# CHAPTER 2

HISTORICAL

In 1982, Yokoyama, Ritter and Neubert reported the synthesis of three novel 2-aryl-pyrazolo-[4,3-c]-quinolin-3-ones (A). These compounds are non-benzodiazepine ligands, all of which possess extremely higher affinity for the benzodiazepine receptors than diazepam. Compounds in this class exhibit various pharmacological activities as agonist, partial agonist (anxioselective, anticonvulsant), antagonist and partial inverse agonist according to their substituent groups. The SAR of this group has not been clearly understood since only limited structural variation has been made. However, there are some interesting structural cosidurations as followed:


(A)
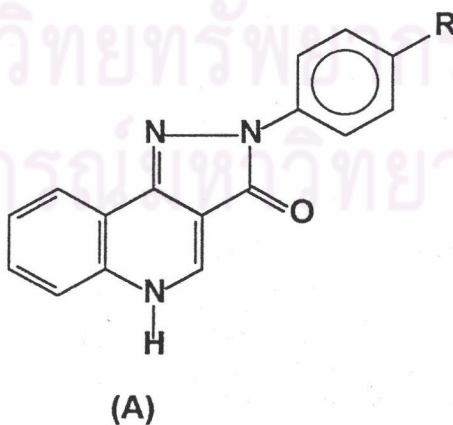
Substitution at position N-2 strongly affects its pharmacological activity. As shown by Yokoyama *et al*,(1982) and Brown *et al*, (1984), when

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

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

R = p-OCH$_3$, it exhibited a weak partial agonist effect at low dose, and antagonist effect at high dose.

In 1987, Takada *et al* reported on a new thienylpyrazoloquinoline compound (AI) which was a potent and series of orally active inverse agonist with high affinity to benzodiazepine receptors and with much greater potency than that of CGS 8216. Its isomer (AII) also exhibited high affinity to benzodiazepine receptors. This compound was classfied as an agonist but was less potent than CGS 9896. There structures were modified at N-2 substitution from phenyl to thienyl group (Takada, *et al*, 1987; 1988).
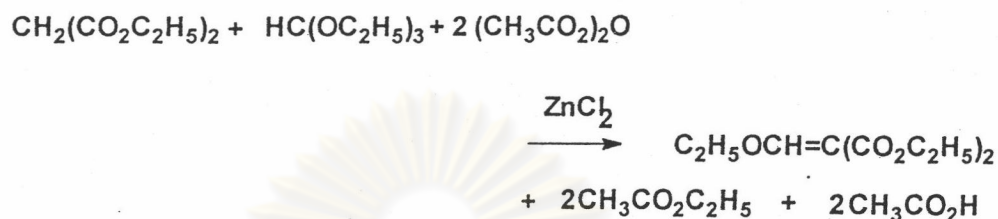

(AI)   (AII)
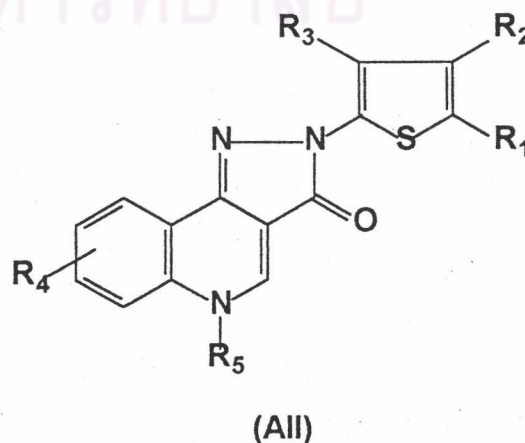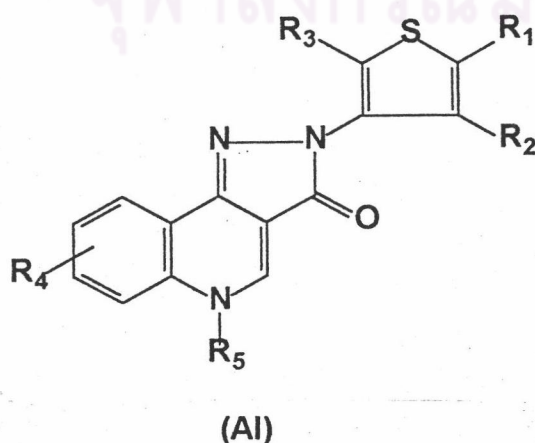
In 1990, Forbes *et al*, reported on modification at phenyl moiety of the quinolone ring. The selective, non-benzodiazepine, pyrazoloquinoline CGS 9896(X) which is a partial agonist at benzodiazepine receptors, is an important lead compound. It has been suggested that the benzodiazepine receptor complex can accommodate a wide variety of aromatic rings (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. Nevertheless, non-aromatic rings such as cycloheptene also produce activity (Martin and Tegeler,1988).

Reduced activity is observed with linear tetracyclic compounds. They are possibly too large to fit into the benzodiazepine receptor binding sites. Replacement of phenyl ring by an electron deficient ring as in naphthyridine, is detrimental to activity. The pyrazolothieno- pyridine possesses potential anxiolytic activity.

Synthesis of 7-Chloro- and 7-Nitro-2-phenylpyrazolo-[4,3-c]-quinolin-3-one ring

Synthesis of the quinoline ring of pyrazoloquinolone involves the cyclization of ethylanilinomethylenemalonate (Gould and Jacobs,1939).

Diethyl ethoxymethylenemalonate was prepared by developed Claisen method of heating a mixture of triethyl orthoformate, diethyl malonate and acetic anhydride with a catalytic amount of zinc chloride.

$$CH_2(CO_2C_2H_5)_2 + HC(OC_2H_5)_3 + 2(CH_3CO_2)_2O$$

$$\xrightarrow{ZnCl_2} C_2H_5OCH{=}C(CO_2C_2H_5)_2$$
$$+ 2CH_3CO_2C_2H_5 + 2CH_3CO_2H$$

The reaction of diethyl ethoxymethylenemalonate with aromatic amines to form anilinomethylenemalonate takes place readily even at room temperature (Price and Roberts, 1946). Claisen carried out the reaction by heating molecular equivalents of aniline and diethyl ethoxymethylenemalonate over the steam-bath for a short time, the anilino-ester could then readily crystallize upon cooling in ice. Other nuclear-substituted anilinomethylenemalonates were similarly obtained by heating the appropriate intermediates on the steam-bath (Duffin and Kendall, 1948).
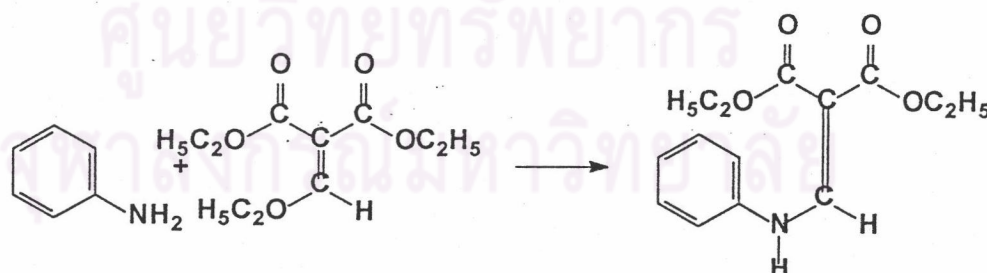

This reaction was found to be very satisfactory on a small scale but for large-scale production, the expense of the starting material become a major disadvantage (Price and Roberts, 1946). In order that

diethyl anilinomethylenemalonate can be prepared by a synthesis avoiding diethyl ethoxymethylenemalonate in the process, ethyl-orthoformate, an active methylene compound, is used to react with aromatic amine (Snyder and Jones, 1946).

Ring-closured synthesis of quinoline derivatives.

In 1887, Conrad and Limparch first prepared 4-hydroxy-quinaldine by condensation of aniline with acetoacetic ester at room temperature followed by heat cyclization at 250°C. Fourty-four years the yield was improved to about 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 achieved by cyclization of diethyl anilinomethylenemalonate (Gould and Jacobs, 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, the solution was then heated at 240°- 250°C for 15-20 minutes. It has been found that both diphenyl ether and Dowtherm (biphenyl and diphenyl ether) are far superior as cyclization medium. These solvents, boiled at optimal temperature for the cyclization, are much less viscous and more easily removed from the product by filtration. Furthermore, the product formed is much less darkened (Price and Roberts, 1946). Diethyl anilinomethylenemalonate with halogen or nitro-group substitution of the aromatic part could be cyclized as mentioned above.
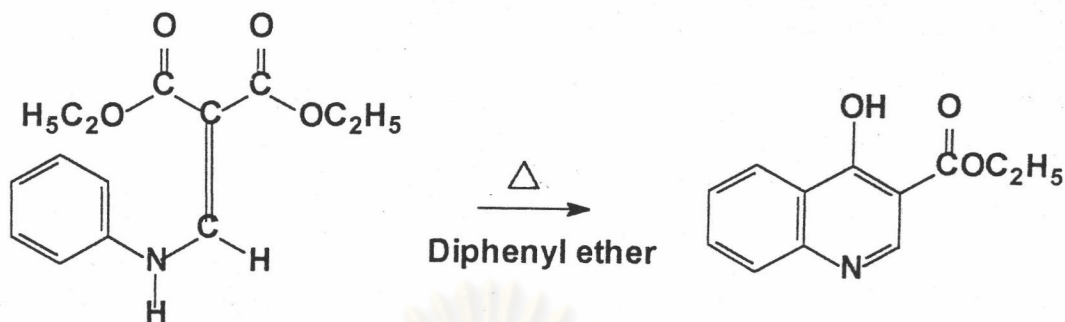
Synthesis of 4- Chloroquinoline carboxylates

4-Chloroquinoline is the intermediate of choice for nucleophilic substitution in the production of 4-alkylaminoquinoline derivatives (antimalarial compounds), quinolone derivatives (antibacterial) or many other because chlorine atom was a good living group.

The 4-chloro-3-quinoline carboxylate is prepared by the reaction of 4-hydroxy-3-quinoline carboxylate with phosphoryl trichloride or phosphorous oxychloride (Kaslow and Clark, 1953). Price and Roberts (1946) have reported the preparation of 4,7- dichloroquinoline and Koga 's group has reported the preparation of 3-carboethoxy-4,7- dichloro-6-fluoro-quinoline based on this method (Koga et al.,1980).
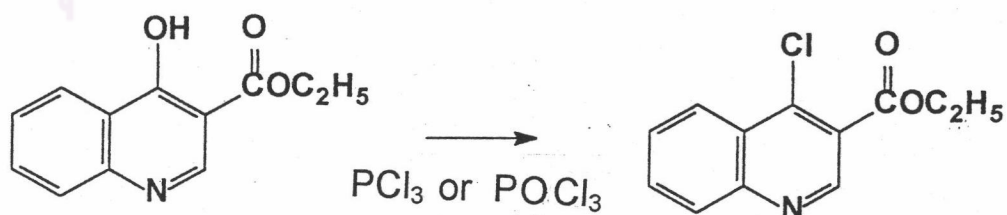
Another reagent used for chlorination is thionyl chloride. For this synthesis 4-chloroquinoline was required as an intermediate and produced in substantial quantity before condensation with amine.

Nucleophilic Substitution Reaction

General reaction formular for the preparation of target compounds by nucleophilic substitution is:

$$R:X + :Z \longrightarrow R:Z + :X^-$$
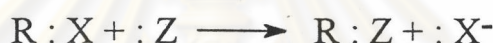
when $Z = NR_2$, NH_3 OH^-, OR^-, NR_3^+, ^-OAC, CN^- and $X = Cl, Br, I$

A typical nucleophilic substitution reaction of aryl halide was employed. Halogen can be substituted by stronger nucleophile such as NR_2, NH_3, OH^-, OR^-, NR_3^+, ^-OAc, CN^-. The aryl halides do undergo nucleophilic substitution readily if the aromatic ring contains, in addition to halogen, other properly placed electron-withdrawal groups, such as NO_2 or CN, located ortho or para to halogen. The reaction of unactivated aryl halides with strong bases occurs at high temperatures. Replacement of halogens by amino groups may be accomplished using ammonia or amines if the halogen is activated. Hydrazine and arylamine also react readily with 2- and 4-halogenopyridines, but may require higher temperatures or a catalyst. The reactivity of leaving groups of alkyl halides follows the sequence R-I> R-Br > R-Cl > R-F.