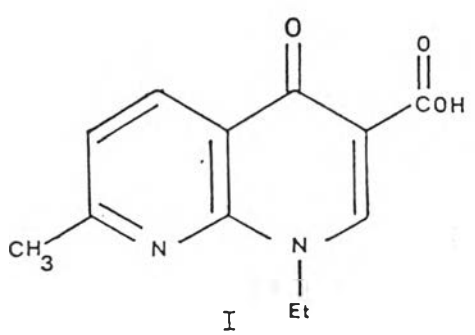
CHAPTER I

INTRODUCTION

Nalidixic acid (I), a 1,8-naphthyridine derivative, was synthesized by Lesher et al. (1962) and introduced into clinical use in 1964 . It was orally used preliminary for the treatment of urinary tract infections associated with the often rapid emergence of resistance. A number of other chemically related drugs which were synthesized in the 1960s and 1970s had a superior antibacterial spectrum. These included oxolinic acid (II), cinoxacin (III), pipemidic acid(IV), flumequine (V), tiaxic acid (VI) and miloxacin (VII). These were either naphthyridine-carboxylic acid or quinoline carboxylic acid derivatives and, along with nalidixic acid, were collectively called quinolone (Paton, Reeves, 1988).



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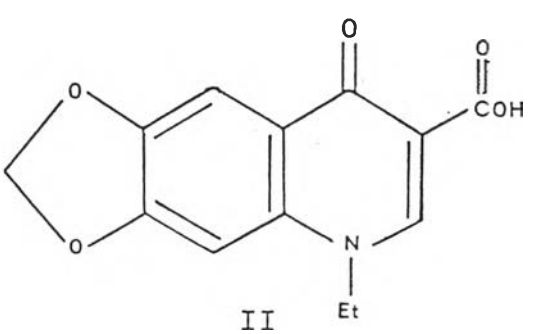

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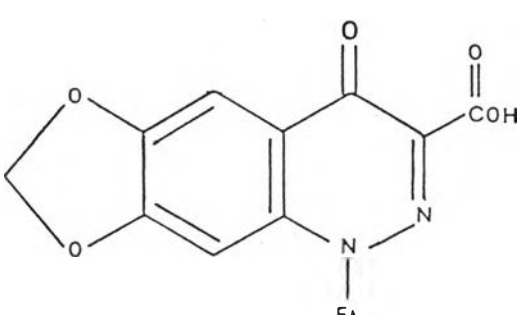

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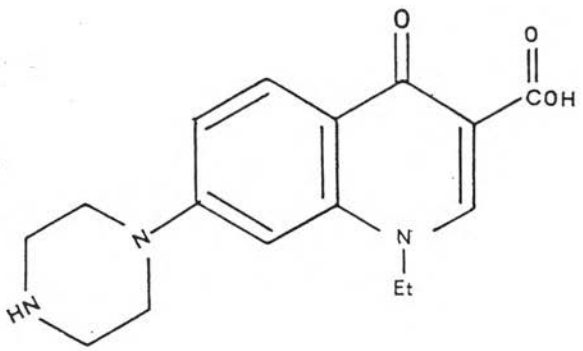

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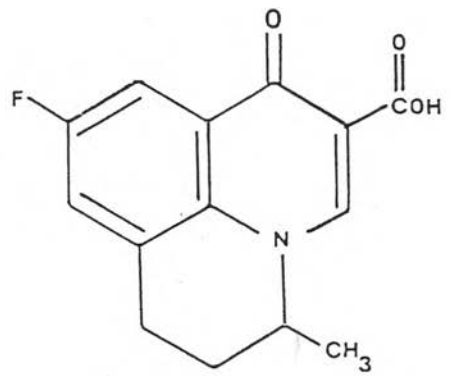

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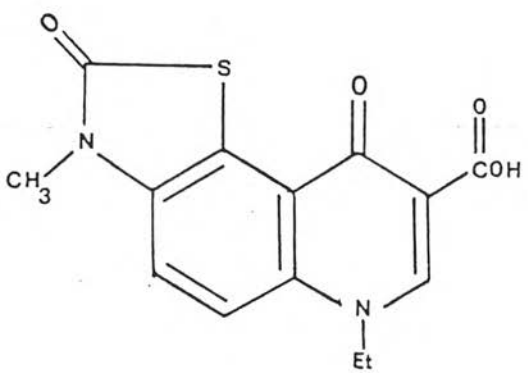

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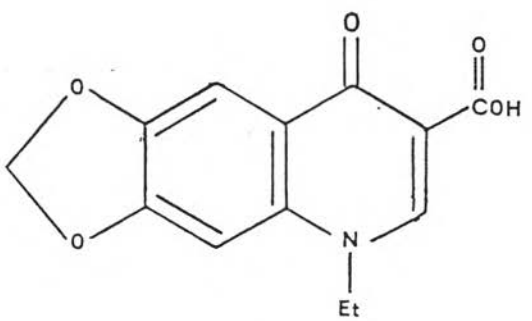
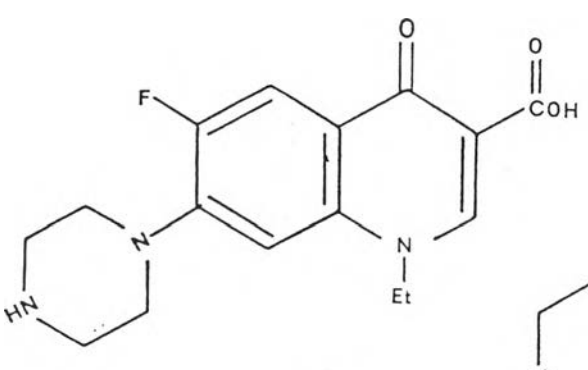


VII

Since 1980, a major advance in antimicrobial chemotherapy came with the synthesis of newer quinolones containing at least one fluorine atom in the chemical structure of molecule such as norfloxacin (VIII), ciprofloxacin (IX), ofloxacin (X), pefloxacin (XI).



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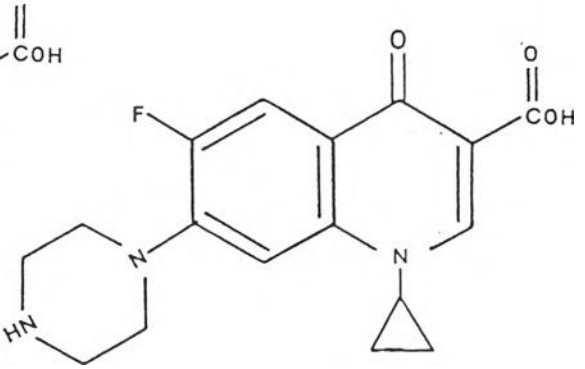

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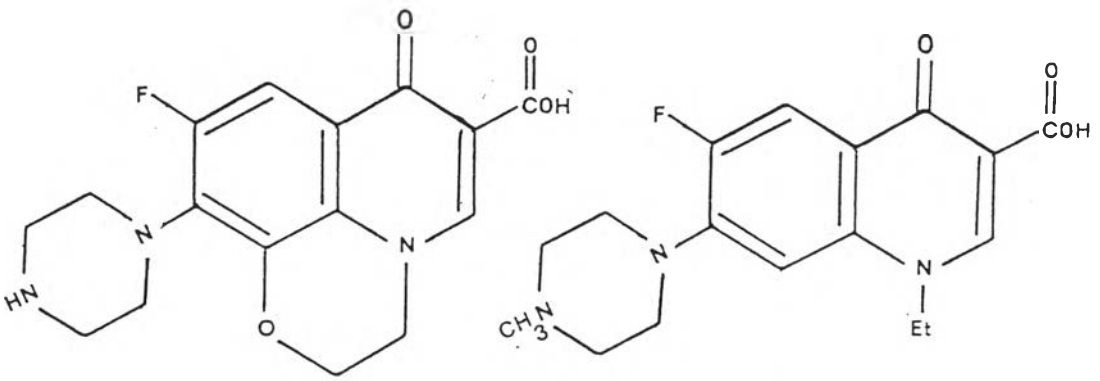


X XI

Mechanism of Action

The primary target of all quinolones were DNA gyrase (topoisomerase II), (Crumphin, Keenwright and Hirst, 1984). This essential bacterial enzyme was discovered in Escherichia coli (Gellert, 1981). DNA gyrase had variety of activities including the introduction of negative superhelical twists into double stranded DNA and the catenation or decatenation of two duplex DNA circles interlocked-like links in a chain. It acted by introducing a double-stranded break into the DNA, passing another DNA duplex through the break, and supertwising and catenation-decatenation activities of DNA-gyrase. Quinolones preferentially and rapidly inhibit DNA synthesis, suggesting interference with movement of the DNA replication fork, in additions causes single strand nicking and limited destruction of the bacterial chromosome, induce the SOS DNA repair system of Escherichia coli, and stimulate synthesis of the bacterial heat shocked protein (Kruger and Walker, 1984).

Antibacterial Activity

1. Gram negative bacteria

All the quinolones had good activities against most gram-negative aerobic pathogens. Ciprofloxacin was generally the most potent compound *in vitro*, followed by less active ofloxacin and norfloxacin. For example, the quinolones were active against Pseudomonase aeruginosa, Neisseria gonorrhoeae, Haemophilus influenzae.

The quinolones were highly active against the enterobacteriaceae such as Escherichia coli, Klebsiella pneumoniae, Salmonella typhi, Proteus vulgaris, including multiresistance strains and frequently as potent or more potent inhibitor *in vitro* than aminoglycosides and new cephalosporins.

2. Gram positive bacteria

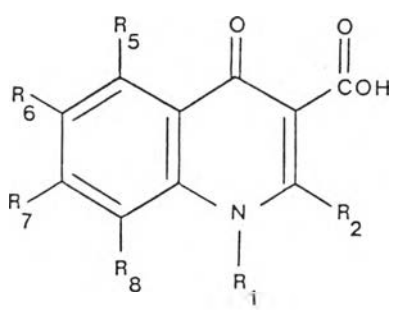
The quinolones were generally less active against gram-positive than gram-negative bacteria. Susceptibillity type of gram-positive bacteria such as Staphylococcus aureus, Streptococcus pneumoniae. Moreover, the quinolones were active against Mycobacterium tuberculosis.

Clinical Uses

With their extended antibacterial spectrum and high potency against many pathogens, the quinolones offered considerable potential in treatment of a wide variety of infections. The clinical used against urinary tract infections, sexually transmitted diseases, gastrointestinal diseases and respiratory tract infections were reported (Paton, Reeves, 1988).

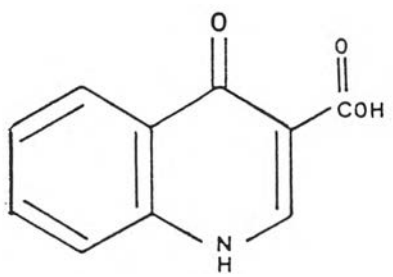
Structure-Activity Relationship of the Quinolones

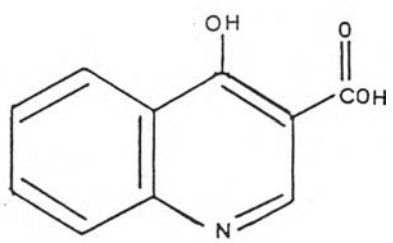
Modification studies of the quinolones have produced compounds with increase potency and spectrum of the therapeutic appilcations. The mechanisms by which these substitutions enhance antimicrobial activity were for the most part unknown, but it seemed possible that many of substitutions affect interaction with DNA gyrase.



Position 1 Earlier studies indicated that substitution at the N-1 position was important to assume antibacterial activity (Albrecht, 1977). It could be

the protection of enolization of keto group at position 4 . The enol form of quinolones lossed bacterial activity (Chemence, et al., 1984; Price, Roberts, 1946; Shak, Coats, 1977).





The optimum substituent for N-1 position were found to be ethyl group and cyclopropyl group because the length of the substituent along the axis of the parent quinolone molecule should be about 0.42 nm. which corresponding to approximate size of these groups (Fujita, 1984).

Position 2 Very few modifications had been explored at position 2. Introduction of nitrogen at position 2 of cinoxacin improved some pharmacokinetic properties, however, it was less active *in vitro* than oxolinic acid. Benzothiazolo[3,2-a] quinolones possessed good antibacterial activities. These derivatives had a sulfur atom at C-2 position; the substituent was part of a ring system annealed to the benzene moiety. No clinical study on these compounds had been reported.

Position 3 Classical studies had produced no active quinolones with a significant modification of the C-3 carboxylic acid group, with the exception of some groups which were converted *in vivo* back to a carboxylic acid group (Pesson, De Lajudie and Antoine, 1971) . For example, replacement of the 3-carboxylic acid group of norfloxacin by a formyl group produced the compound with low *in vitro* antibacterial activity. However, the compound exhibited the increased activity *in vivo*, owing to its rapid conversion to 3-carboxylic acid. A recent attempt to place the 3-carboxylic acid group with a carboxylic mimicking compound 1-H-tetrazol-5-yl, resulted in a total loss of antibacterial activity. However, a compound 62824 in which the 3-carboxylic acid group of ciprofloxacin had been replaced by a bioisostere-fused isothiazolo ring was found to be more potent (Fernandes, Claiborne et al., 1988).

Position 4 In generally, the 4-carbonyl group was considered necessary for the binding of quinolones to DNA gyrase (Schentag and Domagala, 1985). A few development at position 4 had been reported, all of them were biologically inactive (Drake et al,1946; Shah and Coats, 1977).

Position 5 Limited investigations had been done on the C-5 position with substituents, such as nitro, amino, halo, and alkyl gruops. The C-5 amino

substitution might enhance absorption or tissue distribution. Although some reports had suggested that substitution at C-5 position reduced the antibacterial activity (Jack, 1986). The 5-aminoquinolone had been reported to have *in vitro* antibacterial activity far superior over that of ciprofloxacin.(Domagala, Hagen et al., 1988). The amino group at the C-5 position in the 6,8-difluoroquinolone series may enhanced potency.

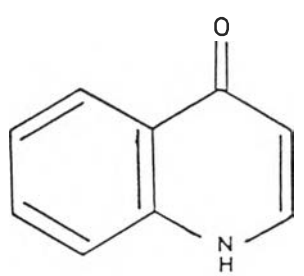
Position 6 Among the various C-6 substituents (F, Br, $\overset{O}{\overset{\|}{C}}CH_3$ and NO_2), the addition of a fluorine atom resulted in a dramatic increase in antibacterial potency (Koga et al., 1980) . The fluoro group at position 6 improved the DNA gyrase complex binding and cell penetration (Domagala, Hanna, et al.,1986) . Because of antibacterial potency enhancement , nearly all of the recently synthesized quinolones carry a C-6 fluorine substituent.

Position 7 Modification of the C-7 position of the quinolone molecule had been extensively studied. In general, the profile of C-7 substituents had been devided into three groups (Domagala, Hanna, et al.). The first group contained quinolone with small or linear-like C-7 substituents (H, Cl, $CH_3NH_2CH_2NH$-, CH_3NH-, OH-N=CH-). It would appear that all the small substituents possesed moderate antibacterial potency due to their loss affinity of binding to the gyrase-DNA complex. The second group of C-7 substituents consisted

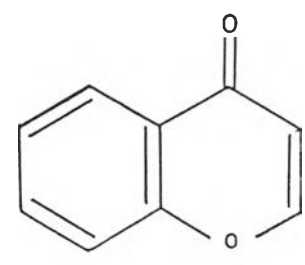
of the medium size of five- and six-membered rings (pyrrolidinyl, pyrrolyl, thiazolidinyl, thiomopholinyl and piperazinyl) possesed good antibacterial activities. Further minor alternation of substitutions on the second group was leading to the third group, for examples, the substitution of methyl at C-4 position of the piperazinyl group enhance the gram positive antibacterial activity of the parent compound and the substitution of 3-aminopyrrolidin-1-yl group at the C-7 position generally enhanced the overall spectrum of activity. However, these substitutions made the product less water soluble at pH 7.4 and might cause absorption problem in human (Wentland et al., 1984).

Position 8 Among many investigated modifications at the C-8 position were the replacement with nitrogen atom or substitution with halogen atom (Cl, F). Ofloxacin, having an oxygen substituent at the C-8 cyclized with ethylene bridge to N-1 position forming morpholine-like ring system was somewhat potent than norfloxacin *in vitro* (Sata et al. 1982). A number of naphthyridines had excellent activity *in vitro* and *in vivo*. However, with similar substitions at N-1, C-5, C-6 and C-7, naphthyridine analogs were less reactive *in vitro* than their quinolone counterparts. This inferior *in vitro* activity was overcomed by better absorption to enhance *in vivo* activity.

The aim of this research is to study the bioisosterism of quinolone compounds with N-1 position modification because the unsubstituted at N-1 compounds were known to lose activity. The bioisosterism concept of two molecules or molecular fragments (ion,radicals) containing similar arrangement of electrons should have the same biological similar properties (Burger, 1977; Foye, 1989). The secondary amine at N-1 position (N-H) was considered to have three bioisostere groups : ether bridge (-O-), thioether bridge (-S-), methylene bridge ($-CH_2-$) . However, the hydrogen atoms of methylene group should produce the enolization of ketone at position 4 so that methylene group was not suitable . The ether bridge was selected in this research for the bioisosterism of N-1 position. Then the Quinolone nucleus is transformed into Chromone nucleus.



Quinolone



Chromone

Figure 1 Structure of quinolone and chromone nucleus

Ethylchromone-3-carboxylate (Figure 1) had been studied (Okumura, et al, 1974) . This compound at the concentration of 50 mcg/ml had an activity against Pricularia orizae.

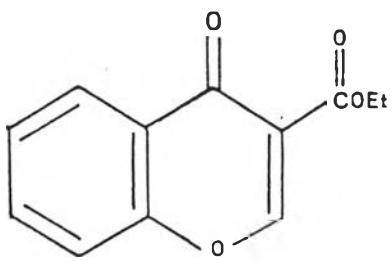
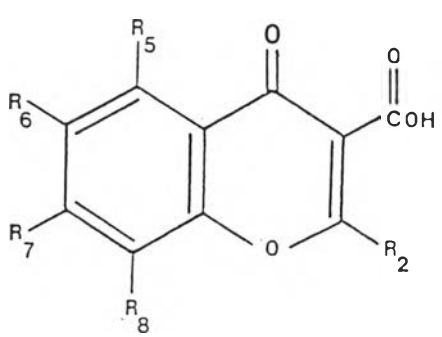


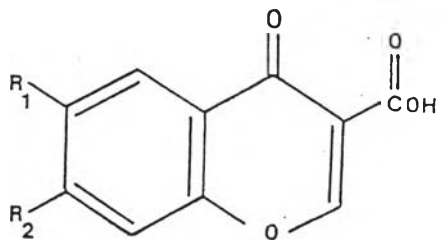
Figure 2 Structure of ethylchromone-3-carboxylate

Ethylchromone-3-carboxylate also had some activity against fungi. The encouraging evidence of chromones with similarity in concept and structure of quinolones, the chromone-3-carboxylic acid derivatives were considered to have good prognostic to study.



Antibacterial activity of chromone-3-carboxylic acid should be increased by substitution of chlorine and fluorine at position 6. Then 6-chlorochromone-3-

carboxylic acid and 7-chloro-6-fluorochromone-3-carboxylic acid were expected to have potential antibacterial activity.

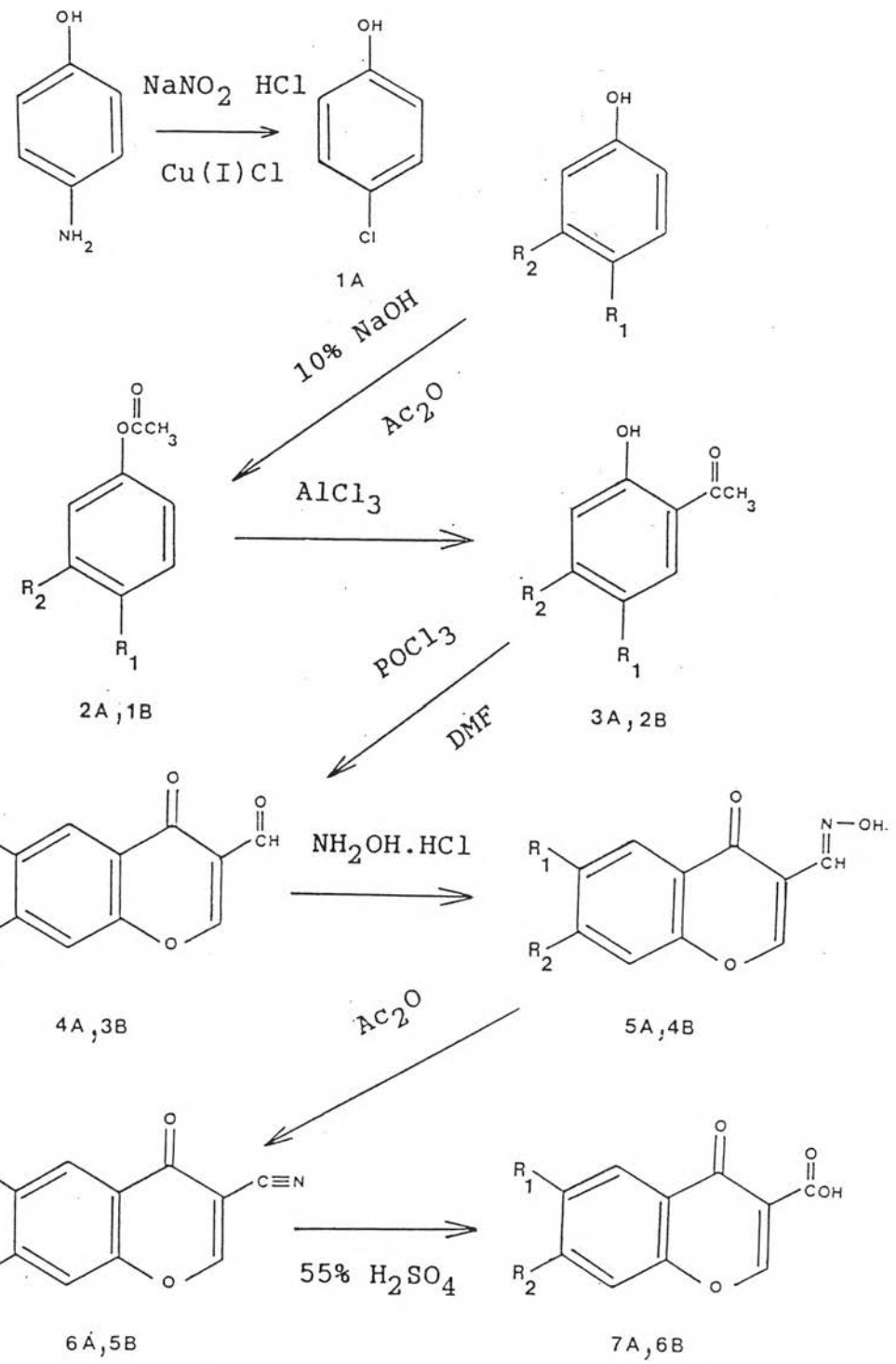


R_1=Cl, R_2=H : 6-Chlorochromone-3-carboxylic acid

R_1=F, R_2=Cl : 7-Chloro-6-fluorochromone-3-carboxylic acid

Figure 3 Structure of chromone-3-carboxylic Acid derivatives

Therefore, the possible route for preparation of the target compounds was outlined in scheme I.



(1-7 A) R_1=Cl, R_2=H : 6-Chlorochromone-3-carboxylic acid

(1-6 B) R_1=F, R_2=Cl : 7-Chloro-6-fluorochromone-3-carboxylic acid

Scheme I Synthesis of Chromone-3-carboxylic acid derivatives