

## The Synthesis of Quinidine Salicylate Ester Compound

Intan Nurjaya<sup>1)</sup>, Muhammad Hanafi<sup>2)</sup>, Puspa D.N. Lotulung<sup>2)</sup>, Teni Ernawati<sup>2)</sup>, Sri Mursiti<sup>1)</sup>

<sup>1)</sup> Faculty of Mathematic and Science, Department of Chemistry, Semarang State University, Semarang, Indonesia

<sup>2)</sup> Research Center for Chemistry, Indonesian Institute of Sciences, Kawasan Puspiptek, Serpong, Indonesia

\*Corresponding author: [intannurjaya45@gmail.com](mailto:intannurjaya45@gmail.com)

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### Abstract

Quinidine is an optical isomer of quinine extracted from the bark of the chicona tree and similar plant species. PT SIL Lembang isolated quinidine from *Chiconia ledgereria*. The purpose of this study was to obtain quinidine salicylate ester through esterification reaction. In this study, the synthesis of a quinidine ester compound by esterification reaction was conducted. Esterification reaction was conducted by using dicyclohexyl carbodi imide (DCC) activator and dimethyl amino pyridine (DMAP) catalyst with one carboxylic acid namely salicylate acid producing new compound namely quinidine salicylate. Subsequent Quinidine salicylate was obtained in the form of oil with 97% yield. The compound obtained from the synthesis was then identified using Thin Layer Chromatography continue analyzed using with Spectrophotometer, LC-ESI-MS spectroscopy. Results show that the target compound has been successfully synthesized.

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## 1. INTRODUCTION

Quinidine (Fig. 1) is an optical isomer of quinine extracted from the bark of the chincona tree and similar plant species. PT SIL Lembang, isolated quinidine from *Chincona ledgereriana* [1], Quinidine has a molecular formula  $C_{20}H_{24}N_2O_2$ .

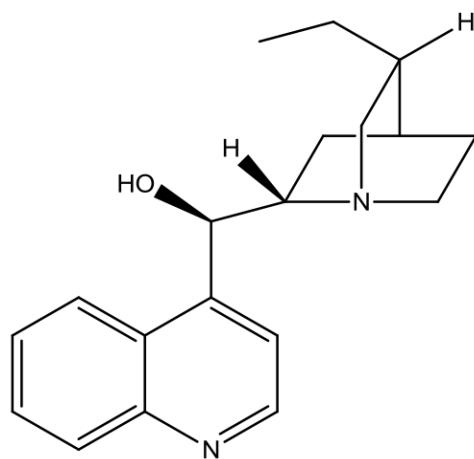


Fig. 1. Quinidine

This alkaloid dampens the excitability of cardiac and skeletal muscles by blocking sodium and potassium current across cellular membranes. It prolongs cellular action potentials and alpha-adrenergic neurotransmission. Quinidine is an alkaloid with class 1A antiarrhythmic, antimalarial effects and cytochrome P450 2D6 inhibitor [2].

Synthesis of esters using salicylic acid was based on three reasons: an ester the purpose of reaching the target and it is readily hydrolyzed [3], it is easily conducted on Quinidine [4], and it right properties for antidiabetic and to increase the activator [5].

The creation of this synthesis is also based on the Lipinski rule concerning the drug compounds that have absorption or permeability. Cinchonidine predicted by ChemDraw has log P value 4.22, molecular weight 364.22, four hydrogen bond acceptors, and no hydrogen bond donor, precisely as described in the Lipinski rule.

Esterification is the reaction between alcohols and carboxylic acids to make esters. It also looks briefly at making esters from the reactions between acyl chlorides (acid chlorides) and alcohols, and between acid anhydrides and alcohols [6]. Esters are derived from carboxylic acid namely salicylate acid producing new compound namely quinidine salicylate. A carboxylic acid contains the –COOH group, and in an ester, the hydrogen in this group is replaced by a hydrocarbon group of some kind.

N, N-Dimethyl-4-pyridine amine (Fig.2.), a very active catalyst, we have found that N, N-dimethyl-4 pyridinamine, alone or mixed with triethylamine, is a superlative acylation catalyst, much superior to pyridine [7].

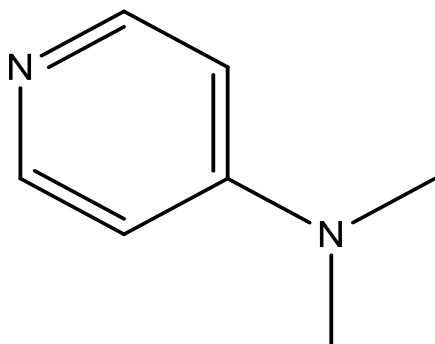


Fig. 2. N, N-Dimethyl-4-pyridinamine

According to a further embodiment, in cases where carbonyl groups are already present in the polysaccharide structure, in the form of carboxyl groups, the transformation to reactive amino groups is performed through the use of the above mentioned alkyl-spaced diamine, via the reaction with carbodiimide (dicyclohexyl), carbodiimide or DCC (Fig.3.) in appropriate solvent [8]. .

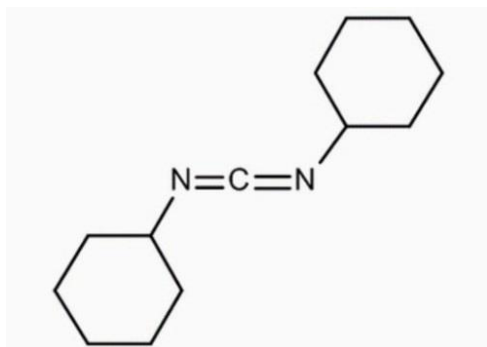


Fig. 3. N, N-dicyclohexylcarbodiimide

The purpose of this study was to obtain quinidine salicylate ester through esterification reaction. In this study, the synthesis of a quinidine ester compound by esterification reaction was conducted. Esterification reaction was conducted by using DCC activator and DMAP catalyst with one carboxylic acid namely salicylate acid producing new compound namely quinidine salicylate.

## 2. EXPERIMENTAL SECTION

### 2.1. Materials and Instrument

Three necks Rounded Flask, Liebig Condenser, Magnetic stirrer (IKA-C MAG HS7), Thin Layer Chromatography, Chromatography Column, LC-ESI-MS spectroscopy UNIFI.

Quinidine obtained from (PT. SIL Lembang), Salicylic acid p. a (Merck), ethyl acetate p.a (Merck), methanol p.a (Merck), dimethylformamide p.a (DMF) (Merck), n-hexane p.a (Merck), dicyclohexyl carbodiimide (DCC, Sigma D3128 p.a.), dimethylamino pyridine (DMAP, Sigma D5640 p.a), thin layer chromatography plates, Merck GF254 0,25mm), Silica gel 60 (Merck).

### 2.2. Methods

#### 2.2.1. Synthesis of Quinidine Salicylate

As much as 324.18 mg (1.0 mmol) of Quinidine was dissolved with Dimethyl formamide p.a (DMF) (Merck) as the solvent 20ml, then 207.045 mg (1.5 mmol) of salicylic acid and 309.495 mg (1.5 mmol) of N, N-dicyclohexylcarbodiimide (DCC) activator were added. The mixture was then stirred using magnetic stirrer for 1 hour. After an hour had passed, N, N-dimethylaminopyridine (DMAP 10%) was then added to the mixture as a catalyst.

The mixture was then stirred with constant speed for 24 hours [5] at 150°C. After the starting materials dissolve in addition to the activator, N, N-dicyclohexylcarbodiimide (1.5mmol) and catalyst, N, N-Dimethyl-4-pyridinamine 10% and stir with a magnetic stirrer at 400 rpm for 24 hours.

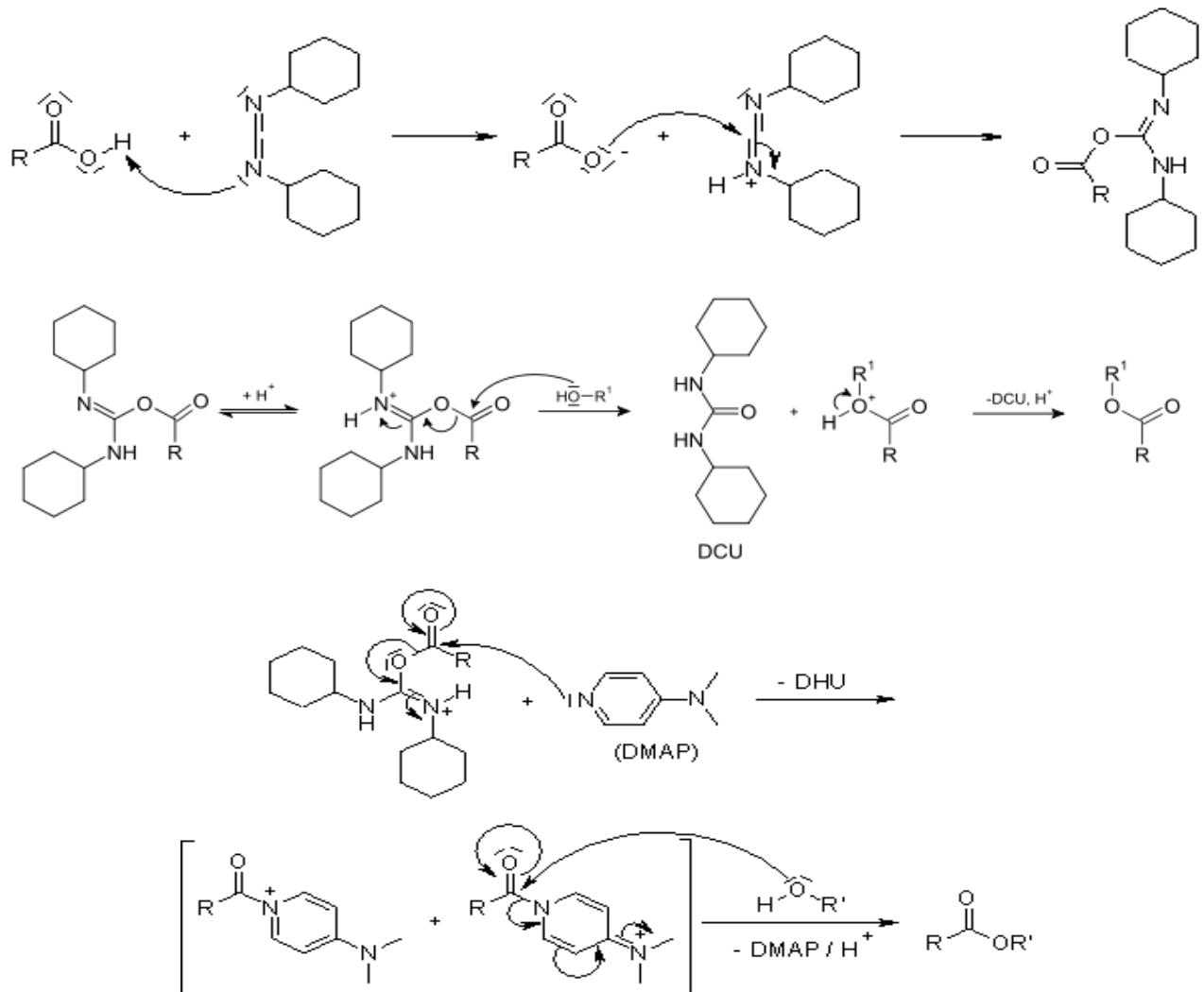


Fig. 4. Mechanism of esterification reaction Steglich

The resulting product was identified using thin layer chromatography [9]. Dicyclohexylurea (DCU) formed was filtered off and washed with n-hexane p. a (Merck), then extraction with water and n-hexane p.a (Merck) 1:1, and then Crude extracts were done then purified over flash silica column chromatography using ethyl acetate 100%. Wich started from n-hexane 100%, 19:1 n-hexane:ethyl acetate, 9:1 n-hexane:ethyl acetate, 4:1 n-hexane:ethyl acetate, 3:1 n-hexane:ethyl acetate, 2:1 n-hexane:ethyl acetate, 1:1 n-hexane:ethyl acetate.

#### 2. 2. 2. Identification of compounds

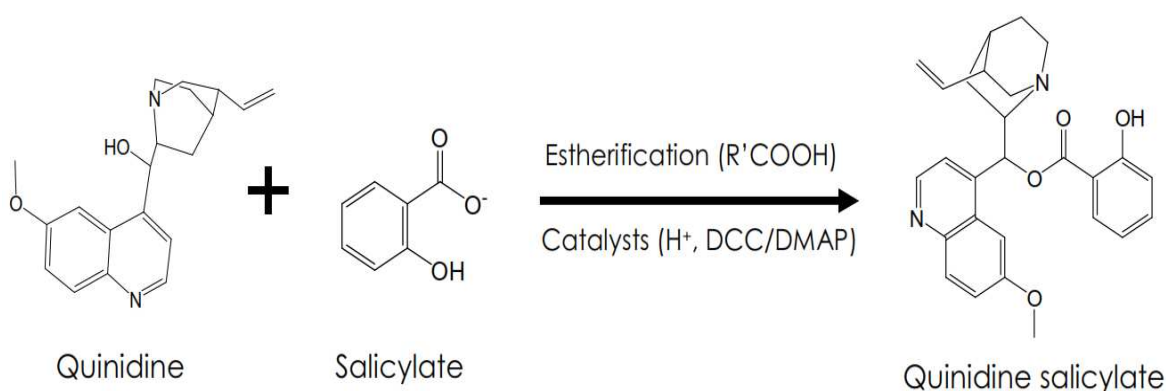
Compounds were identified using Thin Layer Chromatography until obtained one spot, continued with a spectrophotometer, LC-ESI-MS spectroscopy UNIFI.

### 3. RESULT AND DISCUSSION

#### 3.1. Synthesis of Quinidine Salicylate

The quinidine salicylate was successfully synthesized (Fig.5.) with the help of DCC activator as well as the DMAP catalyst in Dimethyl formamide p. a (DMF) (Figure 2). The reaction took 24 hours to finish at 150°C temperature because of the boiling point of DMF at 153°C and pressure inside the round-bottom flask while being stirred continuously at 400rpm.

The combination of activator and catalyst's usage was expected to increase the product's yield and decrease the temperature and energy needed to fuel the reaction.



**Fig. 5.** Esterification of Quinidine Salicylate

The forementioned reaction yielded 97% product, with the resulting product has an oily brown characteristic. The obtained yield was relatively high so optimizing the reaction by the temperature is recommended. The esterification reaction of quinidine salicylate can be depicted in Fig. 5.

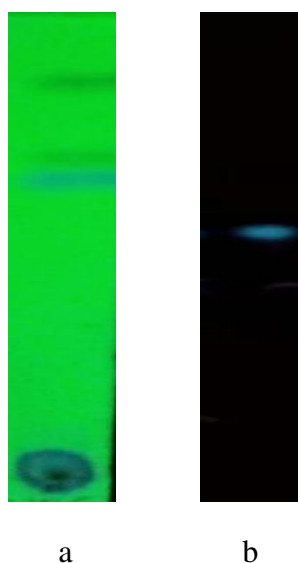
### 3.1.1. Thin Layer Chromatography

The TLC analysis of the extract (Fig.6.) was carried out by staining it on the TLC plate which was elaborated with the mobile phase [10], the mobile phase of hexane and ethyl acetate (4:1), the results obtained were seen under UV light, showing 1 stain on the plate, indicating that the compound was pure due to

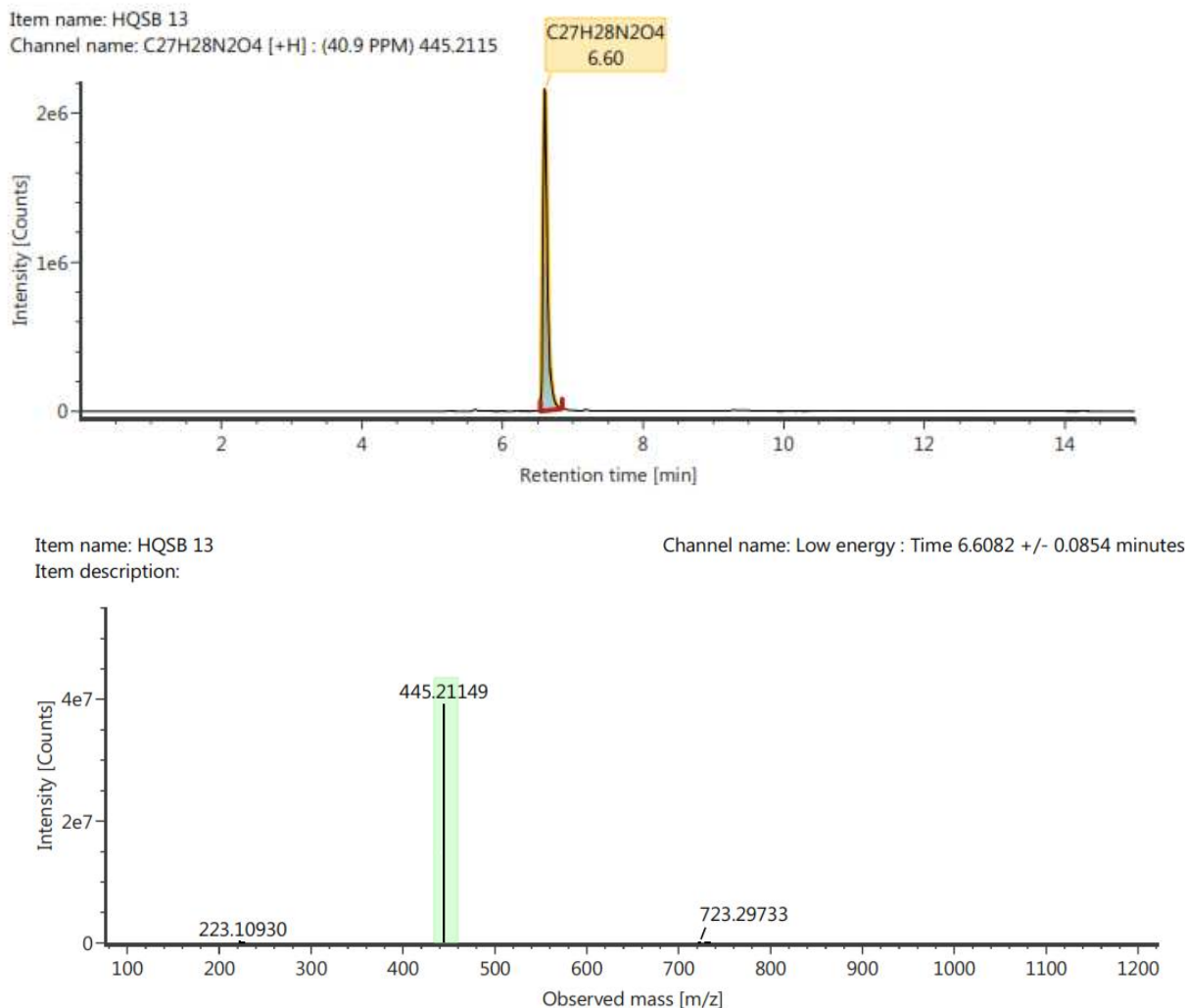
absence Other stains that indicate the presence of other compounds, to prove the structure of the compound was carried out again with an identification test with the LC-IES-MS instrument to find out more precisely whether the compound is quinidine salicylate or other compounds.

### 3.1.2. LC-ESI-MS

The Quinidine Salicylate was identified using LC-ESI-MS with MeOH as the solvent and type C-18 column (15 mm x 1 mm) [7]. The spectral figures in Fig.7. Shows that the compound had a retention time (tR) of 6.6 minutes and the molecule's peak ion (m/z) was at 445.2115.



**Fig.6.** a. Thin Layer Chromatography of reaction b. Thin Layer Chromatography of Quinidine Salicylate (one spot)



**Fig.7.** The Spectrum of LC-ESI-Mass Spectrum

Quinidine Salicylate has the molecular formula of  $C_{27}H_{28}N_2O_4$  and a molar mass of 444,20; as stated by ChemDraw application. A delta of 1 molecule from the spectrum was caused by an additional proton [M+H].

#### 4. CONCLUSION

The conclusion that can be resumed from this research was that the synthesis of quinidine salicylate could be done using DCC and DMAP for yield value of 97%. It must be confirmed with NMR.

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