-2 Tetracyclic derivatives

Compounds of this type, as reported by Kanebo chemists, are considered to be very promising antibacterial agents. Their synthesis starts from trifluoroaniline (CXVII), which provides the required moiety (CXXI) by a reaction sequence,[83] depicted in Figure 36.

Figure 36

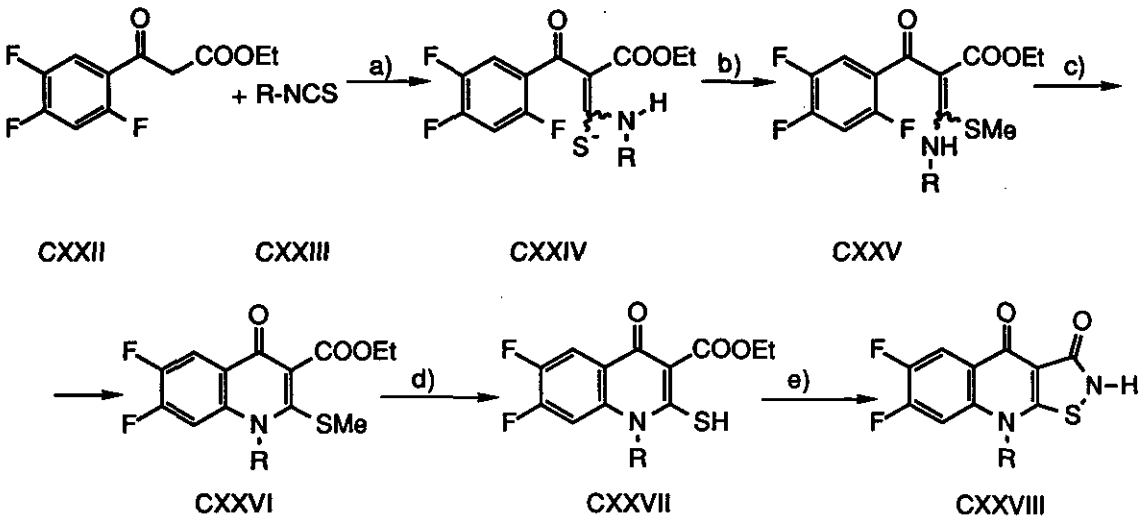


a) CS_2/Et_3N, b) $ClCH_2COCH_2OAc$; c) 1. MeI/DMF, 2. DEM/K_2CO_3; d) PPA/H_2SO_4

2.3.4. C-2,C-3 Tricyclic derivatives

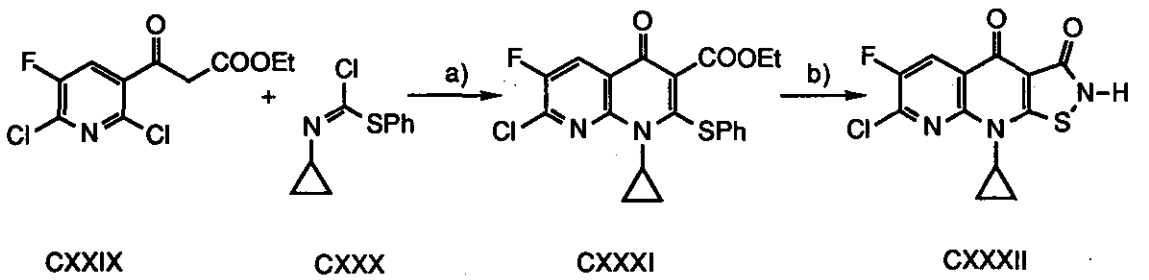
The presence of a carboxylic group at the position 3 was considered essential for antibacterial activity. However, recently Abbott chemists have reported a new group of highly active compounds having a C-2,C-3 isothiazolone ring instead.[84,85] The synthesis of these compounds is depicted in Figure 37. The key step is the synthesis of 2-mercapto-4-quinolone-3-carboxylate (CXXVII), which after *S*-amination spontaneously cyclizes to the required skeleton. Aza analogs (CXXXII) were prepared by an analogous route[86] (Figure 38).

Figure 37



a) NaH/DMF; b) MeI; c) NaH/THF; d) 1. MCPBA, 2. NaSH; e) HOSA/$NaHCO_3$

Figure 38



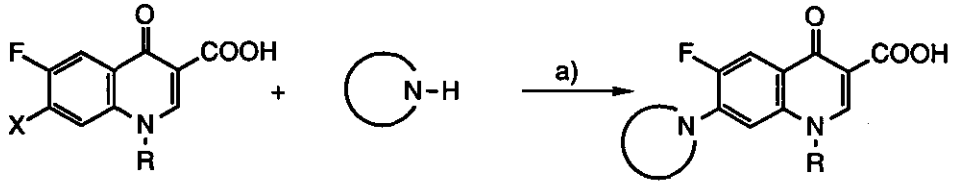
a) NaH/DMF; b) 1. MCPBA, 2. NaSH, 3. HOSA/$NaHCO_3$

3. Introduction of basic substituents into the molecules

The presence of a suitable cyclic amine substituent at the position 7 is essential for potent and broad spectrum of activity of these compounds.[2-6] Though some methods starting from precursors already containing the amino groups have been published,

these amino groups are usually introduced after the basic skeleton is constructed. The introduction is realized by a nucleophilic displacement reaction of suitable 7-chloro[15] or 7-fluoro[87-89] derivatives of quinolonecarboxylic acids with the corresponding amine (CXXXIV) in excess of the used amine or in the presence of a base (Figure 39). Nucleophilic displacement of a fluorine atom at the position 6 is negligible under conditions generally used.

Figure 39



CXXXIII CXXXIV CXXXV

R = alkyl, cycloalkyl, aryl

a) DMF, DMSO, Py or Toluene

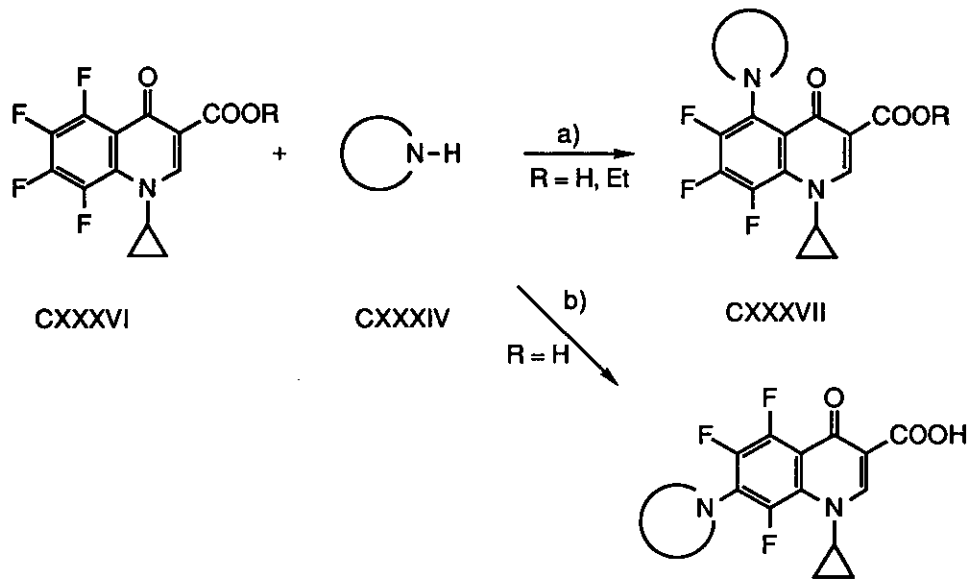
In the case of more reactive 7-fluoroquinoline derivatives or 7-chloronaphthyridines, more mild reaction conditions can be used and therefore more soluble esters are usually used without side reactions (amide formation).[85-87] A similar situation exists with 7-chloro-8-nitro esters, where the C-7 chlorine atom is activated by the presence of the nitro group.[94] Due to the higher reactivity of the C-7 substituent of 1,8-naphthyridine derivatives, sulfinyl or sulfonyl groups could be used as leaving groups in the displacements.[39,41,42,48] Substitution at the position 7 is strongly favored for 6,7-difluoro-,[95-97] 7,8-difluoro-,[95] and 6,7,8-trifluoroquinolonecarboxylic acids[96,97] and their esters.

In the case of 5,6,7,8-tetrafluoroquinolones (CXXXVI) suitable choice of conditions used determines the position where the displacement occurs[22,98,99] (Figure 40). Further treatment of compounds (CXXXVIII) with a nucleophile[22,99] causes additional substitution providing 5,7-disubstituted derivatives.

It should be noted that the position preferred for the nucleophilic displacement reactions in 6,8-difluoroderivatives depends on the character of the nucleophile. In general, substitution by amines[100,101] takes place at the position 6, while thiolate and alcoholate anions[101] attack the C-8 position. Similar situation was also reported[102-

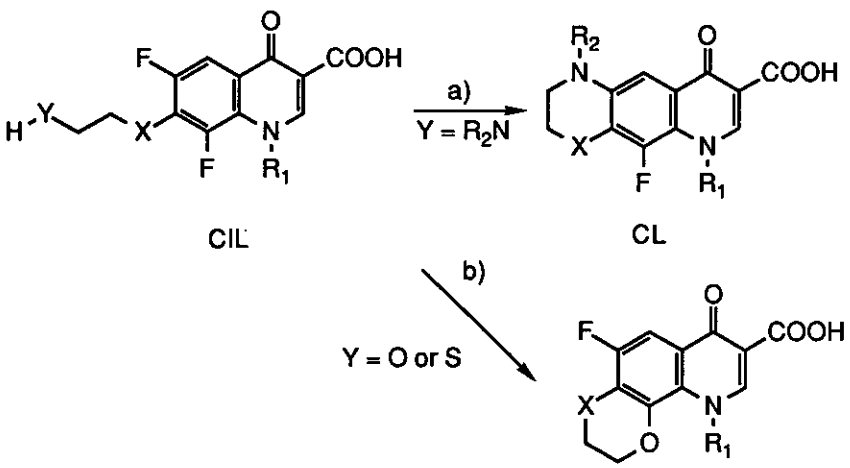
104 for intramolecular cyclization reaction of compounds (CIL) (Figure 41). The same type of selectivity was described[104] for compounds having a 2-aminomethyl-pyrrolidinyl group at the position 7.

Figure 40



a) Toluene; b) Ethanol

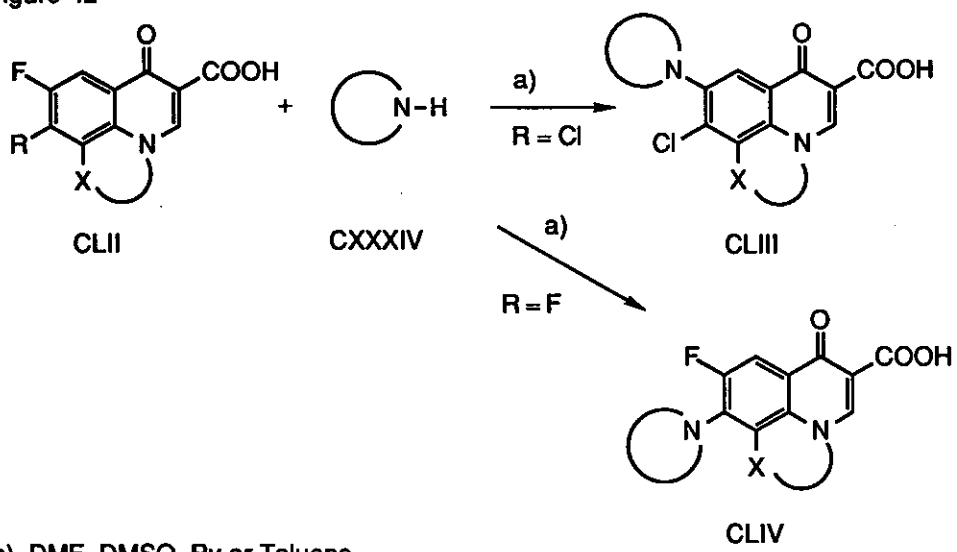
Figure 41



a) 70-150°C/DMF; b) NaH/DMF/70-150°C

Nucleophilic displacement reactions of quinolone analogs having an additional ring condensed have not been studied extensively. Nevertheless, from the data published it is evident, that additional rings in positions N-1,C-2 or C-2,C-3 do not change reactivity of halogen atoms on the benzene ring. A different situation exists with N-1,C-8 condensed compounds (CLII) having X = O or S where electronic influence of the additional ring can substantially change the reactivity. Fluoro derivatives are usually used since chloro derivatives under mild conditions do not react and under more drastic conditions substitution of the fluoro atom occurs[51,53,54,105] (Figure 42).

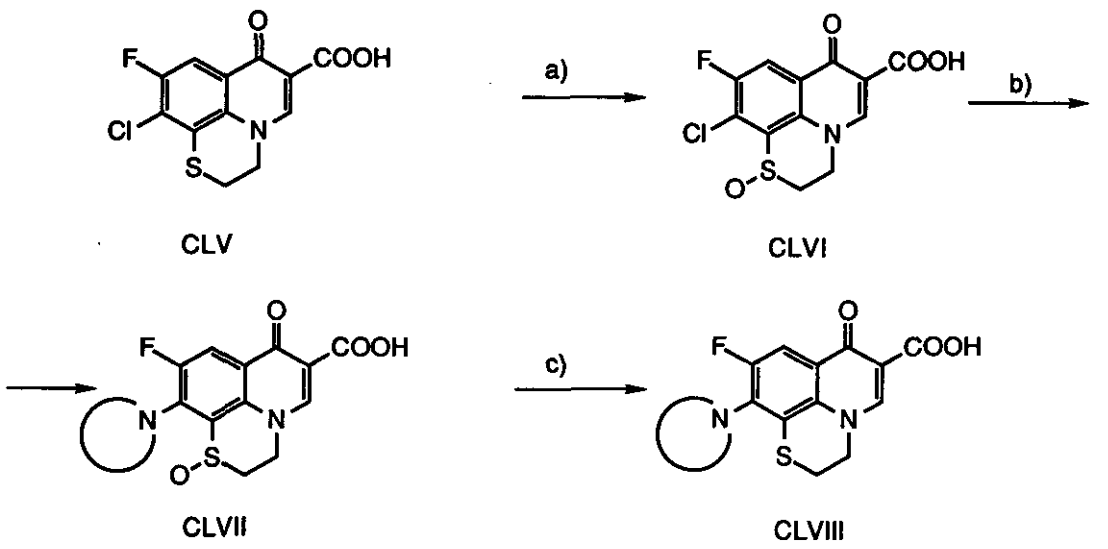
Figure 42



a) DMF, DMSO, Py or Toluene

It is of interest to note that for thia analogs (X = S) this tendency can be circumvented[105] via oxidation to the corresponding sulfoxide (CLVI) which provides compound (CLVIII) after reduction of the intermediate (CLVII) (Figure 43).

Figure 43



a) $Pb(OAc)_4$/AcOH; b) Cycl. amine/Toluene; c) PCl_3/DMF

4. Conclusions

Ten years after the serendipitous discovery of the first antibacterial quinolone, Albrecht published a comprihensive review[1] containing both synthetic and pharmacological aspects of quinolones based upon existing knowledge at the time. However, today even a very extensive monography could not attain such a goal. Therefore in this current review, the authors have decided to choose the most frequent and useful methods, most of which have been proven in their own laboratories, which could be of interest to a wide readership of the Journal.

5. List of abbreviations[106]

Ac = acyl; Ar = aryl; Bu = butyl; *i*-Bu = isobutyl; *t*-Bu = tertbutyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEM = diethyl malonate; diglyme = diethylene glycol dimethylether; DMF = *N*,*N*-dimethylformamide; DMF-DMA = DMF dimethyl acetal; EMME = diethyl ethoxymethylene

malonate; HOSA = hydroxylamine-*O*-sulfonic acid; MCPBA = 3-chloroperbenzoic acid; Me = methyl; Ms = mesyl; Ph = phenyl; PPA = polyphosphoric acid; PPE = ethyl polyphosphate; *c*-Pr = cyclopropyl; PTSA = 4-toluenesulfonic acid; Py = pyridine; R = alkyl; THF = tetrahydrofuran; THP = tetrahydropyranyl; TMS = trimethylsilyl; Tos = tosyl.

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