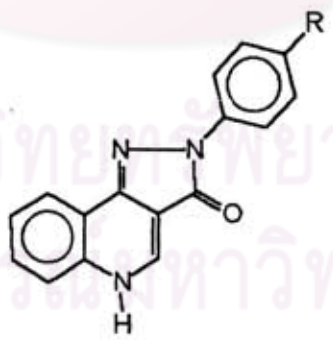
Chapter 2

History

In 1982, Yokohama, Ritterand Neubert reported on three novel 2-Arylpyrazolo-[4,3-c]-quinoline-3-ones (L) , non-benzodiazepine ligands, all of which possess extremely higher affinity for the benzodiazepine receptors than diazepam. Compounds in this class has various pharmacological activity as agonist (as classical benzodiazepine), partial agonist (anxioselective, anticonvulsant), antagonist and partial inverse agonist according to substituent groups. The SAR of this group has not clearly understood since limitted variation has been made.



(L)

Substitution at position N-2 effect to its pharmacological violently. As showed in experiment of (Yokoyama et al, 1982 and Brown et al, 1984); if (L) has :

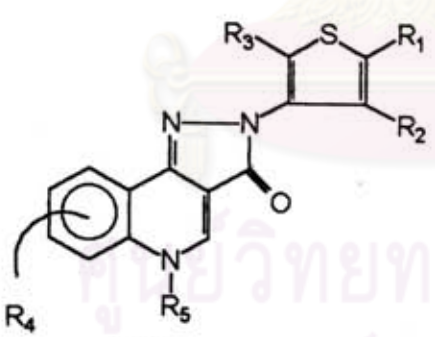
R = H , it exhibited a very potent antagonist of diazepam (Czernik et al, 1982) but later found to have inverse agonist activity.

R = p-Cl , it exhibited a safe antianxiety agent and anticonvulsant (partial agonist) (Braestrup, Honore et al, 1984).

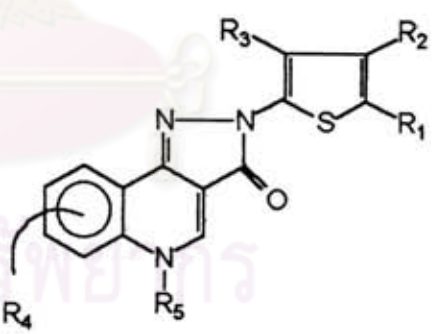
R = p-OCH_3 , it exhibited a weak partial agonist at low dose antagonist at high dose.

In 1987, Takada et al. reported on a new thienylpyrazoloquinoline compound (LI) which was a potent and orally active inverse agonist with high affinity to benzodiazepine receptors and their activity exhibited much greater potency than CGS 8216.

Furthermore its ragioisomer (LII) also exhibit a high affinity to benzodiazepine receptors which is classified as an agonist but less potent than CGS 9896. This structure is modified at N-2 substitution from phenyl to thienyl group (Takada , Shindo, Sasatani and Matsushita et al, 1987 ; Takada, Shindo, Sasatani and Chomei et al., 1988).



(LI)



(LII)

Another modification occured at phenyl part of quinolone ring by Forbes et al. The selective, non-benzodiazepine, pyrazoloquinoline (CGS 9896 (X)) which is a partial agonist at benzodiazepine receptors, is an important structure lead. From literature, suggested that the benzodiazepine receptor complex could tolerate a wide variety of π-aromatic ring (Forbes et al, 1990). Therefore, a series of aromatic isosteric replacements

of CGS 9896 was investigated in order to determine the effect of such changes on receptor-binding activity. However the non-aromatic ring such as cycloheptene still has activity (Martin and Tegeler,1988).

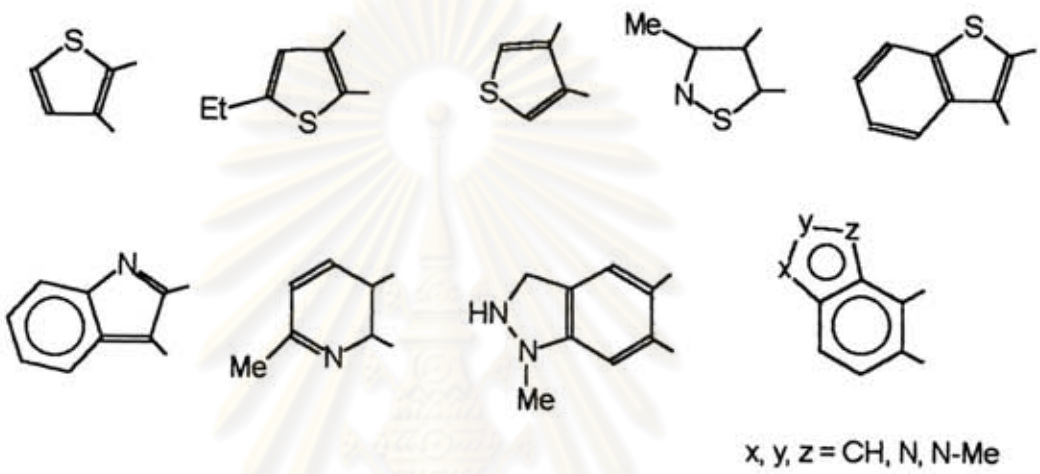


Figure 5. Show aromatic isoster of phenyl (phenyl ring of quinolone).

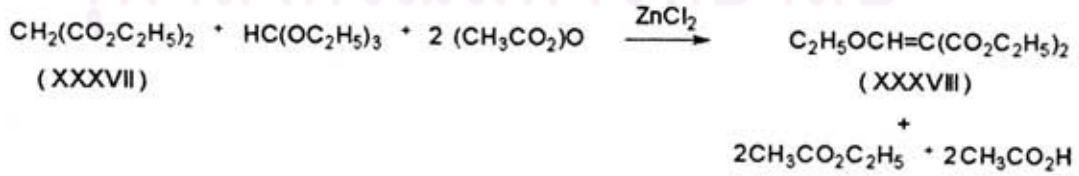
Reduced activity is observed with linear tetracyclic compounds and benzothienopyridine, they are possibly too large to fit into the benzodiazepine receptor binding sites. Dipyrazoloquinolines derivatives and imidazoquinoline showed good *in vitro* potency but poor *in* vivo activity in Vogel behavioral screen (the test for anxiety), possibly reflecting poor oral bioavailability of these compounds. Replacement of phenyl ring by an electron deficient ring as in naphthyridine or isothiazolopyridine are detrimental to *in vitro* activity, but some maintained *in vivo* activity. The pyrazolothienylpyridine process potential anxiolytic activity. On quanlitative basis, more than one-half of the compounds which varies at phenyl ring of pyrazoloquinoline were semilar to CGS 9896 in rat Vogel test but substantially less active than CGS 9896 and diazepam in the anti-

pentylenetetrazole test. From the lack of myorelaxant / sedative properties report for CGS 9896 which has been confirmed in the Wire test and the compound derivatives of CGS 9896 were also less active than diazepam in the mouse Wire test (Forbes et al, 1990). This may suggested the pyrazolopyridines, as a class of compounds, had weaker muscle-relaxant properties than diazepam. From these biological data, it is apparent to benzodiazepine receptors interacting drugs have the potential provide novel anxioselective agents for the treatment of anxiety.

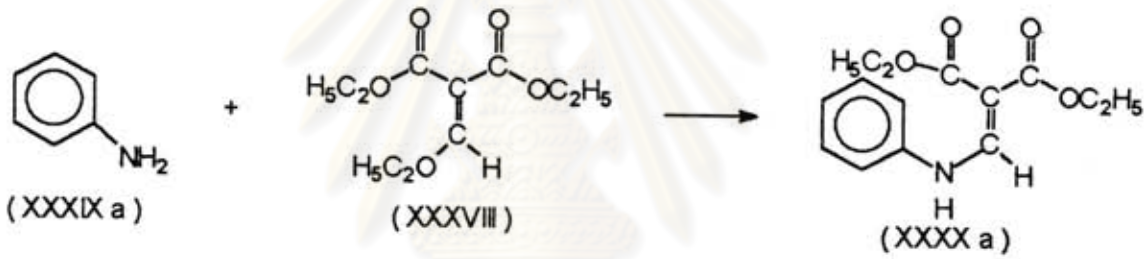
The possible reaction in synthesis of 2-Thiooxopyrimido-[4,3-d]-quinoline-4-one ring :

Synthesis of quinoline ring of Thiooxopyrimido quinolone is the same process as in synthesis of quinoline ring of 4-Amino-quinoline derivatives (antimalarials) and 7-Chloro-6-fluoro-quinoline derivatives (antibacterials) (Koga et al, 1980).

Diethyl ethoxymethylenemalonate (XXXVIII) is the active methylene substance which will be later condensed with aniline (XXXIX a) or 3-chloro-4-fluoro-aniline (XXXIX b), it is prepared by developed method of Claisen by heating a mixture of triethyl orthoformate, diethyl malonate (XXXVII), and acetic anhydride with a catalytic amount of zinc chloride.

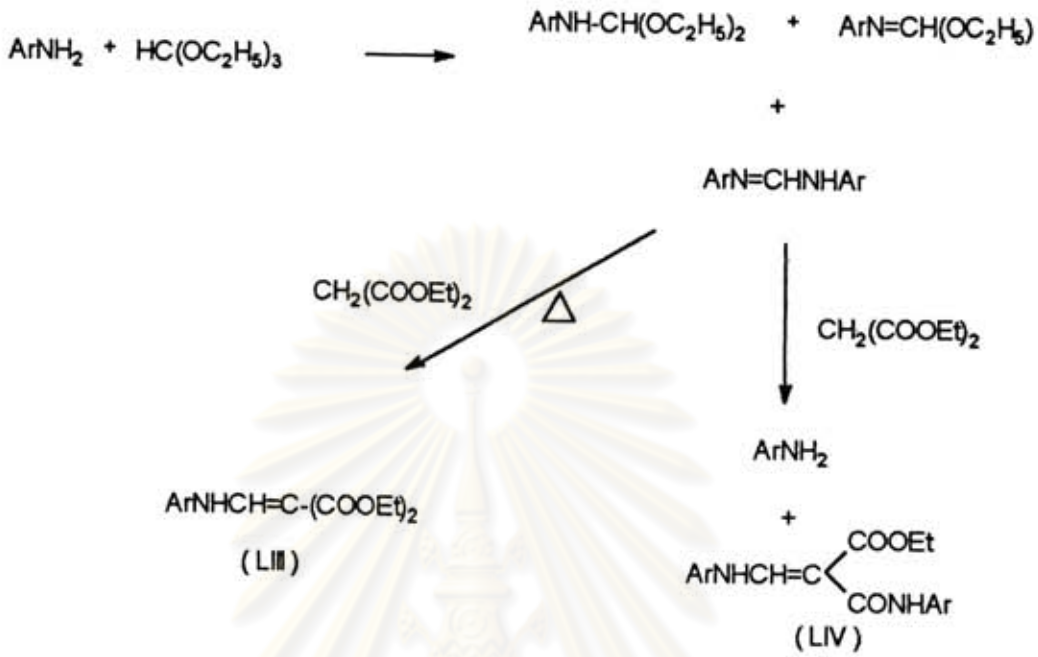


The reaction of diethyl ethoxymethylenemalonate with aromatic amines to form anilinomethylenemalonate (XXXX) took place readily even at room temperature (Price and Roberts 1946). Claisen found better yield by carried out the reaction with aniline by heating the reactants for a short time on the water-bath. This reaction was found to be very satisfactory on a small scale. Other nuclear substituted anilinomethylenemalonates were similarly obtained by heating the appropriate intermediates on the steam-bath (Duffin and Kendall, 1948).



(XXXIX a) (XXXVIII) (XXXX a)

The principal disadvantage for large-scale production by this reaction is the expensive of the starting material (Price and Roberts, 1946). So that diethyl anilinomethylenemalonate can be prepared by a synthesis avoiding diethyl ethoxymethylenemalonate (XXXVIII) in its process. Ethyl orthoformate, an active methylene compound, is used to form reaction with aromatic amine (Snyder and Jones, 1946). But the acrylates impurity (LIV) also can be obtained by heating malonate ester with arylformamidines (LIII) at 115 to 120°c for a few hours (Price and Roberts, 1946) or the replacement of ethoxy group by the amine residue may have occurred before during or after the other reaction. Longer times for reaction or higher temperature led to increase conversion of ethoxy group by the amine residue as shown in the following reaction:



Ring-closured synthesis of quinoline derivatives.

In 1887, Conrad and Limpach first prepared 4-Hydroxy-quinaldine by condensation of aniline and acetoacetic ester at room temperature followed by heat cyclization at 250 °c. Fourty four years later the yield was improved from about 30 to 90-95% by the use of mineral oil as a diluent in the cyclization step (Gould and Jacobs, 1939). Preparation of 4-hydroxyquinoline carboxylates was occured by cyclization of diethyl anilinomethylenemalonate (ibid. , 1939). The original Limpach cyclization, as utilized by Gould and Jacobs involved adding a β-arylaminocrotonate to 2-10 times of its weight of mineral oil preheated to 250-290°c and then heating the solution at 240-250°c for fifteen to twenty minutes. It has been found that both diphenyl ether and Dowtherm A are far

superior as a cyclization medium because they were less viscous and easily to remove from product (Price and Roberts, 1946(b)). Halogen substitution at aromatic part of diethyl anilinomethylenemalonate could also be cyclized as mention above.

(XXXX a)　　(XXXXI a)

Synthesis of 4-Chloro-quinoline carboxylates.

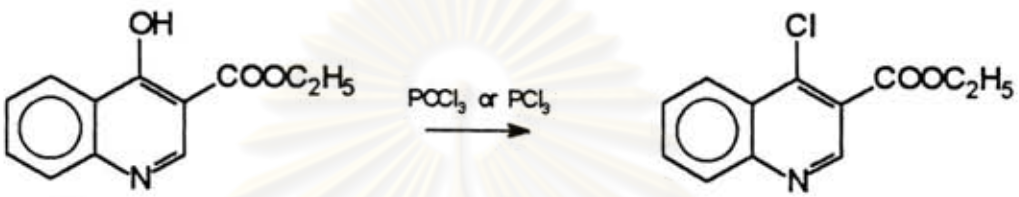
4-Chloroquinoline, an intermediate usually employed in final nucleophilic substitution of 4-alkylaminoquinoline derivatives (antimalarials), is a prototype in this investigation because of good leaving group of its chlorine atom. The main methods of 4-haloquinoline preparation have been reinvestigating :

1. The Meisenheimer procedure is not generally applicable and, for example, is entirely unsatisfactory as a method for the preparation of 4,7-dichloroquinoline.

2. The Oxaloacetic ester synthesis is perhaps more general in application than the Meisenheimer but the cyclization steps require conditions which vary widely depending upon the substituents in the carbocyclic ring.

3. The ethoxymethylenemalonic ester synthesis is the most general method (Riegel et al, 1946).

The 4-chloro-3-quinoline carboxylate (XXXXII a) could be prepared by the reaction of 4-hydroxy-3-quinoline carboxylate with phosphoryl trichloride or phosphorous oxychloride (Kaslow and Clark, 1953). Price and Roberts have reported the preparation of 4,7-dichloroquinoline by the same procedure.



(XXXXI a) (XXXXII a)

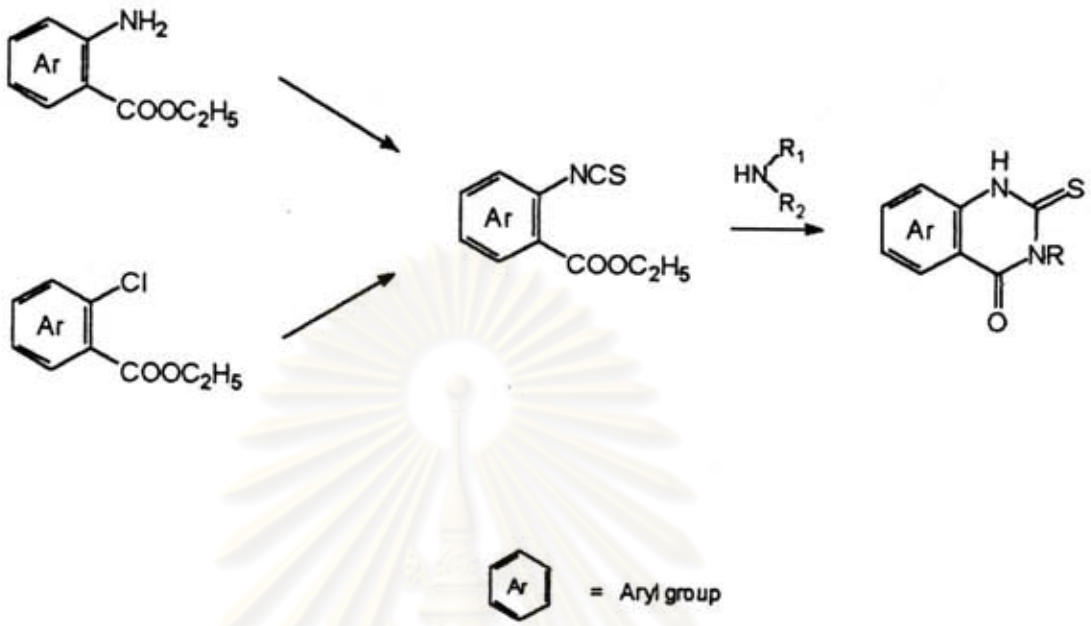
The method of chlorination may also be carried out by using thionyl chloride.

The nucleophilic substitution at position 4 of 4-Chloroquinoline carboxylate.

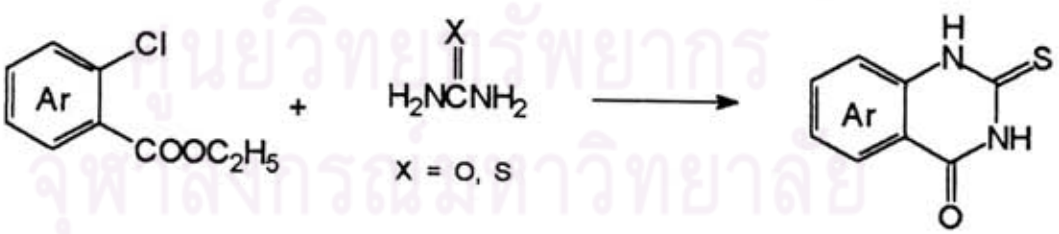
A typical aromatic nucleophilic substitution reaction of aryl halide is employed, halogen is substituted by stronger nucleophiles such as NR_2, NH_3, OH^-, OR^-, NR_3, ^-OAc, CN^- and negative ion having the very polarizable atoms (thiocyanate, thiosulfate, sulfite and sulfide). The reaction of unactivated aryl halides with strong bases was occured at high temperatures. The nucleophilic attack on the ring was assisted when the heteroatom was positively changed from halogen to amino or catalysed by acids or Lewis acids such as zinc chloride and cupric sulphate.

The method for synthesis for a new ring could be produced by the method as followes:

1. Synthesis of Isothiocyanates or Isocyanates (Ozaki,1972 ; Gould, 1959) and ring closure to ester with amines(Urleb, Stanovnik and Tisler, 1990 ; Urleb, Neidlein and Kramer, 1990) for examples :



2. Synthesis of thioureide or ureide by reaction of thiourea or urea with alkyl/aryl halide.



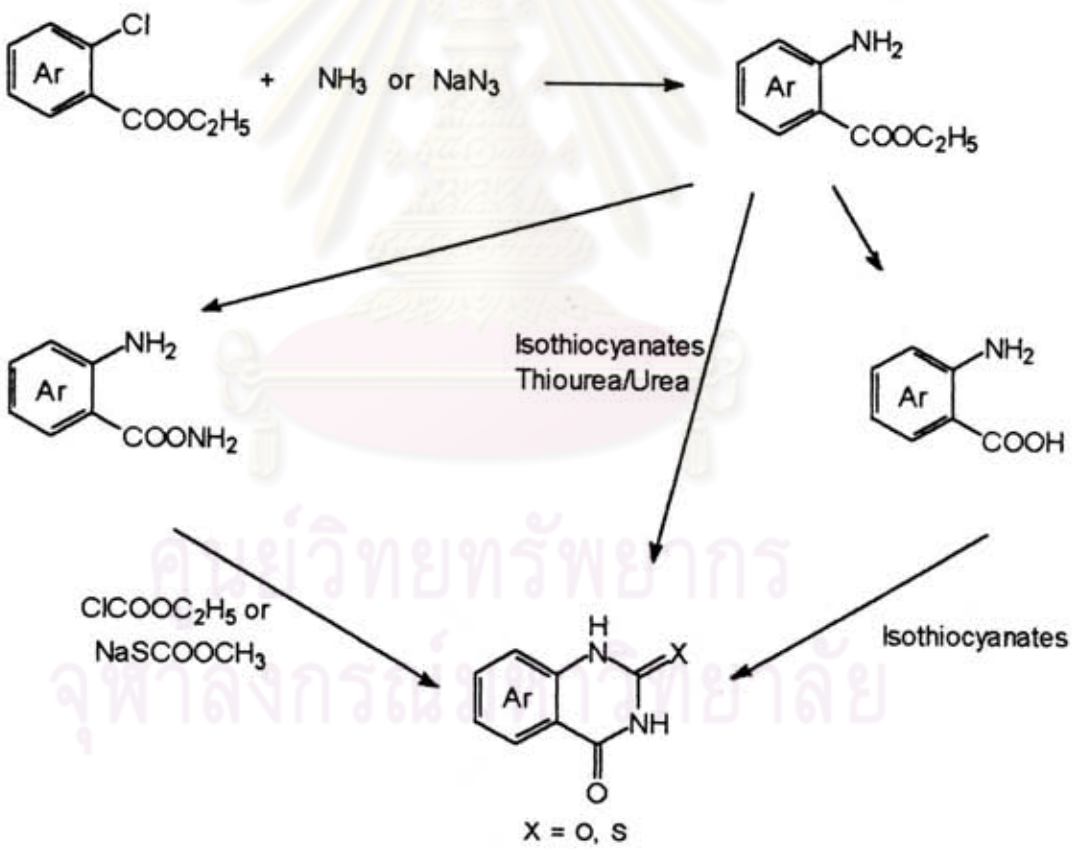
3. Convert aryl halide to amines followed by cyclization:

Aryl halide can be tranform to aromatic amine by ammonia or sodium azide which could be cyclization by the following method.

- Cyclization of ortho aryl amino ester to thiooxpyrimidine ring or pyrimidine ring with isothiocyanatesor thiourea (or urea) (Fox, 1952 ; Kornet, Varia and Beaven, 1984).

- Cyclization of ortho amino amide to pyrimidine ring with $ClCOOC_2H_5$ or $NaSCOOCH_3$.

- Cyclization of ortho amino carboxylic acid to thiooxopyrimidine ring with isothiocyanate compound (Ryczek and Kusowska).



Synthesis of Pyrimido-[4,3-d]-quinoline-2,4-diones derivatives.

The process of synthesis may be the same as of thiopyrimidine derivatives which started with 3-Carboethoxy-4-chloro-quinoline. The starting material should be reacted with corresponding reagents. The other method of synthesis can be derived from oxidation of Thiooxopyrimidine derivatives. The thioketone at position 2 can be converted to sulfines (S-oxides) and sulfenes (S,S-dioxides) with peroxy acid such as hydrogen peroxide, perbenzoic acid etc. (Battagia, 1974). After that one O atom of sulfenes replaced to thiocarbonyl carbon gave carbonyl derivatives.