CHAPTER 1

INTRODUCTION

1.1 **Pepper**[1-6]

Pepper, produced from the berries of the plant *Piper Nigrum* in the family *Piperaceae*, is one of the oldest and world's most important spice. Pepper is a native species of South America that is now cultivated worldwide in warm, dry climates. Pepper is widely cultivated throughout Indonesia, Malaysia, Thailand, Tropicana Africa, Brazil, Sri Lanka, Vietnam and China also. A woody climber, it may reach heights of 10 m by means of its aerial roots. Its broad, shiny green, pointed, etiolate leaves are alternately arranged. The sessile, white, small flowers are borne in pendulous, dense, slender spikes of about 50 blossoms each. The berry-like fruits, or peppercorns, are round, about 0.5 - 1.0 cm in diameter and contain a single seed. They become yellowish red at maturity and bear a single seed. The odor is penetrating and aromatic; the taste is hot, biting and very pungent. The pepper trees were shown in Figure1.

Figure 1 Pepper trees[5]

Black pepper is the dried fruit of *Piper nigrum* Linn. Black pepper is produced from the still-green unripe berries of the pepper plant. White pepper is obtained by removing the outer part of the pericarp of the ripened berries. The flavor is less pungent than that of black pepper. Green pepper is immature berries freeze-dried or mechanically air-dried. They are available pickled in brine or vinegar. The black, white and green peppers[7] were shown in Figure 2.

(a) **(b)**

Figure 2 black (a), white (b) and green (c) pepper

Black pepper fruit shows that it contains 5-9% alkaloids in the berry that also include piperine (**1**), piperidine (**2**), piperettine (**3**) and piperanine (**4**) and comes from the dried fruit,[8] which contains about 3% essential oil (including beta-bisabolene, camphene, beta-caryophyllene, monoterpenes and sesquiterpenes), about 11 % proteins, and small amounts of Minerals.

The most important odorants organoleptically in black pepper are linalool, α-phellandrene, limonene, myrcene and α-pinene.

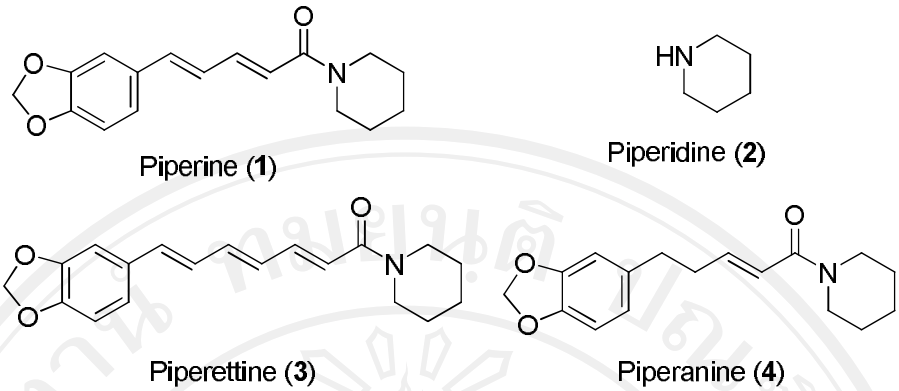


Figure 3 Alkaloids found in black pepper

1.2 Piperine[4,9]

The main compound found in the black pepper is the chemical substance called piperine (**1**). This compound is the agent that gives the pepper its distinctive hot flavor and taste. Piperine (1-piperoyl piperidine) is very abundant in the plant, being extracted from the dry fruits with a yield of 3–7%. The color of piperine can vary between its version in nature and its version created through synthesis. Piperine is naturally a more yellowish powder, while after synthesis it has a stronger green tint to it. Piperine is soluble in alcohol, chloroform, ether and benzene.

Piperine was active against *Entamoeba histolytica in vitro* and *in vivo*.[10] Piperine has also been found enhanced oral bioavailability of Ampicillin and Norfloxacin in animal model[11] and enhanced bioavailability of beta lactam antibiotics, amoxycillin trihydrate and cefotaxime sodium significantly in rats.[12] In addition, piperine has recently been reported to show reduced the MIC and mutation prevention concentration of ciprofloxacin for Staphylococcus aureus.[13] Piperine has shown inhibitory activity against promastigote and amastigote form of *L. donovani in*

vitro.[14,15] Reports have suggested that this activity is enhanced if piperine is delivered in oil-in-water emulsion form or as mannose-coated liposomes.[16,17]

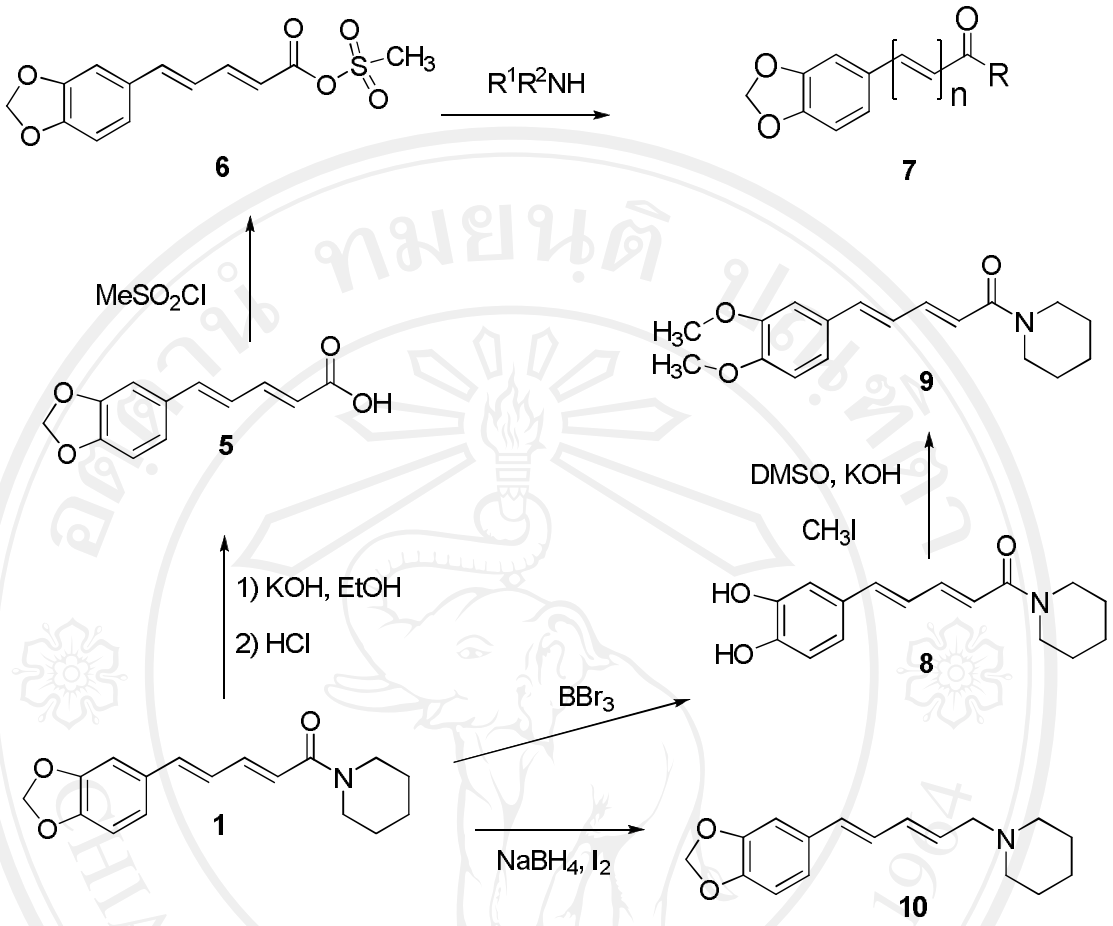
Piperine has been inhibit human CYP3A4[18], cytochrome P4502B1[19] and α-glycoprotein, enzymes important for the metabolism and transport of xenobiotics and metabolites.[20]

More recently, piperine and its derivatives have been evaluated for inhibitory effects against epimastigote and amastigote forms of the protozoan parasite *Trypanosoma cruzi*.[21,22] Piperine is an inhibitor of human P-glycoprotein and/or CYP3A4, digoxin and cyclosporine A transport in Caco-2 cells.[23] In addition, piperine has been reported to show antioxidant action in experimental conditions both *in vivo* and *in vitro* through its radical quenching effect,[24] insecticidal,[25] and inhibition of liver metabolism.[26]

1.3 Literature Review

The application of piperine derivatives have been reported especially as shown bellow.

In 2004, Venkatasamy *et al*.[27] reported that a wide range of piperine analogues have been synthesized in order to undertake a structure–activity study of their ability to stimulate melanocyte proliferation. These derivatives have also been evaluated for their effect on melanocyte morphology and melanogenesis. The piperine analogues altered cell morphology by increasing dendrite formation leading to bi-, tri- and quadric polar cells. These same analogues were found to increase total melanin in cell cultures, although melanin content per cell was not significantly altered from control in the presence of these compounds. Preparation of piperine analogues **5-10** were shown in Scheme 1 and the structure of piperine analogues **11-31** were shown in Table 1 respectively.



Scheme 1 Preparation of piperine analogues **5-10**

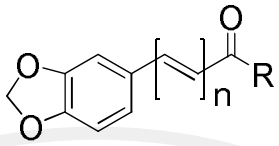
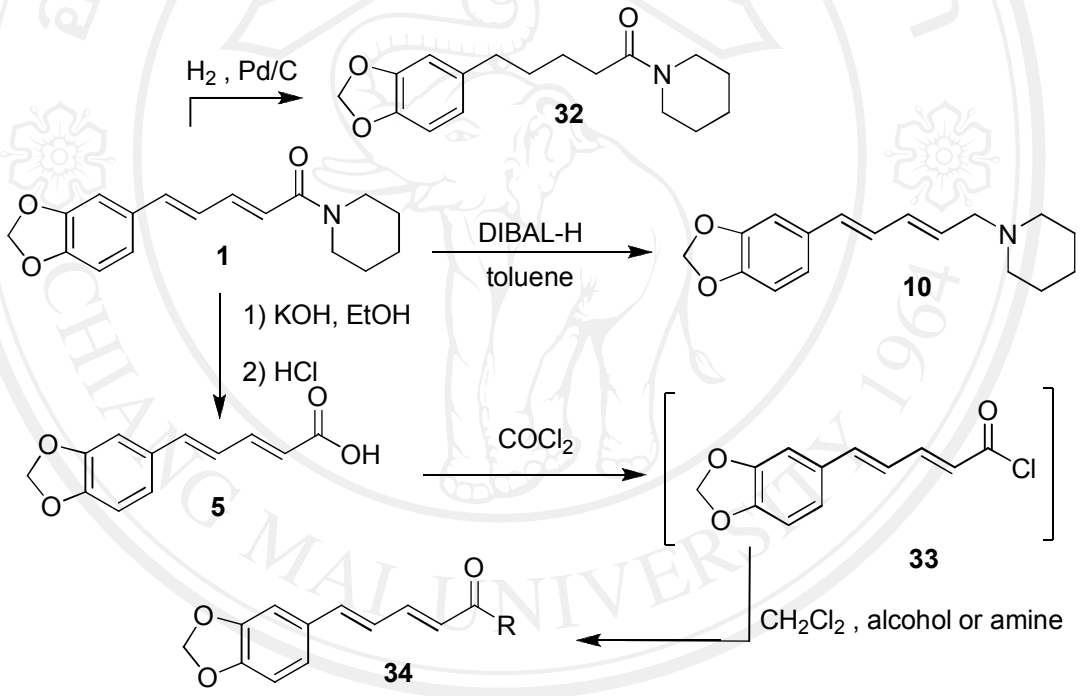


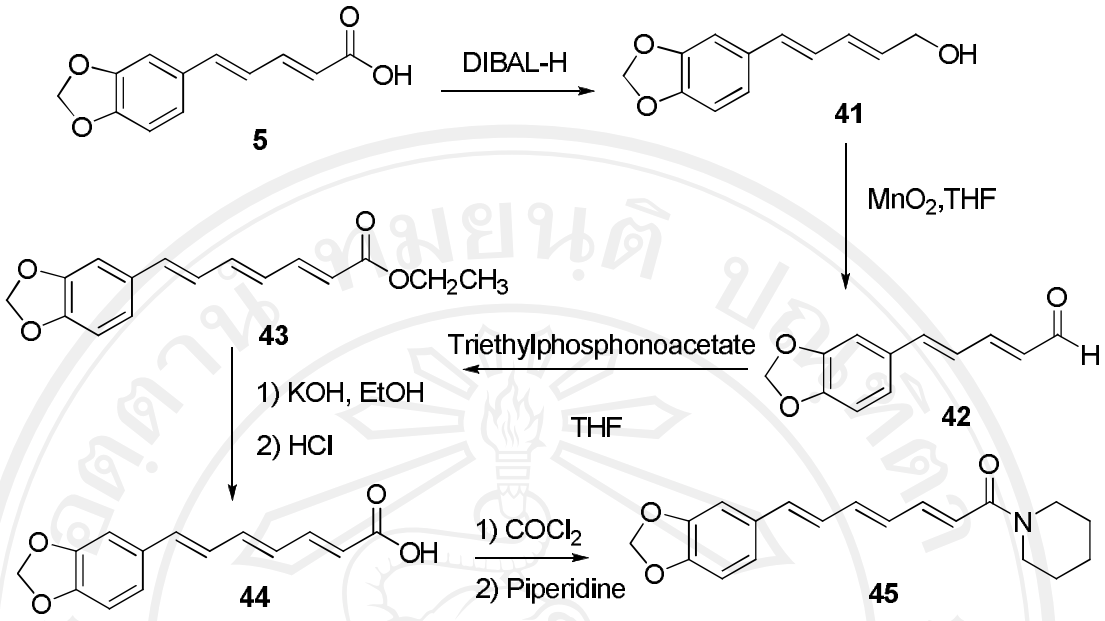
Table 1 Structure of piperine analogues **11-31**

Compound	n	R
11	2	Piperidinyl
12	2	Pyrrolidinyl
13	2	Morpholinyl
14	2	Aminobenzyl
15	2	Amino-5-benzyl
16	2	Aminohexyl
17	2	Aminoisobutyl
18	2	Aminomethyl
19	2	Aminoethyl
20	2	Aminoisoprppyl
21	2	Aminocyclohexyl
22	2	Aminobutyl
23	2	Methoxy
24	2	Ethoxy
25	2	Propyloxy
26	2	Butyloxy
27	1	Piperidinyl
28	1	Pyrrollidinyl
29	1	Morpholinyl
30	1	Methoxy
31	3	piperidinyl

In 2004, Ribeiro *et al*.[28] reported that piperine and twelve synthetic derivatives against epimastigote and amastigote forms of the protozoan parasite *Trypanosoma cruzi*, the causative agent of the incurable human disease. The results obtained point to piperine as a suitable template for the development of new drugs with trypanocidal activity. Preparation of piperine analogues **32-40** and **39-43** were shown in Schemes 2 and 3 respectively.

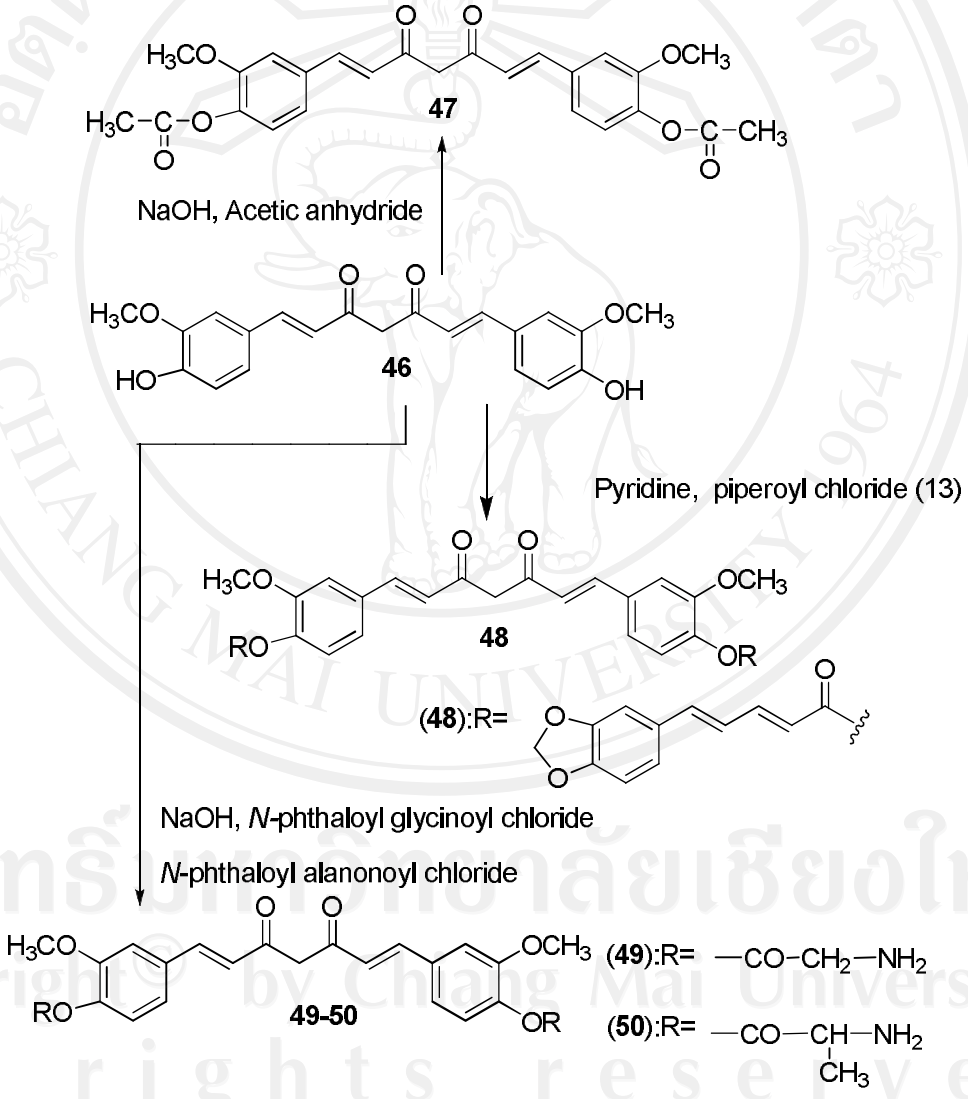


Scheme 2 Preparation of piperine analogues **32-40**

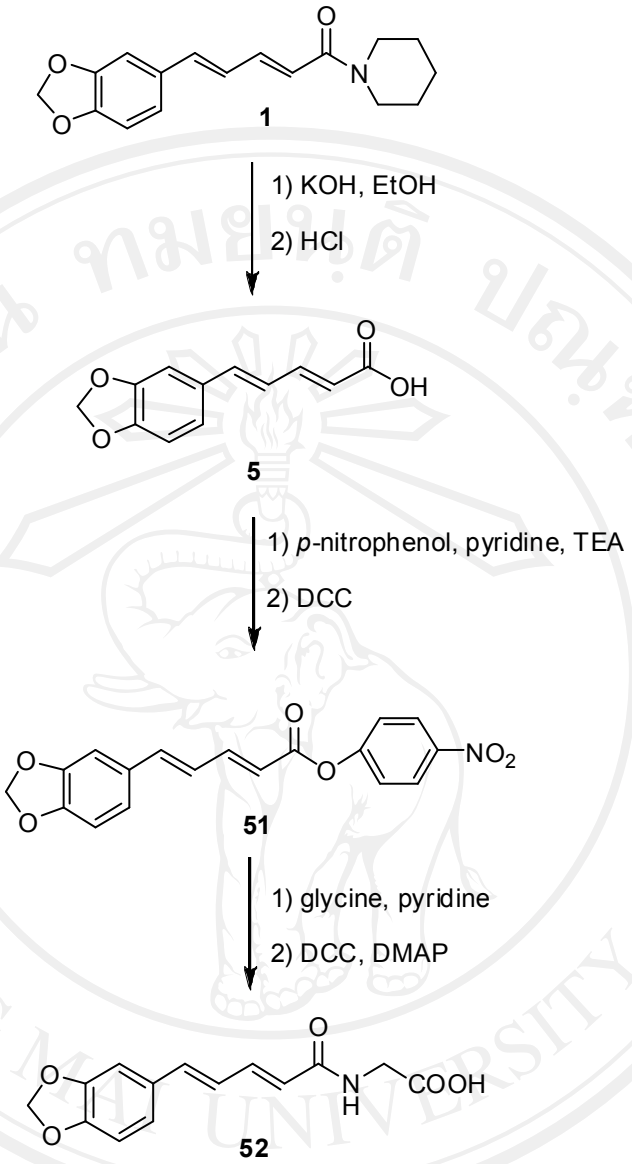


Scheme 3 Preparation of piperine analogues **41-45**

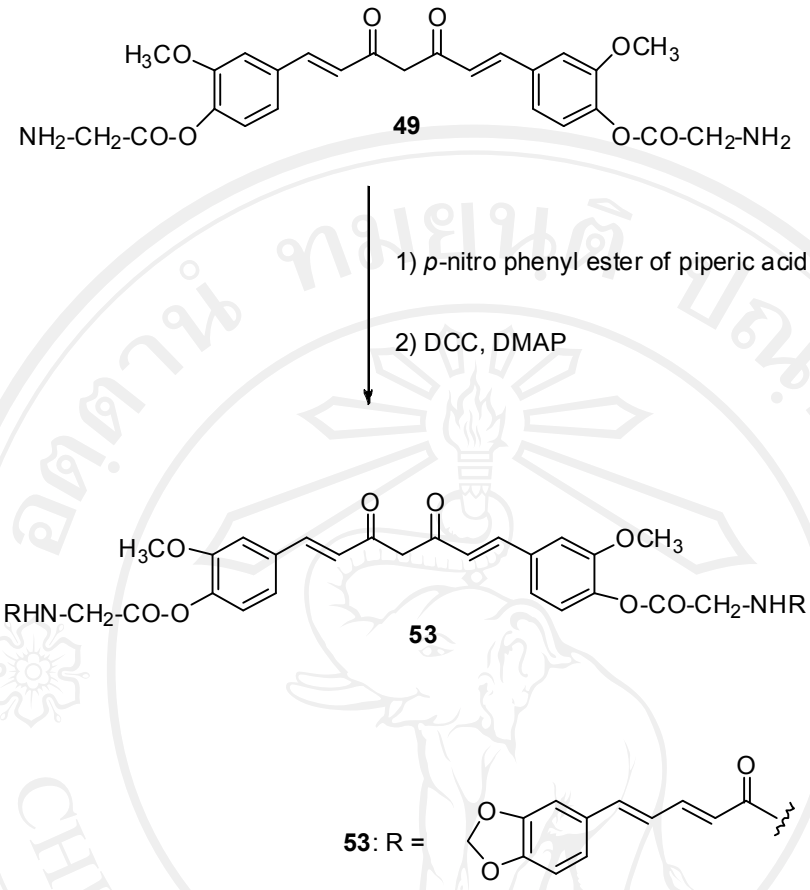
In 2005, Mishra *et al*.[29] reported that piperic acid is added to enhance bioavailability of curcumin. The derivatives of curcumin, linked with piperic acid and piperoyl glycine, were used for testing their apoptotic potential on tumor cells. Preparation of piperine analogues **47-50**, **51-52** and **53** were shown in Schemes 4, 5 and 6 respectively.



Scheme 4 Preparation of piperine analogues **47-50** from curcumin (**46**)

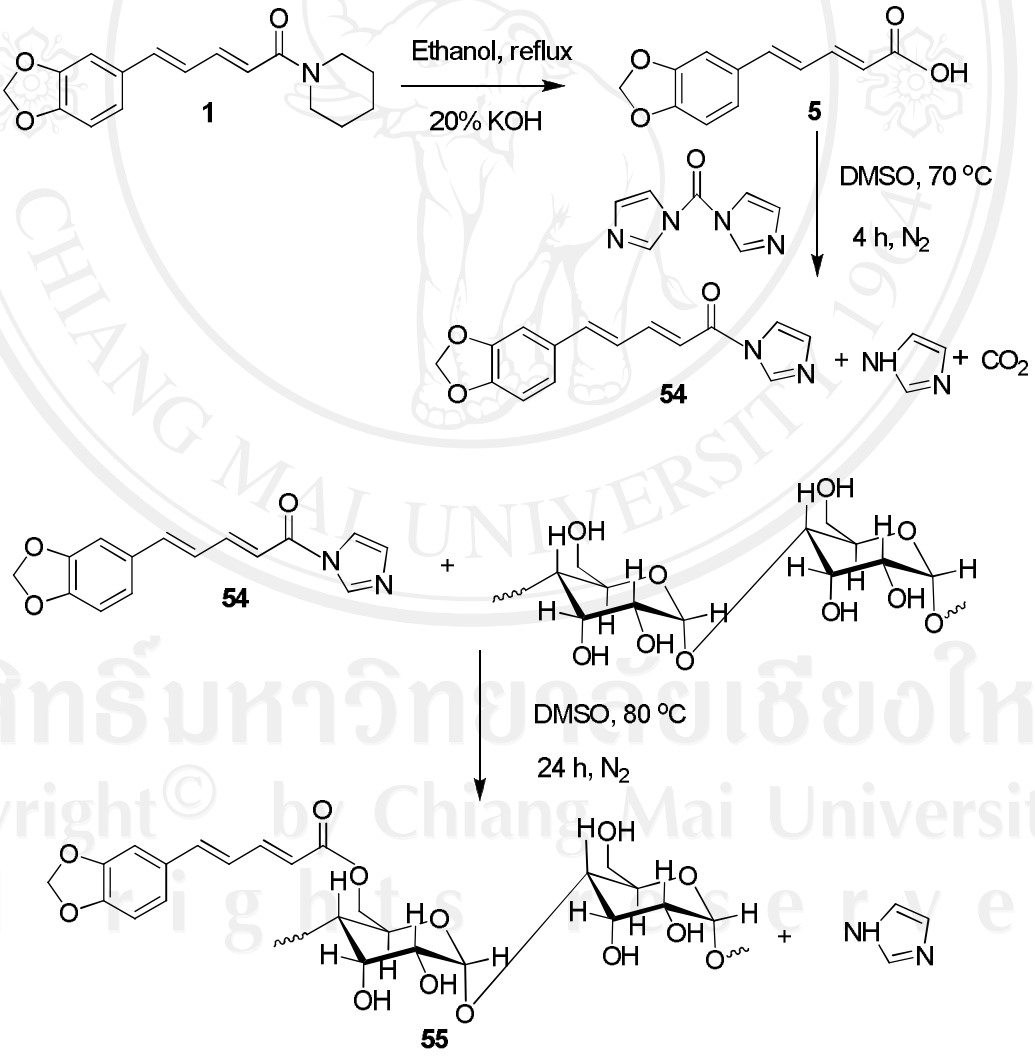


Scheme 5 Preparation of piperine analogues **51-52**



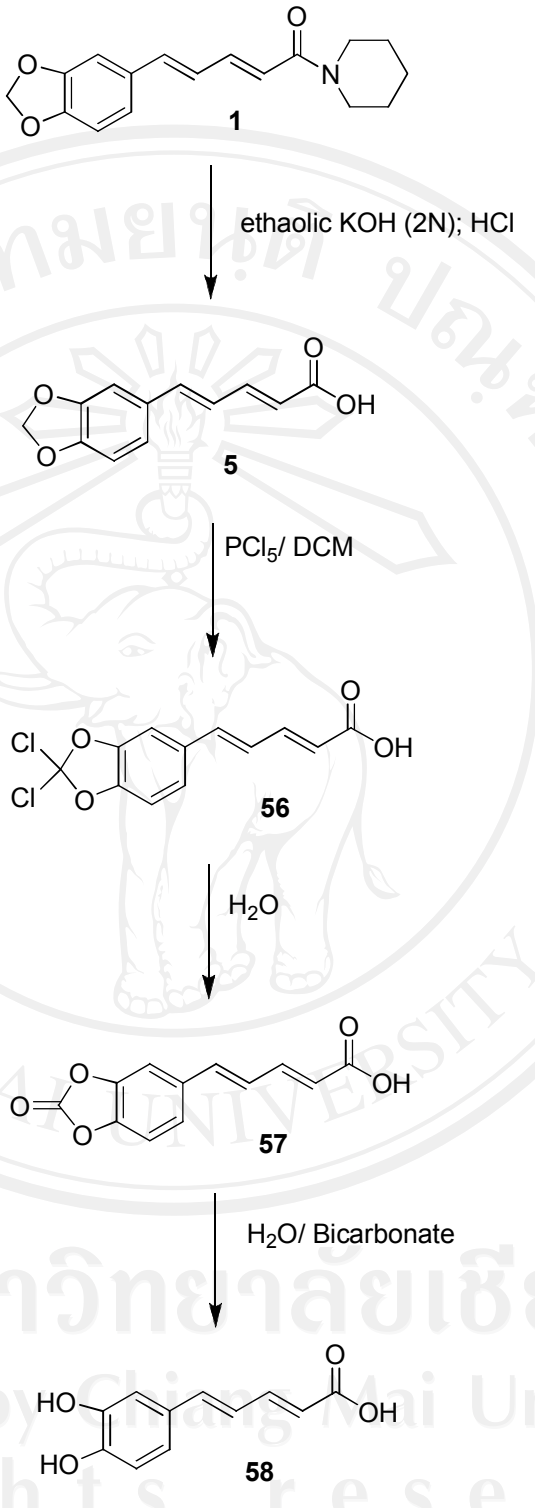
Scheme 6 Preparation of piperine analogue **53** from **49**

In 2008, Jingfen *et al*.[30] reported that a novel starch piperinic ester (SPE) was synthesized. The synthetic process includes piperic acid was obtained by hydrolyzing piperine, piperic acid was reacted with Carbonyldiimidazole (CDI) in DMSO, starch piperinic ester was obtained by the reaction of activated Piperic acid with water soluble starch. Anti-hyperlipidemic activity of SPE was assayed by pharmacological testes and the results indicated that the SPE had high anti-hyperlipidemic activity and would be one kind of new potential candidate of anti-hyperlipidemia pro-drug. Preparation of piperine analogues **54** and **55** were shown in Scheme 7.

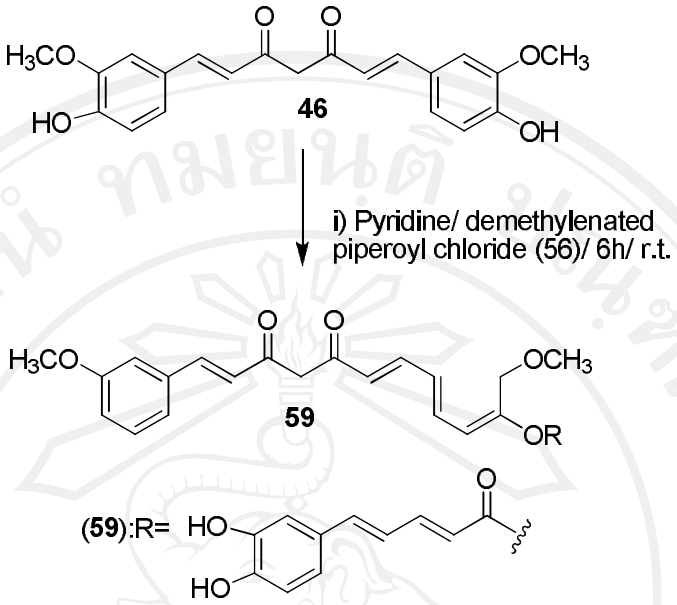


Scheme 7 Preparation of piperine analogue **55** from **54**

In 2008, Dubey *et al*.[31] reported demethylenated piperic acid have been prepared by alkali hydrolysis of piperine to give piperic acid and selective cleavage of methylenedioxy group was accomplished by halogenation followed by hydrolysis with phosphoruspentachloride. Demethylenated piperic acid shows activity against bacteria and fungi. Preparation of piperine analogues **56-58** and **59** were shown in Schemes 8 and 9 respectively.

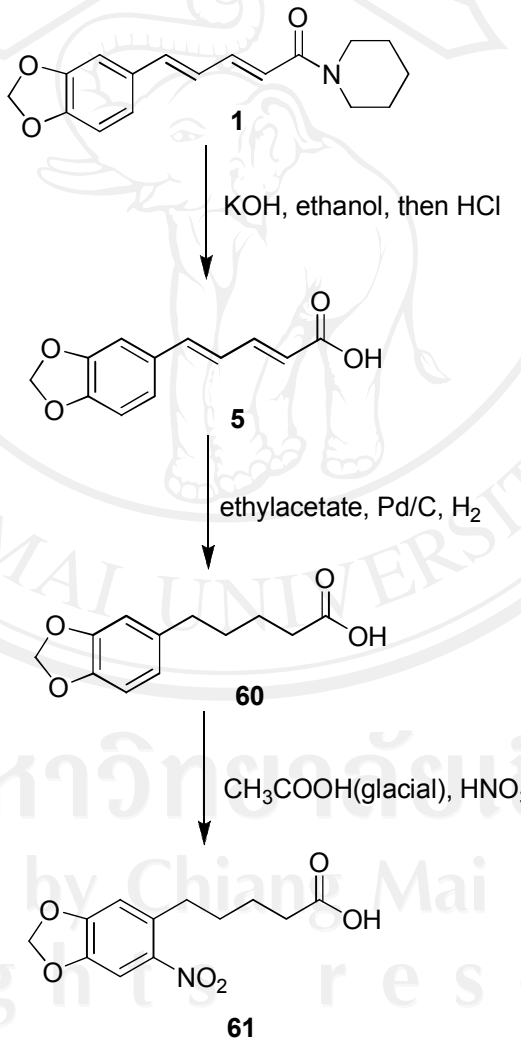


Scheme 8 Preparation of piperine analogues **56-58**

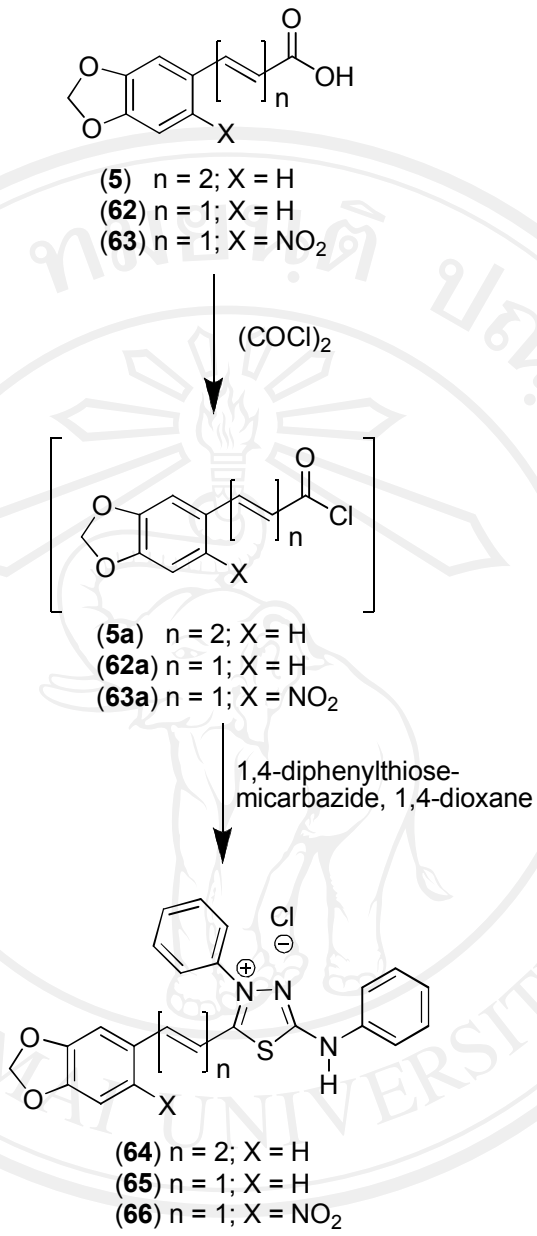


Scheme 9 Preparation of piperine analogue **59** from **46**

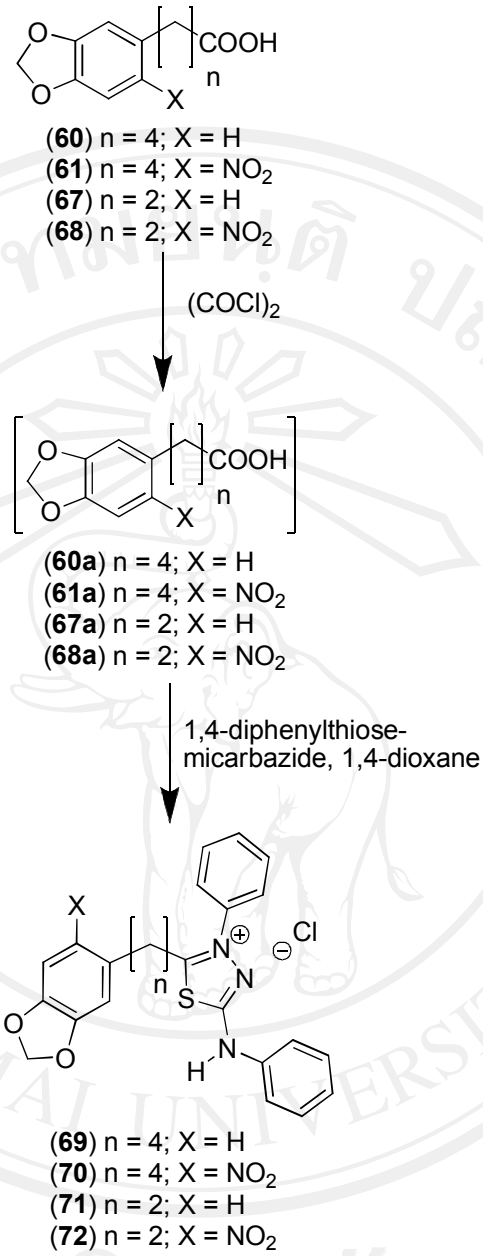
In 2008, da Silva Ferreira *et al.*[21] reported that the synthesis and characterization of nine new 1,3,4-thiadiazolium-2-phenylamine chlorides derived from natural piperine and evaluate their toxic effects against the different form of *Trypanosoma cruzi*, and its cytotoxicity on murine macrophages. These analogues may be prototype for use in the development of a new drug with high efficiency. Preparation of piperine analogues **60-61, 64-66**, **69-72** and **75-76** were shown in Schemes 10, 11, 12 and 13 respectively.



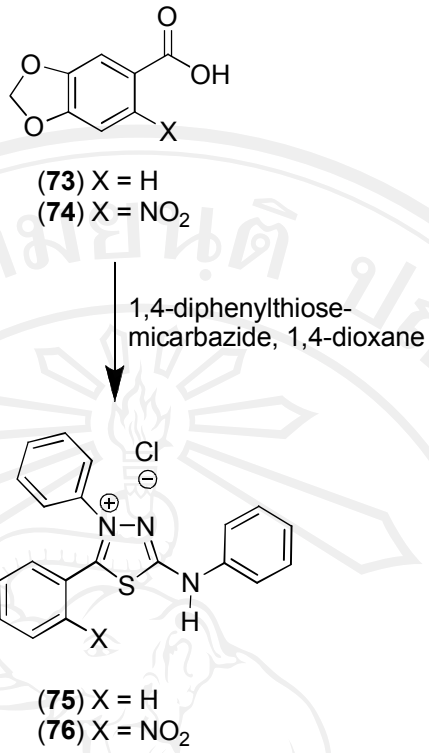
Scheme 10 Preparation of piperine analogues **60-61**



Scheme 11 Preparation of **64-66** from **5**, **62-63**



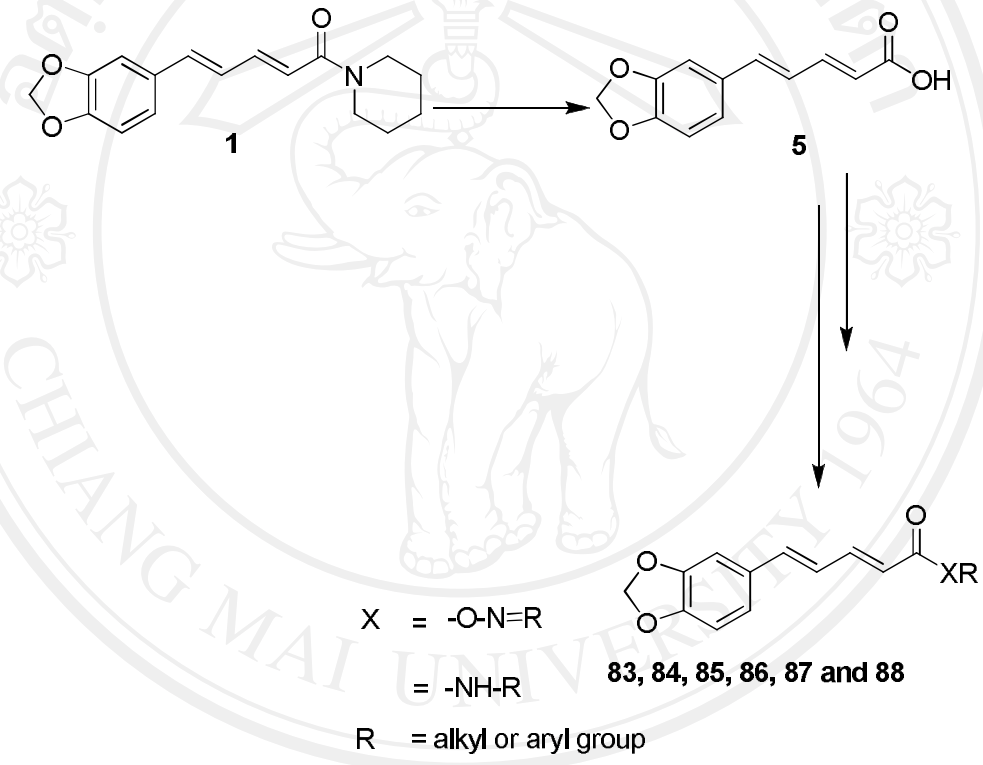
Scheme 12 Preparation of **69-72** from **60-61**, **67-68**



Scheme 13 Preparation of **75-76** from **73-74**

1.4 The research objectives

The aim of this research is to synthesize the novel piperine derivatives. These analogues will be subjected to tests *in vitro* against bacteria and fungi. Moreover, the novel piperine derivatives will be tested for their effective antioxidant property. Preparation of piperine analogues **83, 84, 85, 86, 87** and **88** were shown in Scheme 14.



Scheme 14 Preparation of piperine analogues **83, 84, 85, 86, 87** and **88**