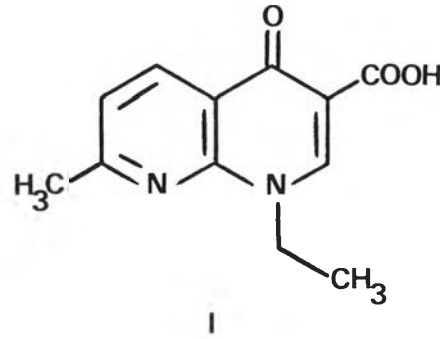
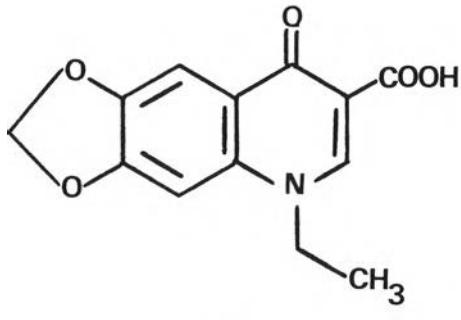
CHAPTER I

INTRODUCTION

Nalidixic acid (1-ethyl-1,4-dihydro-7-methyl--4-oxo-1,8-naphthyridine-3-carboxylic acid, I) was first synthesized by Lesher et al. (1962). It was found to be highly effective antibacterial agents both *in vitro* and *in vivo* and was introduced into clinical use in 1964. It has been widely used for the oral treatment of urinary tract infections and associated with the often rapid emergence of resistance. At the time of its introduction, nalidixic acid was a completely new structural type of chemotherapeutic agents. Since then, a number of other chemically related drugs have been synthesized. These included oxolinic acid (II), cinoxacin (III), pipemidic acid (IV), flumequine (V), tioxic acid (VI) and miloxacin (VII). These were either napthyridine-carboxylic acid or quinoline carboxylic acid derivatives along with nalidixic acid, were collectively known as quinolones.



I



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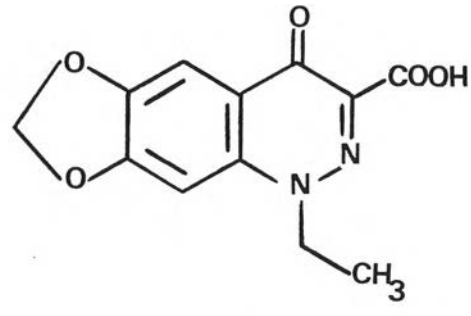

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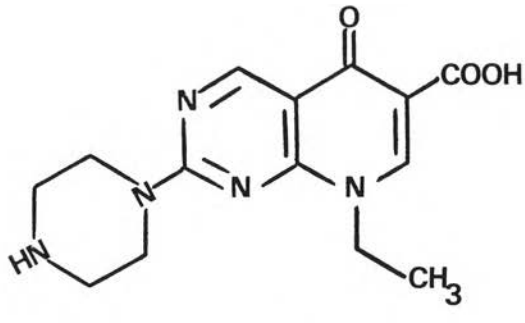

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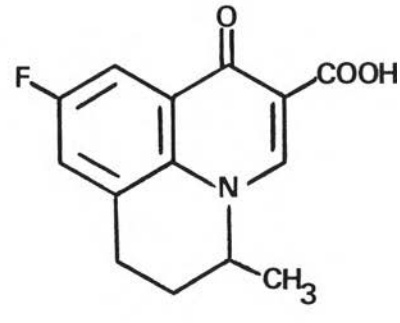

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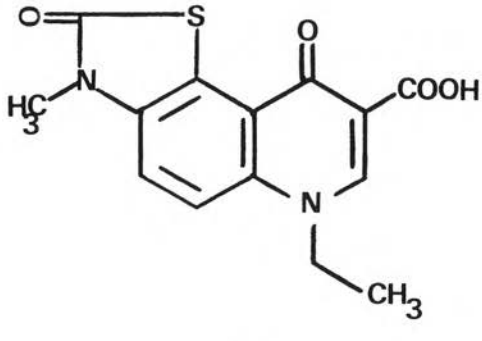

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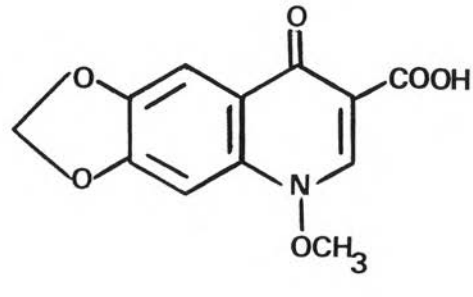
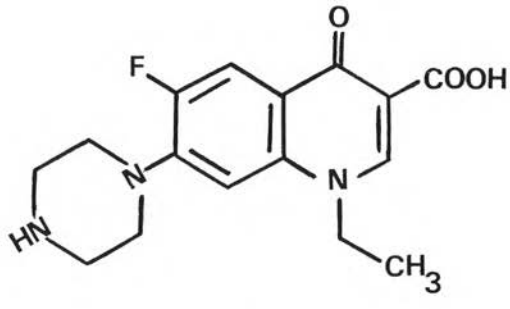


VII

Since 1980, a numerous of new quinolones have been synthesized. For example, norfloxacin (VIII), ciprofloxacin (IX), ofloxacin (X), enoxacin (XI), pefloxacin (XII), amifloxacin (XIII), etc.



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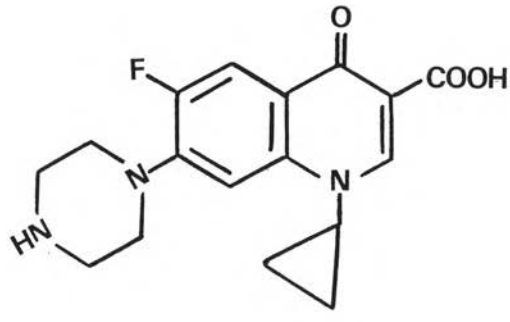

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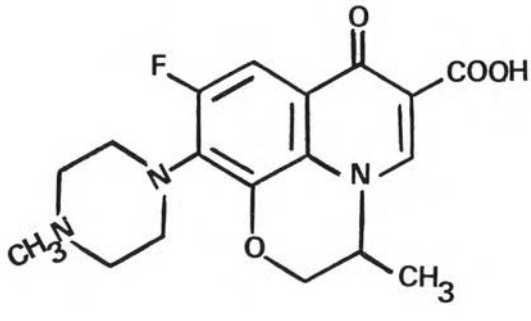
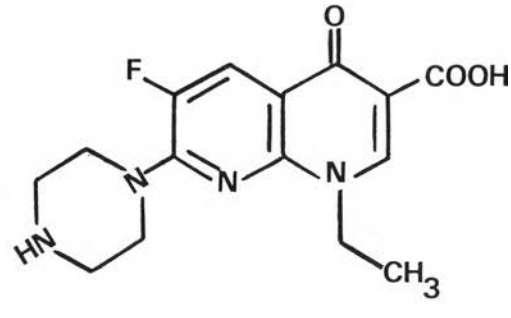


X



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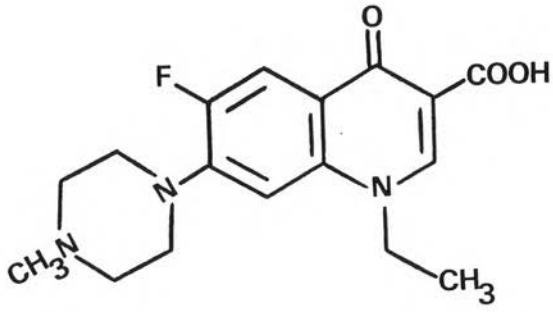
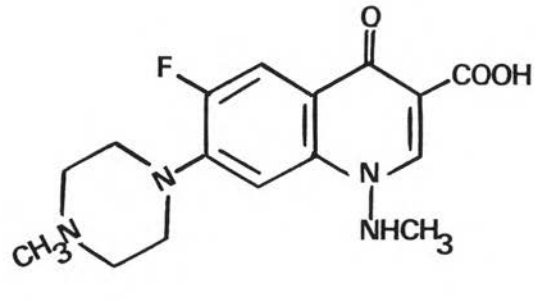


XII

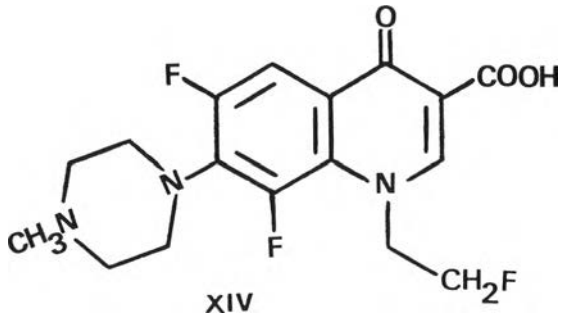


XIII

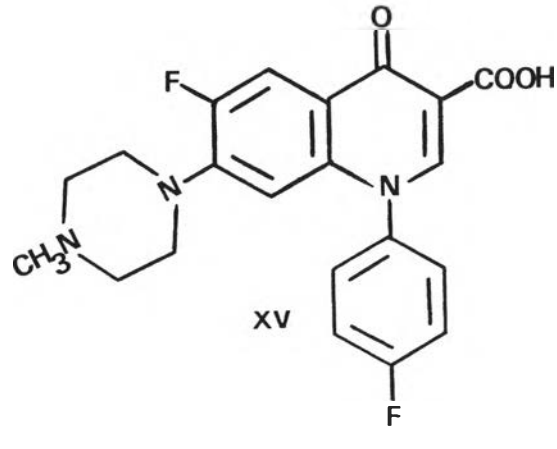
The major advance in antimicrobial chemotherapy of the quinolones is the DNA gyrase enzyme inhibition for the supercoiling activity, thus exerting another action on DNA and RNA synthesis, resulting in a biphasic response and killing ceptible organisms (Crumplin and Smith, 1976; Shen and Pernet, 1985). Quinolones are highly active against most gram-negative pathogens including the *Enterobacteriaceae* and *Pseudomonas aeruginosa.* They are generally less active against gram-positive bacteria (King and Phillips, 1986). Resistance has occurred and is proving a problem against *P. aeruginosa*, but as yet no plasmid-mediated resistance developed. Cross-resistance occurred among the quinolones but only rarely with other antibacterial drugs (Wolfson and Hooper, 1985). The quinolones have an excellent safety record. Thus, the quinolones are an attractive option in the research.

The quinolone structure-activity relationship is mainly focused on C-6, C-7 and N-1 substituents. These positional modification of the parent structure showed that higher potency as well as broader bacterial spectrum occurred with a fluorine at C-6. These compounds were called fluoroquinolones and the concomitant presence of an

heterocyclic base of optimal size, preferentially a piperazine or a pyrrolidine moiety at C-7. Nevertheless, recent reports showed that heterocyclic nitrogen by sp^2 carbon; these derivatives showed equal or greater antimicrobial activity than their nitrogen-bonded counterparts (enoxacin) (Lecher, 1989; Himmler et al., 1989). In general, optimum activity requires a substituent at the N-1 position such as ethyl or its bioisosteres; such as fluoroethyl (fleroxacin, XIV) methylamino (amifloxacin), and methoxy (miloxacin) (Agui et al., 1977) but today the cyclopropyl group is recognized as one of the most effective substituents (ciprofloxacin) (Domagala, Heifetz et al., 1988) even if other potent quinolones have a tert- butyl or a fluoro phenyl group such as difloxacin (XV) (Fernandes, Swanson et al., 1986), temafloxacin (XVI) (Fernandes, Shipkowitz et al., 1988), tosufloxacin (XVII) (Hardy et al., 1987).



XIV



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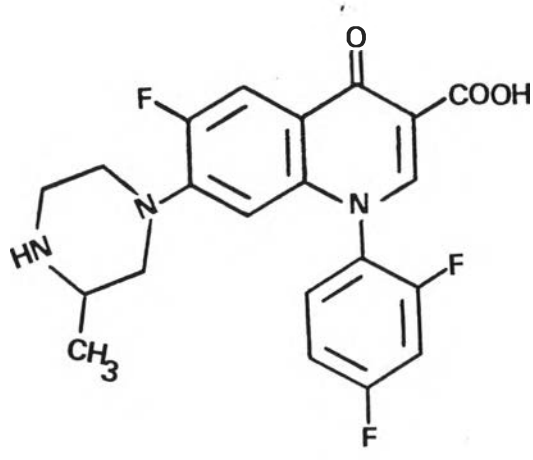
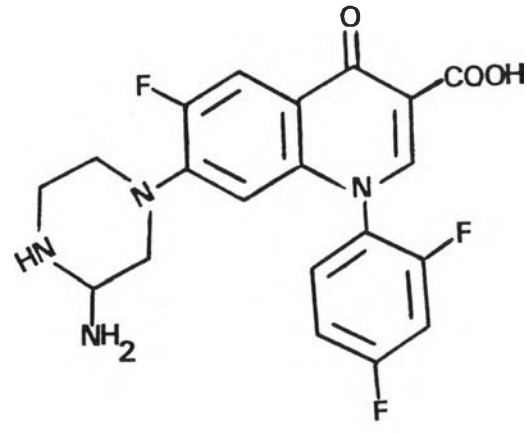
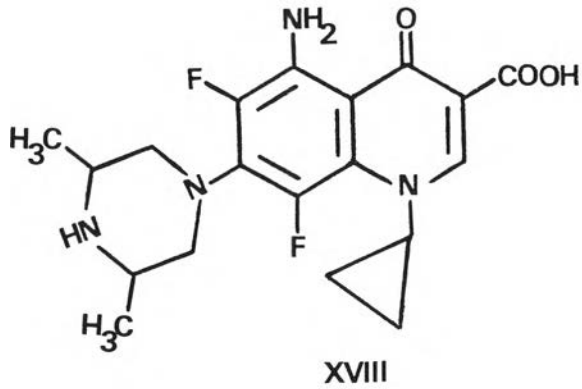


XVI

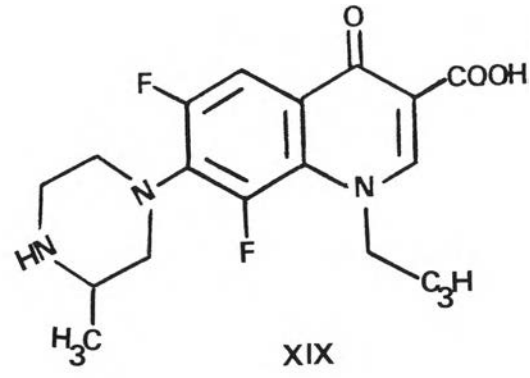


XVII

Although the substitution at C-5 are generally considered unfruitful. The 5-amino derivative, such as sparfloxacin (XVIII) (Miyamoto et al., 1990) recently resulted in significantly more potent products than their no amino analogues. Substitution at C-8 with halogen, fluorine being better provided potent quinolones; lomefloxacin (XIX), PD 117558 (XX), PD 127391 (XXI) (Wise, Ashby, and Andrews, 1988). Annelation of a third ring between the N-1 and C-8 position gave equally potent tricyclic compounds; ofloxacin (Hayakawa, Hiramitzu, and Tanaka, 1984; Schuppan et al., 1985), rufloxacin (XXII) (Cecchet et al., 1987), OPC-7241 (XXIII) (Ishikawa et al., 1989).



XVIII



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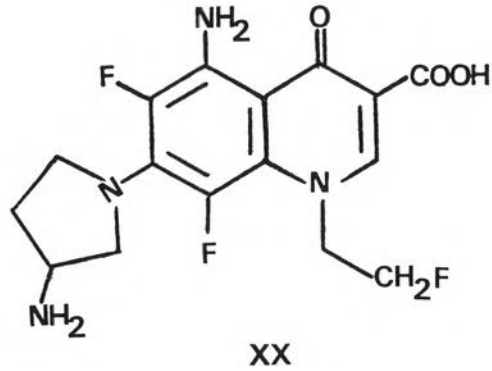
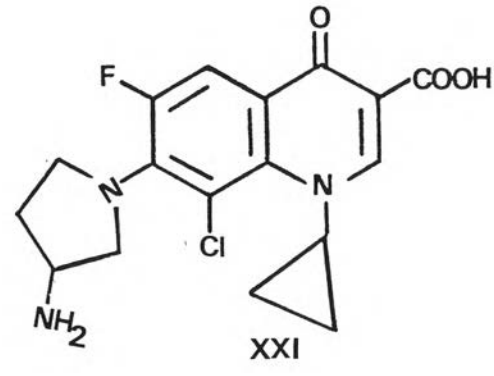
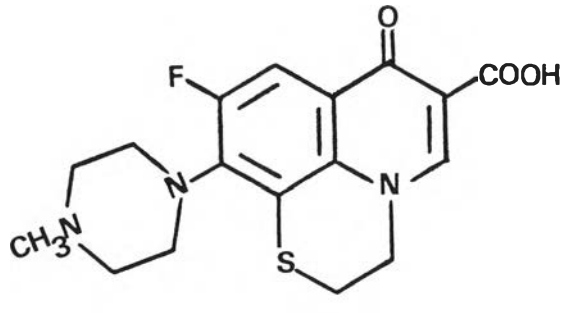


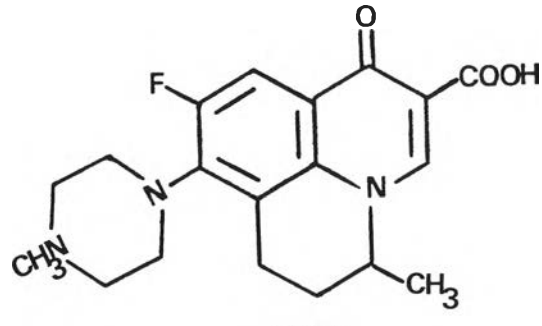
XX



XXI



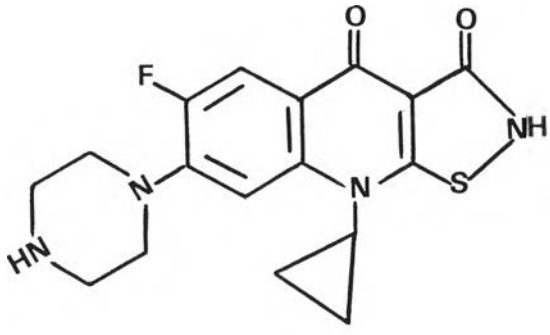
XXII



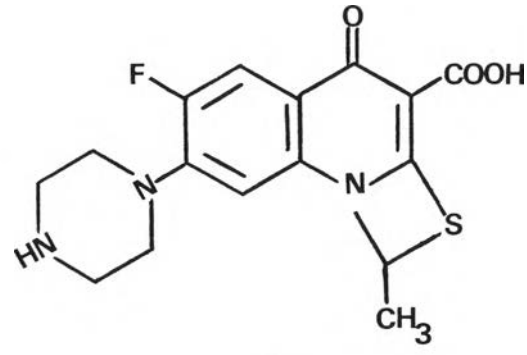
XXIII

The alterations of the 1,4-dihydro-4-oxo-pyridine-3-carboxylic acid moiety, a fundamental structure in antibacterial activity such as 4-keto and 3-carboxylic acid group are generally considered necessary for the binding of quinolone to DNA gyrase. The carbonyl

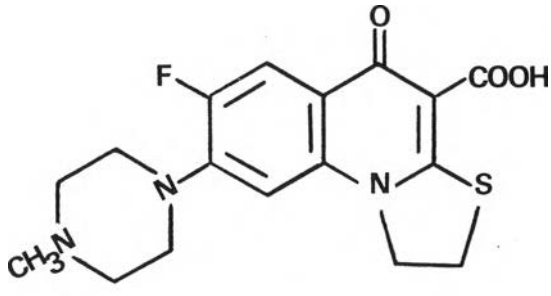
replacement by methylsulfinyl and methylsulfonyl groups, sulfonic acid (Kim and Luh, 1988), phosphonic acid (Yamagisawa, Nakao, and Ando, 1973) and formyl (Kondo et al., 1988) and tetrazolyl groups (Gilis, Haemers, and Bellaert, 1980) always led to inactive products. In contrast the modification of carboxylic acid moiety by a thiohydroxamic acid chain to form an isothiazole ring at C-2 and C-3 furnished a series of extremely potent antibacterials such as A-62824 (XXIV) (Fernandes, Claiborne et al., 1988). Modification at C-2 were generally considered as unfavourable, however this is not the case for cinoxacin (III). Moreover, thio-substituted derivatives between N-1 and C-2, recently developed, were reported to be extremely active *in vitro*; NAD-3942 (XXV) (Kise et al., 1986) thiazoline [3,2-a] quinoline (XXVI) (Matsumura et al., 1983) and benzothiazolo [3,2-a] quinoline derivative (XXVII) (Fernandes and Pernet, 1986). The other substantial modifications, such as nitrogen replacement at the 1-position by carbon always gave inactive (Hogberg et al., 1984).



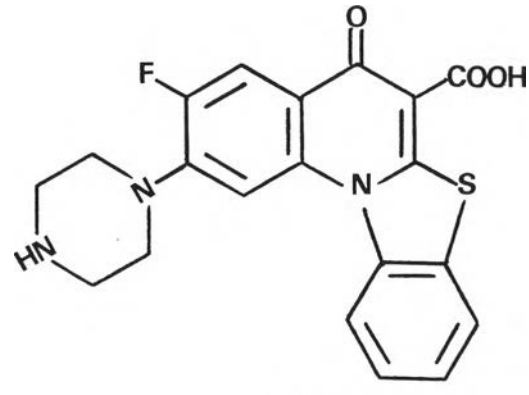
XXIV



XXV



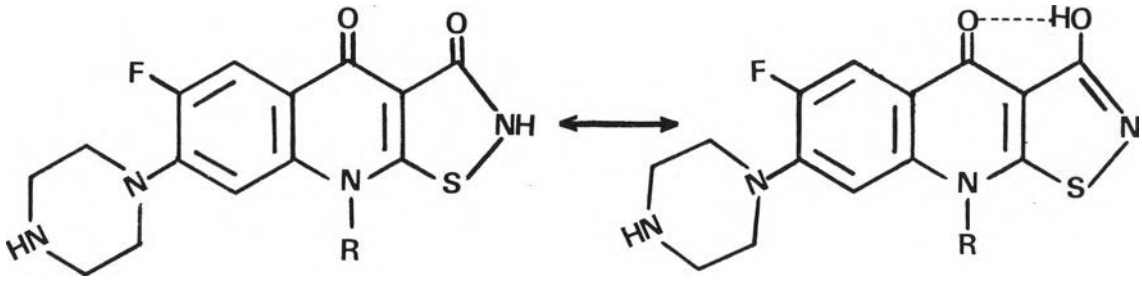
XXVI



XXVII

Isothiazoloquinolones; such as A-62824 (XXVIII), in which the 3-carboxylic acid group of ciprofloxacin has been replaced by a bioisostere-fused isothiazolo ring, is substantially 4 to 10 times more potent than ciprofloxacin and possesses enhanced activity against DNA gyrase. This discovery offers a new insight into the understanding of the structure-activity relationships among the quinolones and the present to find inhibition of DNA gyrase structurally different from this established class of compounds, in particular compounds lacking a ß-keto acid, which has been a hallmark of inhibitors of A subunit of DNA gyrase.

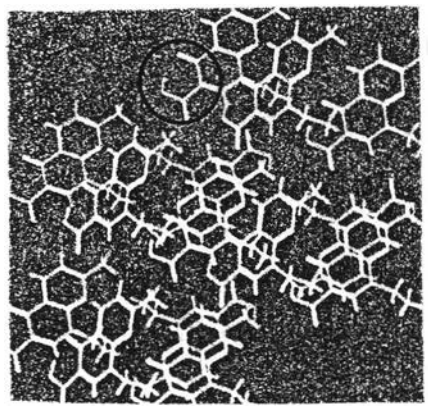
The isothiazolo ring system in structure A-62824 (XXVIII) possesses an aromatic character and the nitrogen proton is very acidic and can be considerred to mimic carboxylic acid. The enolized thiazoloquinolones (XXIX) have conformation for hydroxyl group upward in plane and have the possible to form intramolecular hydrogen bond with oxygen atom at position 4. Its imino group is downward in plane, and nitrogen atom was fixed by thiol-linkage. The coplanarity between the 4-keto group and the enolized isothiazolo group may be important for binding to the DNA gyrase (Fernandes, Claiborne, Shen et al., 1988).



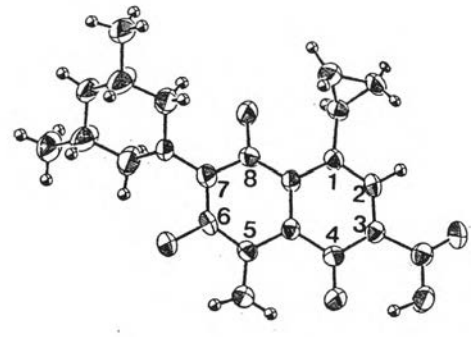
XXVIII XXIX

X-ray crystallographic studies of some quinolones; such as nalidixic acid (XXX), (Shen, Mitscher et al., 1989), sparfloxacin (XXXI) (Miyamoto et al., 1990) show that hydroxyl group in 3-carboxylic acid is upward in

plane and forms intramolecular hydrogen bond with oxygen atom at C-4 position. Whereas, its keto group is downward in plane.



XXX

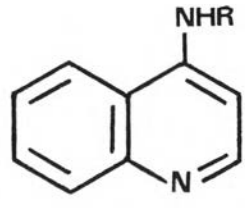


XXXI

In according, the hypothesis of this research is to increase the rigidity of 3-carboxylic acid group with respect to the conformation of 3-carboxylic acid and coplanarity between 4-keto and 3-carboxylic acid groups which might enhance for binding to DNA gyrase.

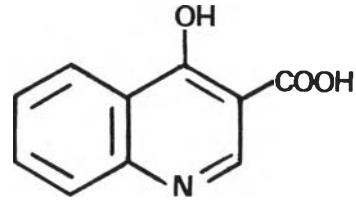
Nevertheless, nowadays the position 4 has not been extensively explored. The replacement of the 4-keto group with other groups; such as amino group (XXXII) (Drake et al., 1946; Pearson, Jone, and Cope, 1946; Singh et al., 1971), hydroxyl group (XXXIII) (Shah and Coats, 1977) or so have no antibacterial activity. The derivatives with

4-imino group have also not been investigated for the syntheses and the biological activities are not available.



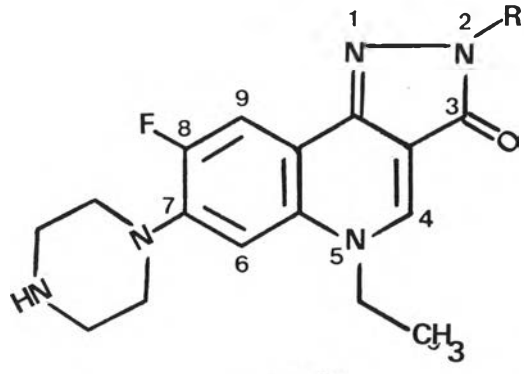
R : H , $(CH_2)_nNH_2$, $(CH_2)_nNH(CH_2)_n$

XXXII

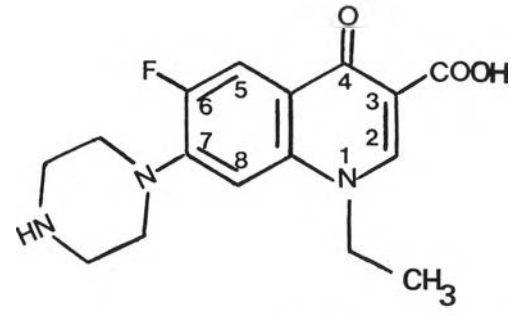


XXXIII

In order to shed new light on quinolones SAR and as novel research on rigid structure of the quinolones, so of pyrazolo [4,3-c] quinolin-3-one (XXXIV) analogs will be explored. By application of bioisosteric replacement strategy, the 4-keto-3-carboxylic acid moiety of a quinolone will be replaced by an imino group to form a pyrazolo ring at C-3 and C-4 with the hypothesis that mentioned above the fused ß-imino amide moiety might have the conformation and planarity of pyrazolo ring which may satisfy requirements in the putative mechanism of action. While, other related positions of quinolones structure, as norfloxacin are maintained.

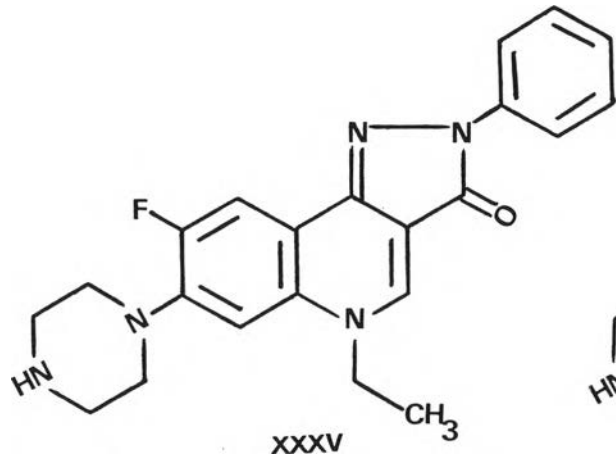


XXXIV

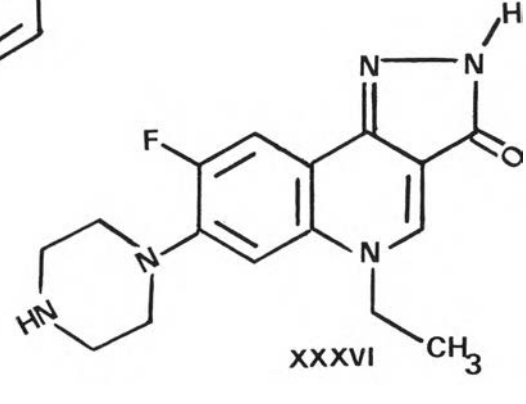


norfloxacin

In pyrazoloquinolones series, the N-2-phenyl-derivative (XXXV) was prepared, that represented the model of this series. The pyrazoloquinolone derivative within the group of compound with R = H (XXXVI), in addition to rigidity of its ß-imino amide, it also has acidic nitrogen proton which could be considered mimicking carboxyl group. This compound also expected to has potential antibacterial activity.

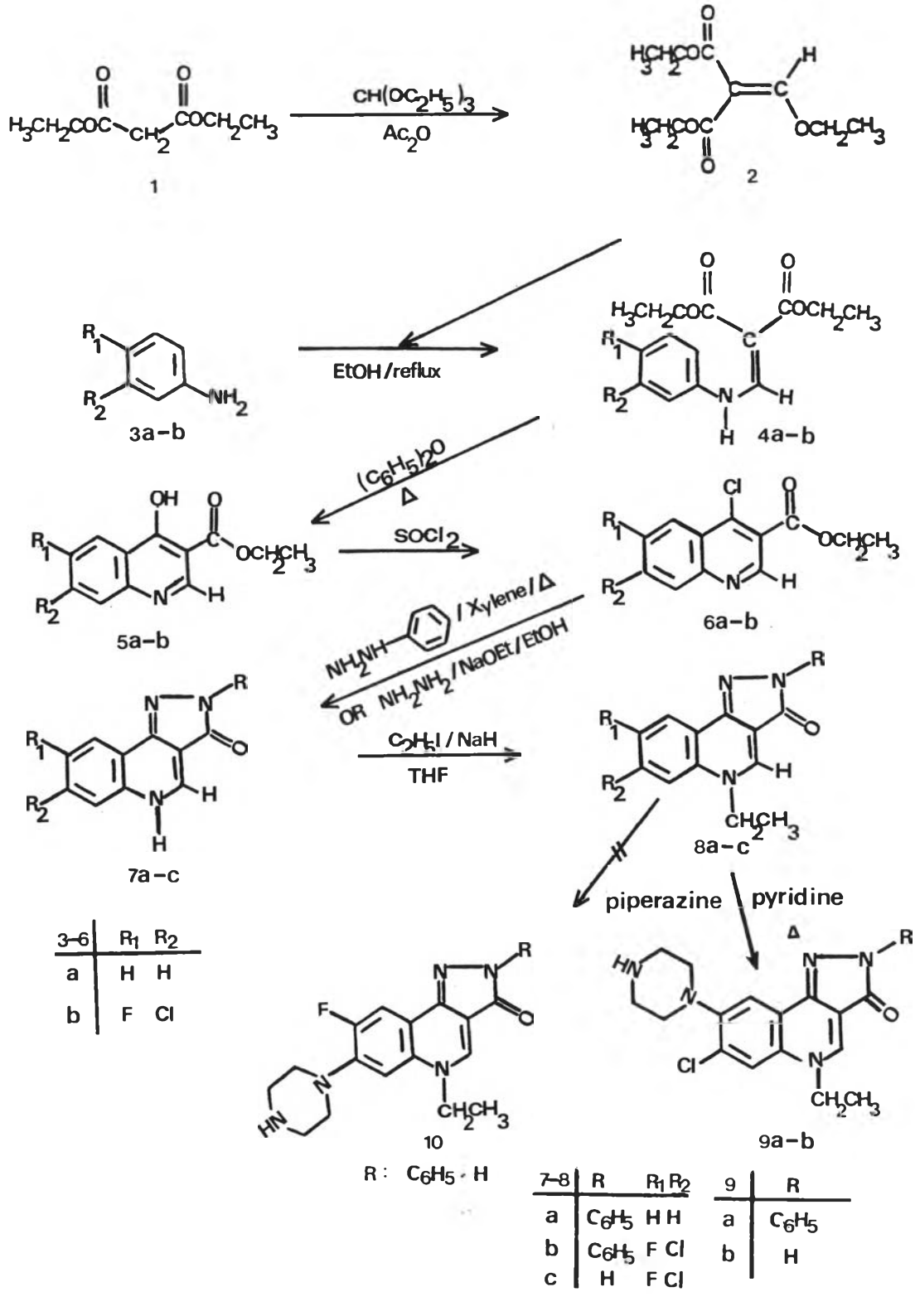


XXXV



XXXVI

Therefore, the possible route for preparation of the target compounds were outlined in Scheme I.



3-6	R_1	R_2
a	H	H
b	F	Cl

7-8	R	R_1 R_2
a	C_6H_5	H H
b	C_6H_5	F Cl
c	H	F Cl

9	R
a	C_6H_5
b	H

Scheme I : Synthesis of Pyrazoloquinolones.